THE STATUS OF RESEARCH INTO VACCINE SAFETY AND AUTISM

HEARING

BEFORE THE

COMMITTEE ON GOVERNMENT REFORM

HOUSE OF REPRESENTATIVES

ONE HUNDRED SEVENTH CONGRESS

SECOND SESSION

JUNE 19, 2002

Serial No. 107–121

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THE STATUS OF RESEARCH INTO VACCINE SAFETY AND AUTISM

WEDNESDAY, JUNE 19, 2002

HOUSE OF REPRESENTATIVES,
COMMITTEE ON GOVERNMENT REFORM,
Washington, DC.

The committee met, pursuant to notice, at 11:10 a.m., in room 2154, Rayburn House Office Building, Hon. Dan Burton (chairman of the committee) presiding.

Present: Representatives Burton, Morella, Horn, Davis of Virginia, Weldon, Duncan, Waxman, Maloney, Norton, Cummings, Kucinich, Tierney, and Watson.

Staff present: Kevin Binger, staff director; David A. Kass, deputy chief counsel; Pablo Carrillo Jennifer, Hall, counsels; S. Elizabeth Clay and John Rowe, professional staff members; Blain Rethmeier, communications director; Robert A. Briggs, chief clerk; Robin Butler, office manager; Elizabeth Crane, deputy communications director; Joshua E. Gillespie, deputy chief clerk; Michael Layman and Susie Schulte, legislative assistants; Nicholis Mutton, assistant to chief counsel; Leneal Scott, computer systems manager; Corinne Zaccagnini, systems administrator; Lisa Wilson and Katie Yee, interns; Phil Schiliro, minority staff director; Phil Barnett, minority chief counsel; Sarah Despres, minority counsel; Josh Sharfstein, minority professional staff member; Ellen Rayner, minority chief clerk; and Earley Green, minority assistant clerk.

Mr. BURTON. Good morning. A quorum being present, the Committee on Government Reform will come to order.

I ask unanimous consent that all Members' and witnesses' written statements be included in the record. Without objection, so ordered.

I ask unanimous consent that all articles, exhibits and extraneous or tabular material referred to be included in the record. Without objection, so ordered.

In April, the committee conducted a hearing reviewing the epidemic of autism and the Department of Health and Human Services' response. Ten years ago, autism was thought to affect 1 in 10,000 children in the United States. When the committee began its oversight investigation in 1999, it was thought to affect 1 in 500 children. Today, the National Institutes of Health estimates that autism affects 1 in 250 children. Think about that. It has gone from 1 in 10,000 to 1 in 250. We have an absolute epidemic.

In April, we looked at the investment our Government has made in autism as compared to other epidemics. We showed in that hearing that the CDC and NIH have not provided adequate funding to

address the issues in a manner that our public health service agencies have used to address other epidemics. We have some charts I think are being put on the screen to show this.

After our hearing, I joined with my colleagues on the Coalition on Autism Research and Education to request from our appropriators that at least $120 million be made available in fiscal year 2003 for autism research across the NIH and an additional $8 million be added to the CDC's budget for autism research. Giving more money to research is not the only answer though. Oversight is needed to make sure research that is funded will sufficiently answer the questions regarding the epidemic, how to treat autism and how to prevent the next 10 years from seeing the statistic of 1 in 250 children go to 1 in 25 children.

High quality clinical and laboratory research is needed now, not 5 or 10 years from now. Independent analysis of previous epidemiological and case control studies is needed as well. We have learned that a majority of parents whose children who have late onset or acquired autism believe it is vaccine-related. They deserve answers. We have also learned that parents have been our best investigators in looking for both causes of autism and for treatment. It has been parents who have formed nonprofit organizations to raise research dollars to conduct the research that the CDC, the FDA and NIH have neglected to do. We have heard from many of these parents in the past, Elizabeth Birt, Rick Rollens, Shelley Reynolds and Jeanna Smith to name a few. Each of these parents had healthy babies who became autistic after vaccination.

I might have been like many of the officials within the public health community denying a connection had I not witnessed this tragedy in my own family. I might not have believed reports from parents like Scott and Laura Bono, Jeff Sell, Jeff and Shelly Segal and Ginger Brown who came to me with pictures, videos and medical records. I might have been like so many pediatricians who discounted the correlation between vaccination and the onset of fever, crying and behavioral changes. Because both of my grandchildren, not one but both of my grandchildren suffered adverse reactions to vaccines, I could not ignore the parents plea for help and I could not ignore their evidence. My only grandson became autistic right before my eyes, shortly after receiving his federally recommended and State mandated vaccines. Without a full explanation of what was in the shots being given, my talkative, playful, outgoing, healthy grandson, Christian, was subjected to very high levels of mercury through his vaccines. He also received the MMR vaccine and within a few days, he was showing signs of autism. I won't go into the details but those of you who have autistic children know what I am talking about.

As a part of our investigation, the committee has reviewed ongoing concerns about vaccine safety, vaccine adverse events tracking and vaccine safety data link, VSD Project, and the National Vaccine Injury Compensation Program. I have joined with Congressmen Weldon, Waxman and 32 other Members of Congress in introducing H.R. 3741, the National Vaccine Injury Compensation Program Improvement Act of 2002 to realign the compensation program with congressional intent.

In today's hearing, we will receive a research update from several previous witnesses as well as new research findings that further support a connection between autism and vaccine adverse events. We will learn more about both the possible link between the use of mercury containing preservative thimerosal in vaccines in autism as well as autistic entercolitis resulting from the measles, mumps, rubella vaccine, MMR vaccine.

Through a congressional mandate to review thimerosal content in medicines, the FDA learned that childhood vaccines when given according to the CDC's recommendations exposed over 8,000 children a day in the United States to levels of mercury that exceed Federal guidelines. Is there a connection between this toxic exposure to mercury and the autism epidemic? We will hear from Dr. James Bradstreet and Dr. Vera Stejskal on this issue.

We have twice received testimony from Dr. Andrew Wakefield regarding his clinical research into autism entercolitis. We will learn today that not only has he continued to conduct clinical research but this research is confirming the presence of vaccine-related measles, RNA, in the biopsies from autistic children. Dr. Wakefield, like many scientists who blazes new trails, has been attacked by his own profession. He has been forced out of his position at the Royal Free Hospital in England. He and his colleagues have fought an uphill battle to continue the research that has been a lone ray of hope for parents whose children have autistic entercolitis.

Dr. Arthur Krigsman is joining us today as well to discuss his clinical findings of inflammatory bowel disorder in autistic children. He will share with us his initial findings as well as discuss his research plans currently with his institutional review board for approval.

Do the epidemiological and case control studies which the CDC has attempted to use to refute Dr. Wakefield's laboratory results answer the autism vaccine questions honestly? Epidemiologist Dr. Walter Spitzer is back today to answer this question. What else is needed to prove or disprove a connection?

Unfortunately, rather than considering the preliminary clinical findings of Dr. Wakefield as a newly documented adverse reaction to a vaccine, the CDC attempted to refute these clinical findings through an epidemiological review. While epidemiological research is very important, it cannot be used to disprove laboratory and clinical findings. Valuable time was lost in replicating this research in determining whether the hypothesis was accurate. Officials at HHS have aggressively denied any possible connection between vaccines and autism. They have waged an information campaign endorsing one conclusion on this issue where the science is still out. This has significantly undermined public confidence in the career public service professionals who are charged with balancing the dual roles of assuring the safety of vaccines and increasing immunization rates.

Increasingly, parents come to us with concerns that the integrity and honest public health response to a crisis has been left by the wayside in lieu of protecting the public health agenda to fully immunize children. Parents are increasingly concerned the Department may be inherently conflicted in its multiple roles of promoting immunization, regulating manufacturers, looking for adverse

events and managing the Vaccine Injury Compensation Program, and developing new vaccines. Families share my concern that vaccine manufacturers have too much influence as well. That is something we continue to look into.

How will HHS restore the public's trust? One of the primary topics to be discussed at this hearing is access to the vaccine safety data link. To help fill scientific gaps, the CDC formed partnerships with eight large health maintenance organizations through an agreement with the American Association of Health Plans to continually evaluate vaccine safety. This project is known as the Vaccine Safety Datalink or VSD and includes medical records on millions of children and adults.

Until this year, access to data from the VSD has been limited to researchers affiliated with the CDC and a few of their hand picked friends. This good old boy network practice has predictably led to questions about the objectivity of the research and the fairness of the results. The VSD data should be made available to all legitimate scientific researchers so that independent studies can be conducted and the results verified. This data base contains a wealth of data involving millions of patients over a 10-year period. If properly utilized, it can help researchers study vitally important questions about the safety of vaccines, the effects of mercury-based preservatives and childhood vaccines and many other questions.

The committee first raised this issue with the CDC 2 years ago. For 2 years the CDC delayed. Six months ago, we were informed the CDC was developing a plan to expand access to the data base. Finally, in February of this year after a great deal of prompting from the committee, Dr. Robert Chen, Chief of Vaccine Safety and Development at the National Immunization Program, informed our committee staff that the CDC had finalized its plan and that it was poised to put it into effect. Under this plan any legitimate scientist could submit a proposal to the CDC to conduct research using VSD data and access to the data would be provided along with some scientific or basic safeguards.

In preparation for today's hearing, committee staff asked the CDC why the plan describe to us in February had not been put into effect. The staff was informed that it had been put into effect. However, there has been no public announcement. They put it into effect but didn't tell anybody. How are researchers supposed to know about availability of the data if there is no announcement? It took 2 years of prodding by this committee to get the CDC to open up access to the data base. For 4 months, it appears the CDC didn't inform anybody but this committee of the data's availability. That doesn't make it appear that the CDC is making a good faith effort to open up this data base. It looks to me like the CDC is trying to do the bare minimum they have to do to get us off their backs, and that is not acceptable.

That is why I insisted that Dr. Chen be here today. I just wanted to ask him why they didn't tell anybody about the data base being available. I would like to know how he expects researchers to use this data if nobody tells them it is available. Dr. Roger Bernier is here from the CDC to testify about these issues. He is accompanied by both Dr. Chen, the creator of the VSD Project, and Dr. Frank DeStefano, the CDC official who is also co-author of the MMR IVD

study. They are here to address our questions on the VSD Project and the vaccine autism research. The CDC employees are accompanied by Dr. Stefan Foot and the National Institutes of Health from the National Institutes of Health and Dr. William Egan of the FDA.

As representatives of the people, we have a responsibility to ensure that our public health officials are adequately and honestly addressing this epidemic and its possible links to vaccine injury.

I look forward to hearing from our witnesses and the hearing record will remain open until July 3.

[The prepared statement of Hon. Dan Burton follows:]

Opening Statement
Chairman Dan Burton
Committee on Government Reform

"The Status of Research into Vaccine Safety and Autism"

June 19, 2002
2154 Rayburn House Office Building
11:00 a.m.

Good afternoon, a Quorum being present, the Committee on Government Reform will come to order. I ask unanimous consent that all Members' and witnesses' written and opening statements be included in the record. Without objection, so ordered.

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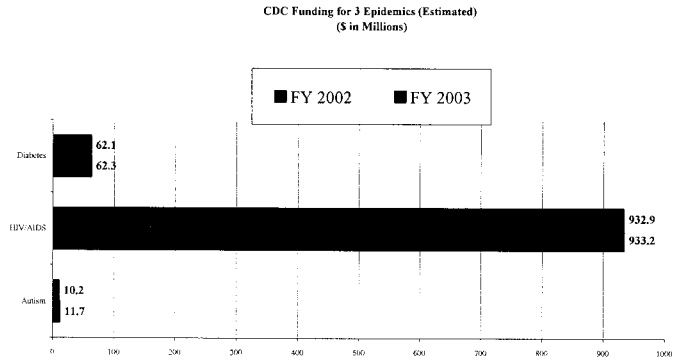
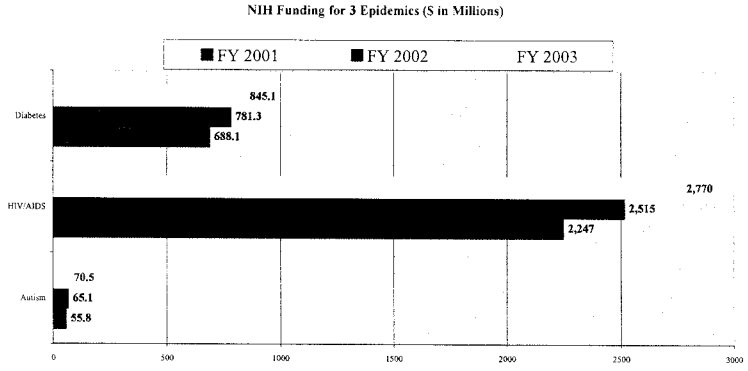
[Chairman's Opening Statement]

In April the Committee conducted a hearing reviewing the epidemic of autism and the Department of Health and Human Service's (HHS) response. Ten years ago, autism was thought to affect 1 in 10,000 individuals in the United States. When the Committee began its oversight investigation in 1999, autism was thought to affect 1 in 500 children. Today, the National Institutes of Health (NIH) estimates that autism affects 1 in 250 children.

In April we looked at the investment our Government has made into autism as compared to other epidemics. We showed in that hearing that the CDC and NIH have not provided adequate funding to address the issues in the manner that our Public Health Service agencies have used to address other epidemics.





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investigators in looking for both causes of autism and for treatments.

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Access to the Vaccine Safety Datalink (VSD)

One of the primary topics to be discussed at this hearing is access to the Vaccine Safety Datalink. (VSD). To help fill scientific gaps, the CDC formed partnerships with eight large health maintenance organizations through an agreement with the American Association of Health Plans to continually

evaluate vaccine safety. This project is known as the Vaccine Safety Datalink (VSD) and includes medical records on millions of children and adults. Up until this year, access to data from the VSD has been limited to researchers affiliated with the CDC and a few of their handpicked friends. This 'good old boy's network" practice has predictably led to questions about the objectivity of the research and the fairness of the results.

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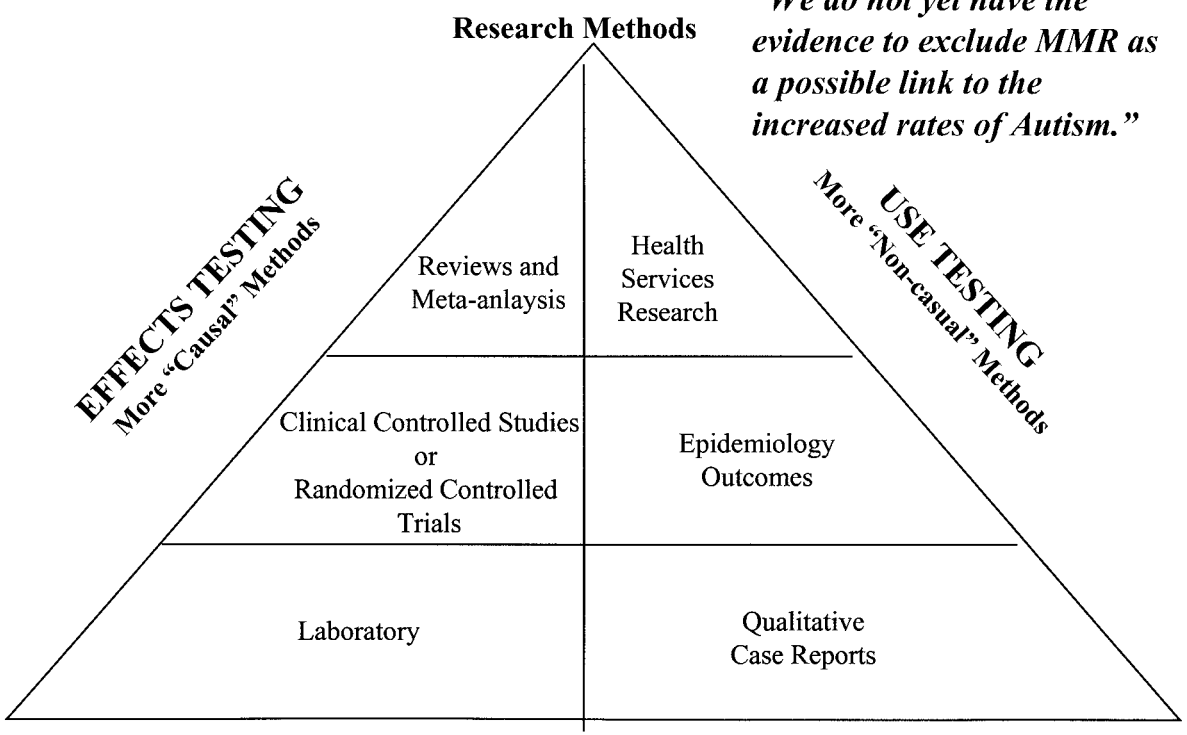
As representatives of the people, we have a responsibility to ensure that our public health officials are adequately and honestly addressing this epidemic and its possible links to vaccine injury.

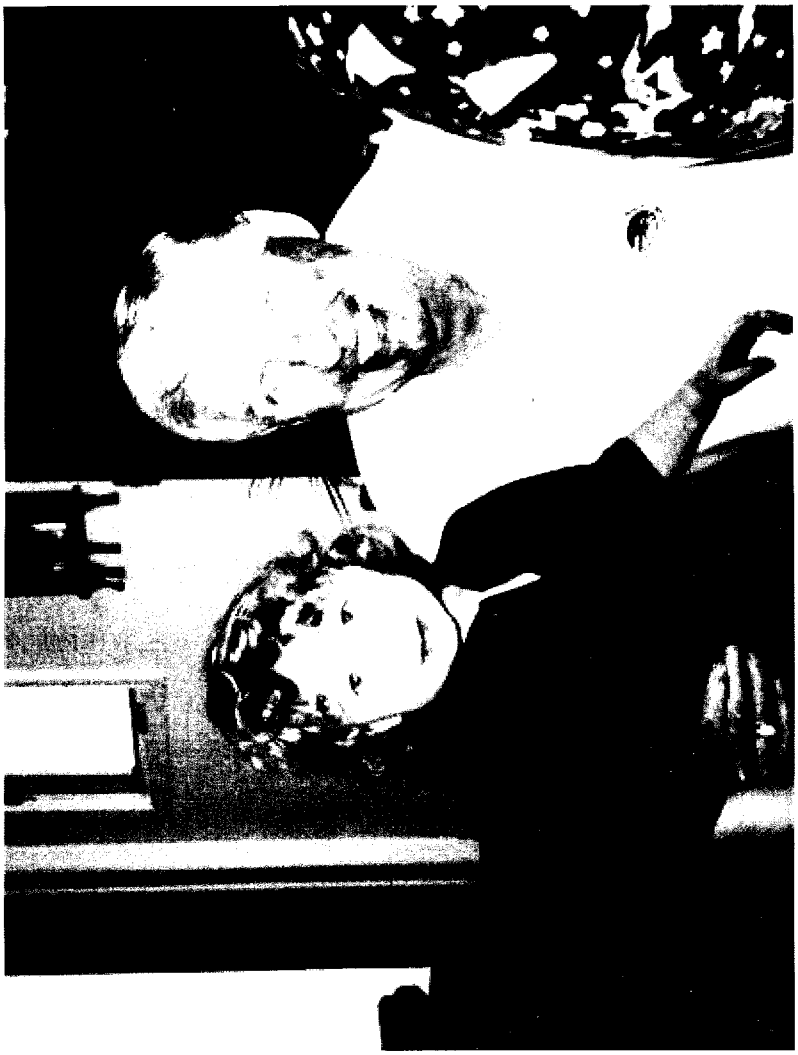
I look forward to hearing from our witnesses today. Our hearing record will remain open until July 3.

I now recognize the ranking minority member, Mr. Waxman for his opening statement.

"Balanced" Evidence Hierarchy



"We do not yet have the evidence to exclude MMR as a possible link to the increased rates of Autism."



Mr. BURTON. I now recognize Mr. Waxman.

Mr. WAXMAN. Mr. Chairman, today you have convened a hearing about the safety of vaccines. This is an important topic and also a familiar one to this committee. Over the last several years, you have held a series of hearings raising questions about the safety of vaccines, questions that undoubtedly have caused real concern among some parents and clinicians. These hearings have had some positive effects. Your interest over the years has led to unprecedented attention to vaccine safety. Since your first hearing on the topic, many respected researchers have chosen to investigate whether vaccines are associated with inflammatory bowel disease, autism, diabetes and other assorted conditions among children.

While rare side effects from vaccines are always possible, these studies have not found that vaccines are associated with any of these serious health problems. Since your first vaccine safety hearing, a blue ribbon panel of scientists convened by the Institute of Medicine has reviewed many of the most widely disseminated theories alleging harm from vaccines. This esteemed panel evaluated the allegation that the MMR vaccine causes autism. It studied the claim that thimerosal, a vaccine preservative, caused developmental delay. It reviewed whether the Hepatitis B vaccine causes neurological injury. It assessed the theory that multiple vaccinations cause allergies and asthma. In each case, the Institute of Medicine panel has found that scientific evidence does not validate the theories. Expert panels in other nations have reached similar conclusions.

Mr. Chairman, you have challenged the public health system to defend itself against numerous allegations that vaccines cause a wide variety of problems. I am not aware of any allegations about the safety of vaccines that you have not pursued. So far, the subsequent investigations and expert reviews have found vaccines to be safe. Because of your efforts in this area, Americans can have more confidence today in the safety of the vaccine supply than ever before.

There has also been a negative consequence to your approach. You have repeatedly provided a forum for unsubstantiated allegations about vaccine safety that have alarmed and confused parents. Although the scientific evidence for vaccine safety has grown stronger, parental concerns about vaccine safety have also increased since you started these hearings. This is a potentially dangerous development because it can lead to lower immunization rates and more disease.

I recently asked the Centers for Disease Control to describe what would happen if MMR immunization rates dropped. According to CDC, if immunization rates dropped to the levels they were in 1989, we could see over 26,000 hospitalizations for measles, 8,500 cases of pneumonia, 135 cases of encephalitis, and 224 deaths. According to the CDC, even a drop in immunization rates of 10 percent could result in an additional 2 million kids being susceptible to measles. It would also significantly increase susceptibility to rubella and congenital rubella syndrome which can cause serious birth defects such as blindness, deafness, and stillbirths. Congenital rubella syndrome is also a well known cause of autism, a disease we all want to prevent. How tragic it would be if an unjusti-

fied vaccine scare caused some children to die, others to have permanent brain deficits, and still others to suffer from autism. I ask that the information from the CDC be placed in the record at the conclusion of my statement.

While I am strongly opposed to reckless allegations about vaccine risks that scare parents and are not supported by the science, I also recognize that questions about vaccines will always arise. That is why I support efforts to fund additional research on vaccine safety. Some of the theories on the agenda for today do require additional research and I am pleased the Government is supporting such studies.

I also want to ensure that the Government does not lose the ability to conduct valid vaccine safety studies. We must assure the future of initiatives like the Vaccine Safety Datalink Project. This is a unique collaboration between CDC and several large health maintenance organizations that allows for valid and timely research on vaccine safety. Indeed this research has led to many important policy changes over the years.

Today, we will hear from scientists at CDC who work closely with the Vaccine Safety Datalink Project. These scientists are quite concerned about your threats to subpoena the raw data from this data base to pursue a vaccine related allegation because the raw data contain identifiable information from the medical records of more than 6 million Americans. A congressional subpoena would constitute a serious violation of medical privacy. According to CDC, a subpoena could have the effect of driving health maintenance organizations from the program and destroying CDC's ability to scientifically test hypotheses relating to adverse effects potentially associated with vaccines. In other words, we are going to end up causing more harm than doing good if we pursue this subpoena approach.

You have an alternative to a subpoena, Mr. Chairman. The CDC has worked with HMOs to create a process for allowing independent researchers access to this data. I continue to urge you to accept this solution and renounce your subpoena threat.

Finally, I would like to address some allegations that Dr. Wakefield makes in his written testimony. Dr. Wakefield implies that a witness who testified here last year, Dr. Michael Gershon, either perjured himself or was guilty of sloppy science by noting problems in the lab that Dr. Wakefield used in his research. Dr. Gershon did not lie to this committee and this portion of his testimony did not involve his scientific expertise and thus was not sloppy. Dr. Gershon related what he was told by Dr. Michael Oldstone of the Scripps Institute, who has performed an evaluation of this lab. Dr. Gershon continues to stand by his testimony.

Dr. Wakefield also is planning to make a needless attack on Dr. Gershon's wife, who he alleges may have a financial interest in the chicken pox vaccine. In fact, according to Dr. Gershon, while his wife did conduct research relevant to a chicken pox vaccine patent, neither he nor his wife has any financial interest in the vaccine or its manufacturers. Dr. Wakefield's allegation is therefore groundless as well as gratuitous. Dr. Gershon's testimony last year was quite lengthy and he raised many scientific issues but Dr. Wakefield has not refuted any of them. Instead, he is resorting to name

calling which does not move these scientific issues along and is unproductive.

I am going to ask unanimous consent that the written testimony of Dr. Elizabeth Miller of the Public Health Laboratory Service of the United Kingdom be entered into the record and I also alluded to other information which I would also like attached to this opening statement and made a part of the record.

I thank the witnesses for coming today. I look forward to your testimony and I yield my time.

[The prepared statement of Hon. Henry A. Waxman follows:]

Statement of Rep. Henry A. Waxman
Ranking Minority Member
Committee on Government Reform
Hearing on
"The Status of Research Into Vaccine Safety and Autism"

June 19, 2002

Mr. Chairman, today you have convened a hearing about the safety of vaccines. This is a important topic, and also a familiar one to the committee. Over the last several years, you have held a series of hearings raising questions about the safety of vaccines -- questions that undoubtedly have caused real concern among some parents and clinicians.

These hearings have had some positive effects. Your interest over the years has led t unprecedented attention to vaccine safety. Since your first hearing on the topic, many respected researchershave chosen to investigate whether vaccines are associated with inflammatory boweldisease, autism, diabetes, and other assorted conditions among children. While rare side effects from vaccines are always possible, these studies have not found that vaccines are associated with any of these serious health problems.

Since your first vaccine safety hearing, a blue-ribbon panel of scientists convened by the Institute of Medicine has reviewed many of the most widely disseminated theories alleging harm from vaccines. This esteemed panel evaluated the allegation that the MMR vaccine causes autism. It studied the claim that thimerosal, a vaccine preservative, causes developmental delay. It reviewed whether the hepatitis B vaccine causes neurological injury. It assessed the theory that multiple vaccinations cause allergies and asthma. In each case, the Institute of Medicine panel has found that the scientific evidence does not validate the theories. Expert panels in other nations have reached similar conclusions.

Mr. Chairman, you have challenged the public health system to defend itself against numerous allegations that vaccines cause a wide variety of problems. I am not aware of an allegation about the safety of vaccines that you have not pursued. So far, the subsequent investigations and expert reviews have found vaccines to be safe. Because of your efforts in this area, Americans can have more confidence today in the safety of the vaccine supply than ever before.

But there has also been negative consequences to your approach. You have repeatedly provided a forum for unsubstantiated allegations about vaccine safety that have alarmed and confused parents. Although the scientific evidence for vaccine safety has grown stronger, parental concerns about vaccine safety have also increased since you started these hearings. This is a potentially dangerous development because it can lead to lower immunization rates and more disease.

I recently asked CDC to describe what could happen if MMR immunization rates dropped. According to CDC, if immunization rates dropped to the levels they were in 1989 we could see over 26,000 hospitalizations from measles, 8500 cases of pneumonia, 135 cases of encephalitis, and 224 deaths.

According to CDC, even a drop in immunization rates of 10% could result in an additional 2 million kids being susceptible to measles. It would also significantly increase susceptibility to rubella and Congenital Rubella Syndrome, which can cause serious birth defects such as blindness, deafness, and stillbirths.

Congenital Rubella Syndrome is also a well-known cause of autism, a disease that we all want to prevent. How tragic it would be if a unjustified vaccine scare caused some children to die, others to have permanent brain deficits, and still others to suffer from autism. I ask that this information from CDC be placed in the record.

While I am strongly opposed to reckless allegations about vaccine risks that scare parents and are not supported by the science, I also recognize that questions about vaccines will always arise. That's why I support efforts to fund additional research on vaccine safety. Some of the theories on the agenda for today do require additional research, and I am pleased that the government is supporting such studies.

I also support making sure that the government does not lose the ability to conduct valid vaccine safety studies. We must assure the future of initiatives like the Vaccine Safety Datalink Project. This is a unique collaboration between CDC and several large HMOs that allows for valid and timely research on vaccine safety. Indeed, this research that has led to many important policy changes over the years.

Today, we will hear from scientists at CDC who work closely with the Vaccine Safety Datalink project. These scientists are quite concerned about your threats to subpoena the raw data from this database to pursue a vaccine-related allegation. Because the raw data contain identifiable information from the medical records of more than 6 million Americans, a Congressional subpoena would constitute a serious violation of medical privacy. According to CDC, a subpoena could have the effect of driving HMOs from the program and "destroying CDC's ability to scientifically test hypotheses relating to adverse events potentially associated with vaccines."

You have an alternative to a subpoena. CDC has worked with the HMOs to create a process for allowing independent researchers access to the data. I continue to urge you to accept this solution and renounce your subpoena threat.

Finally, I would like to address some allegations that Dr. Wakefield makes in his written testimony. Dr. Wakefield implies that a witness who testified here last year, Dr. Michael Gershon, either perjured himself or was guilty of sloppy science by noting problems in the lab that Dr. Wakefield used in his research. Dr. Gershon did not lie to this committee and this portion of his testimony did not involve his scientific expertise and thus was not sloppy. Dr. Gershon related what he was told by Dr. Michael Oldstone of the Scripps Institute, who had performed an evaluation of this lab. Dr. Gershon continues to stand by his testimony. Dr. Wakefield also is planning to make a needless attack on Dr. Gershon's wife, who he alleges may have a financial interest in the chickenpox vaccine. In fact, according to Dr. Gershon, while his wife did conduct research relevant to a chickenpox vaccine patent, neither he nor his wife has any financial interest in the vaccine or its manufacturer. Dr. Wakefield's allegation is therefore groundless as well as gratuitous. Dr. Gershon's testimony last year was quite lengthy and he raised many scientific issues, but Dr. Wakefield has not refuted any of them. Instead, he resorts to name-calling, which does not move these scientific issues along and is unproductive.

I ask unanimous consent that the written testimony of Dr. Elizabeth Miller of the Public Health Laboratory Service of the United Kingdom be entered into the record.

I thank the witnesses for coming today, and I look forward to their testimony.

APR-03-02 16:52 From: T-185 P.02/04 Job-124

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30333

APR - 3 2002

The Honorable Henry A. Waxman
House of Representatives
Washington, D.C. 20515-6143

Dear Mr. Waxman:

Thank you for your letter regarding the health of the United States' population if vaccination coverage decreased for measles, mumps and rubella. The Centers for Disease Control and Prevention (CDC) shares the concern that decreases in vaccination coverage with the measles, mumps, and rubella (MMR) vaccine would result in a re-emergence of disease with consequent deaths and long-term disability. Please excuse the delay of this response.

There are no published estimates of the potential impact of a decrease in U.S. measles vaccination coverage. Until such estimates have been made from mathematical models and have undergone peer review, the best data for evaluating potential impact come from analysis of historical U.S. data when vaccination coverage was lower than it is now. With current measles vaccine coverage of approximately 91 percent in children 19-35 months of age and approximately 97 percent at school entry, only about 100 cases of measles have been reported per year. Many of the cases are imported, and endogenous transmission of measles no longer occurs. By contrast, before the 1989-1991 U.S. measles epidemic with approximately 55,000 cases of measles, vaccination coverage was estimated at 61-66 percent nationally and at 51-79 percent in 15 major cities. These outbreaks stopped only when vaccination coverage increased. Thus, if preschool coverage dropped 25-30 percent below current levels, large measles outbreaks would once again occur.

The estimates below represent the number of complications per 100,000 measles cases – a total that would occur in less than 5 years at rates similar to those observed between 1989-1991.

Complication	Number of cases
Hospitalization	26,400
Pneumonia	8,500
Encephalitis*	135
Death	224

*Encephalitis is infection of the brain and can result in deafness, mental retardation, and other long-term neurological deficits.

These national totals, however, do not present the complete spectrum of possible consequences. For example, of 124 children with measles admitted to a children's hospital in Texas, 15 (12 percent) were treated in the intensive care unit, 10 (8 percent) were intubated because of pneumonia or narrowing of the airway, 4 (3.2 percent) died, and 3 (2.4 percent) required a tracheostomy in order to breathe.

Although the impact of a smaller decrease in vaccination coverage is more difficult to assess, the risks associated with even a 10 percent decline are substantial. With approximately 4 million children born in the United States each year, a 10 percent decrease in coverage would result in 2 million additional susceptible children before school entry at 5 years of age. Increased disease inevitably would follow increased susceptibility. Each year, measles virus is imported into the United States on multiple occasions, either by U.S. citizens who return from abroad with the disease or by foreign citizens who come to the United States while incubating measles. These exposures would lead to measles outbreaks, particularly in urban areas and among populations where coverage is lower than the national average.

The rubella disease burden also would increase substantially if MMR vaccination coverage decreased. Rubella and the congenital rubella syndrome (CRS) – a complex of severe defects that include stillbirth, heart abnormalities, blindness, and deafness – have been virtually eliminated in the United States. Although a 10 percent decline in vaccination coverage would initially have little impact on CRS, with an accumulation each year of an additional 400,000 susceptible unvaccinated persons, rubella would again begin to circulate and CRS would occur with infection of pregnant women. In 1964-1965, when serological data indicated that 80-85 percent of women 20-29 years old had protective antibody, a national epidemic of rubella and CRS occurred. This resulted in an estimated 12.5 million rubella cases, of which 2,084 included encephalitis as a complication. In addition, there were 11,250 stillbirths or therapeutic abortions among women infected during pregnancy, and 20,000 cases of CRS with 2,100 excess neonatal deaths and thousands of infants who suffered deafness, blindness, and mental retardation.

Vaccination coverage is monitored by the National Immunization Survey (NIS) conducted by CDC. NIS provides statistically valid estimates of coverage nationally and in all states and major metropolitan areas. Because NIS measures coverage among children who are between 19 and 35 months of age and MMR vaccine is given at 12 months of age, there would be at least a year delay before a change in MMR coverage would likely be detected. Small changes would take longer to detect.

In summary, decreased MMR vaccination coverage would reverse the tremendous accomplishments of past decades and result in a resurgence of disease. Both measles and rubella/CRS disease can result in death and severe disability. To protect the U.S. population from infectious diseases, we must maintain vaccination coverage and high levels of immunity.

Immunizations are critical toward eliminating diseases that previously caused millions of infections in the United States each year and still remain global leading causes of death and preventable birth defects.

I appreciate your interest in this public health issue and hope this information is helpful.

Sincerely,

David W. Fleming, M.D.
Acting Director

May 2, 2002

The Honorable Dan Burton
Chairman
Committee on Government Reform
2157 Rayburn House Office Building
Washington, DC 20515

Dear Mr. Chairman:

I am writing to ask you to drop your threats to subpoena reams of patient information from the most important national database for monitoring vaccine safety, the Vaccine Safety Datalink (VSD) project. According to the Centers for Disease Control and Prevention, issuance of a subpoena could lead to the collapse of the VSD database, "destroying CDC's ability to scientifically test hypotheses relating to adverse events potentially associated with vaccines." It would also jeopardize the medical privacy of millions of Americans. Despite these risks, you and your staff have drawn up a draft subpoena. I urge you to reverse course and state clearly that you will not subpoena patient data from these medical records.

The database in question is the Vaccine Safety Datalink project, a federal effort established over a decade ago that now combines information from the medical records of eight large health maintenance organizations. HMO officials have expressed their concern that a subpoena would jeopardize the medical privacy of approximately 7.5 million Americans and would lead the HMOs to reconsider their participation in the project altogether.

The consequences of the loss of this database would be grave. It was the VSD project that demonstrated an association between rare cases of intestinal obstruction and the vaccine to prevent rotavirus infection, contributing to its withdrawal from the market. Studies using the VSD also helped make the measles-mumps-rubella, polio, and pneumococcal vaccines safer. In the future, according to CDC, the VSD will "be critical to our ability to monitor the safety of smallpox vaccinations in a timely and accurate manner." For these reasons, top public health officials and experts contacted by my staff uniformly expressed alarm at the possible collapse of the VSD.

A confrontation with CDC over the VSD is needless. In recognition of your interest in

confirming some of the results of VSD studies involving vaccines containing thimerosal, CDC and the HMOs have offered a way for independent investigators to analyze VSD data without compromising medical privacy. You should endorse this approach rather than continue to seek to subpoena the records themselves.

The rest of this letter explains my concerns in more detail.

The Vaccine Safety Datalink System

Understanding whether a particular vaccine is safe, and what side effects it may produce, begins with pre-licensure studies. While the size of these studies has increased in recent years, in some cases adverse outcomes are too rare to be detected before licensure. To identify quickly such rare events, public health officials rely on several mechanisms to monitor adverse effects after approval. The two largest and most important mechanisms are the Vaccine Adverse Event Reporting System (VAERS) and the VSD.

VAERS is a compilation of spontaneous reports of suspected adverse events from parents, health care providers, and pharmaceutical manufacturers. VAERS reports can be a signal that there may be a problem with a vaccine. However, because VAERS is a passive system, it rarely can answer the question of whether a vaccine is truly associated with a problem or at what rate the adverse effect is occurring.

In order to enhance the understanding of rare adverse effects of vaccines, CDC developed the VSD project in 1990. This project now utilizes the databases of eight large HMOs, pooling information from the medical records of approximately 7.5 million people, or 2.5% of the U.S. population. The records include diagnoses, laboratory test results, prescriptions, and immunizations, but do not include the names of patients. Even without the names, however, these data can be combined with information from publicly available sources to identify some patients. For this reason, the HMOs share information from medical records with CDC only after assurances that confidentiality will be strictly maintained.

The VSD yields an enormous benefit to the public health. Using this large and complex database, CDC can quickly design and implement sophisticated studies that take into account confounding factors and use proper control groups. The VSD allows public health officials not only to carry out planned research activities, but also to conduct timely investigations into adverse events.

One example of how the VSD enabled quick action to protect children is the case of the vaccine to prevent rotavirus infection, a cause of severe diarrhea in infants. In 1999, several cases of intestinal obstruction following rotavirus vaccination were reported to the VAERS system. While the number of cases were suggestive of a possible association, it was still unclear

whether these cases were coincidences or truly linked with the vaccine. Very quickly, CDC officials conducted a study using VSD data, which determined that this rare condition was associated with the rotavirus vaccine. The results contributed heavily to the manufacturer's decision to withdraw the vaccine from the market before more children could be injured.[1]

Over the last decade, public health officials and researchers have used the VSD to answer many vaccine-related questions. VSD studies, for example, have supported policy changes that have reduced adverse effects from the MMR vaccine,[2] maintained high levels of polio vaccination using a formulation that does not cause vaccine-associated polio,[3] and enhanced the safety of the pneumococcal vaccine schedule.[4] Other VSD research has examined theories of vaccine harm and failed to find empirical support for them. Such studies have provided evidence that childhood vaccines are not associated with diabetes,[5] that the MMR vaccine is not associated with inflammatory bowel disease[6] or aseptic meningitis,[7] and that the rubella vaccine is not

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[1]P. Kramarz, E. France, F. DeStefano et al., *Population-Based Study of Rotavirus Vaccination and Intussusception*, Pediatric Infectious Disease Journal, 410-6 (April 2001).

[2]R. Davis, E. Marcuse, S. Black, et al., *MMR2 Immunization at 4 to 5 years and 10 to 12 Years of Age: A Comparison of Adverse Clinical Events After Immunization in the Vaccine Safety Datalink Project*, Pediatrics, 767-71 (November 1997).

[3]R. Davis, T. Lieu, L. Mell, et al., *Impact of the Change in Polio Vaccination Schedule on Immunization Coverage Rates: A Study in Two Large Health Maintenance Organizations*, Pediatrics, 671-8 (April 2001).

[4]L. Jackson , P. Benson, V. Sneller, et al., *Safety of Revaccination with Pneumococcal Polysaccharide Vaccine*, Journal of the American Medical Association, 243-8 (Jan. 20, 1999).

[5]F. DeStefano, J. Mullooly, C. Okoro et al., *Childhood Vaccinations, Vaccination Timing, and Risk of Type 1 Diabetes Mellitus*, Pediatrics, E112 (December 2001).

[6]R. Davis, P. Kramarz, K. Bohlke, et al., *Measles-Mumps-Rubella and Other Measles-Containing Vaccines Do Not Increase the Risk for Inflammatory Bowel Disease: A Case-Control Study from the Vaccine Safety Datalink Project*, Archives of Pediatrics and Adolescent Medicine, 354-9 (March 2001).

[7]S. Black, H. Shinefield, P. Ray, et al., *Risk of Hospitalization Because of Aseptic Meningitis After Measles-Mumps-Rubella Vaccination in One- to Two-Year-Old Children: An Analysis of the Vaccine Safety Datalink (VSD) Project*, Pediatric Infectious Disease Journal, 500-3 (May 1997).

associated with chronic joint disease in adults.[8]

The VSD has played a significant role in making the current vaccine supply safer than ever. Your subpoena threats, however, represent a serious risk to the viability of the entire VSD system.

The Committee's Actions

On July 18, 2000, at a hearing entitled "Mercury In Medicine--Are We Taking Unnecessary Risks," Dr. Roger Bernier of CDC testified about the results of studies using VSD data to examine whether exposure to thimerosal in vaccines is associated with developmental delays. According to his testimony, an initial study suggested a connection between thimerosal and certain developmental symptoms. Subsequent studies in the VSD have not confirmed these findings, and further research is ongoing.[9]

On November 21, 2000, you sent a letter to CDC Director Jeffrey P. Koplan asking for VSD data "in both printed and electronic format."[10] After CDC refused, your staff has repeatedly threatened CDC officials with a subpoena for the raw data from the VSD, including asking for the name and address of the person who should receive the subpoena. Earlier this year, on February 21, 2002, your staff faxed to my staff a draft subpoena to CDC for "all records collected under the Vaccine Safety Datalink Project."[11]

In defending the subpoena threats, you have indicated that your interest in obtaining this medical information is to double check the results of the thimerosal study and to conduct independent analyses of vaccine safety. To accommodate this concern, CDC has developed a protocol to allow independent researchers access to VSD data through the National Center for Health Statistics (NCHS) under certain reasonable conditions. These conditions include: (1) the study is approved by the HMOs' Institutional Review Boards charged with assuring the protection of human subjects; (2) the study has a clear protocol; and (3) the study is conducted at NCHS, with the researchers able to leave with their results but not the raw data.

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[8]P. Ray, S. Black, H. Shinefield, et al., *Risk of Chronic Arthropathy Among Women After Rubella Vaccination*, Journal of the American Medical Association, 551-6 (Aug. 20, 1997).

[9]Institute of Medicine, *Thimerosal-Containing Vaccines and Neurodevelopmental Disorders* (Oct. 1, 2001).

[10]Letter from Chairman Dan Burton to Dr. Jeffrey P. Koplan (Nov. 21, 2000).

[11]Draft Subpoena Duces Tecum to Dr. Jeffrey P. Koplan (February 2002).

Despite this reasonable solution, which does not compromise patient confidentiality and would protect the future of the VSD, you have yet to abandon your subpoena threats.

The Threat to Medical Privacy and the VSD

Your draft subpoena asks CDC to "redact personal information, such as names, social security numbers, or other unique identifiers that would allow for the identification of individual patients."[12] However, even without names, social security numbers, and other unique identifiers, the VSD data can be used to identify individuals. The reason is that the dataset includes many non-unique variables, such as birthday, diagnosis, HMO, and date of immunization that can be patched together with information from publicly available sources to identify individuals. CDC explained:

> In order to assess the ease with which an individual could identify a patient's medical record, one of the VSD HMOs conducted an exercise. They imagined a scenario in which an HMO employee had access, via the internet, to the complete VSD database in its current format. If this employee knew that a co-worker was an HMO member, was able to learn the co-worker's birth date (e.g., through an office birthday party), and knew that the co-worker recently broke an arm and required medical attention, then that employee could find the co-worker's record in the VSD file easily. Once the co-worker's file was found, all of that person's medical history – such as information concerning other medical visits, diagnoses (including HIV and mental health status) and prescriptions filled - was available for review by this person. The Principal Investigator at one VSD HMO tested this scenario using his daughter. With her birth date and knowledge that she recently sprained an ankle, an HMO analyst was able to find her records in the VSD data. Such identification of individuals could have devastating consequences to the individual as well as to the HMO.[13]

CDC has informed my staff that the thimerosal study could not be replicated without identifying the diagnoses and medical records of many children who were excluded from the study for scientific reasons because of unrelated serious medical conditions. Identifying these records carries the risk of disclosure of confidential and sensitive medical information. If your desire is to verify the results of the VSD studies, then it is important to acknowledge the very important privacy interests at stake.

In addition to these privacy threats, a subpoena may threaten the viability of the VSD. Concern by participating HMOs was heightened last summer after a group called SAFE MINDS

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[12]Draft Subpoena Duces Tecum to Dr. Jeffrey P. Koplan (February 2002).

[13]Information sent to minority staff by Centers for Disease Control (Apr. 23, 2002).

filed a request under the Freedom of Information Act (FOIA) for raw VSD data. Researchers from the HMOs wrote to CDC urging the agency not to provide the medical records. Dr. Richard Platt and Dr. Tracy Lieu of Harvard Medical School, for example, sought "explicit assurance that health plans will have ongoing control over any new uses and distribution of their data."[14] These physicians explained that information at stake included HIV diagnoses and other identifiable information that would constitute a profound violation of medical privacy.

CDC responded to these concerns by denying the FOIA requests and then affording the VSD data the highest level of protection for privacy available under public health law.[15] However, representatives of SAFE MINDS claimed in the presence of my staff that a refusal by CDC would be met by a subpoena from you for the same information. Your subsequent subpoena threats led investigators at the participating HMOs to realize that even CDC's protection may not be able to guarantee the confidentiality of the records. As a direct result, according both to CDC and HMO officials, a subpoena may force the HMOs to reconsider their participation in the VSD. According to CDC, "If the currently participating HMOs withdrew from the Project because of lack of assurances of confidentiality, it is extremely unlikely that other HMOs would consider providing such complete and specific data to CDC, thus destroying CDC's ability to scientifically test hypotheses relating to adverse events potentially associated with vaccines."[16]

Because of medical privacy concerns, CDC is working on developing a new secure system that would allow public health officials to review rapidly the databases without ever having possession of highly confidential patient data. However, HMO officials have told my staff that a subpoena from you on existing data at CDC would even threaten their participation in this new system.

The logic is understandable: If millions of their patients lose their medical privacy, then they may lose confidence in their health plan. To convince patients that such a violation would never come to pass again, the HMOs may be forced to terminate the VSD project.

Reaction of Experts and Key Officials

Health officials and experts contacted by my staff uniformly expressed the belief that the

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[14]Letter from Dr. Richard Platt and Dr. Tracy Lieu to Dr. Robert Chen, (July 25, 2001).

[15]CDC has obtained protection under section 308(d) of the Public Health Service Act for Vaccine Safety Datalink data. This protection does not extend to a congressional subpoena, however.

[16]Information sent from CDC to minority staff (Apr. 23, 2002).

VSD is an essential tool to protect children. Dr. Georges Peter, chairman of the National Vaccine Advisory Committee, explained:

> The VSD program has been of vital importance in our continuing efforts to assess causal associations between adverse events in vaccine recipients and specific vaccines. One of the critical elements of the program is the large patient base which allows the investigators to assess possible associations between rare events and vaccines. Without the participation of large HMOs, the sensitivity of the program would be significantly limited and our nation's efforts to continue to enhance vaccine safety efforts would be very much compromised. These scientific studies are necessary for the children and parents who rely on safe and effective vaccines to prevent once common childhood diseases such as poliomyelitis, measles and meningitis."[17]

Dr. Neal Halsey, director of the Institute for Vaccine Safety at Johns Hopkins University, wrote:

> If the subpoena power of Congress is used in a misguided effort to find additional associations with thimerosal exposures, this will undermine the ability of CDC to undertake future research in the area of vaccine safety.[18]

Similarly, Dr. Lou Cooper, president of the American Academy of Pediatrics, noted:

> The Vaccine Safety Datalink (VSD) project has been our best instrument for studying longer term and low incidence consequences of immunization. It is a unique tool, and I am not sure how we could replace it. Any threat to the confidentiality of these data, which are in fact patient medical records, would violate the trust relationships between patients and their doctors and would force the HMOs to withdraw from the program, an irreplaceable loss in our effort to insure vaccine safety. The precedent set by such an action would be a major setback to research on vaccine safety and would have a chilling impact on other vitally needed public health research.[19]

Bioterrorism and the Future of the VSD

CDC officials have said that the loss of the VSD would compromise the agency's ability to protect the American people from future bioterrorist threats. According to CDC:

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[17]E-mail communication from Dr. Georges Peter to minority staff (Apr. 23, 2002).

[18]E-mail communication from Dr. Neal Halsey to minority staff (Apr. 23, 2002).

[19]E-mail communication from Dr. Louis Cooper to minority staff (Apr. 24, 2002).

A study is underway within the VSD to more accurately estimate the number of persons likely to suffer complications from smallpox vaccination. Should the decision be made for its broader use in the U.S., the VSD will be critical to our ability to monitor the safety of smallpox vaccinations in a timely and accurate manner. The VSD can also serve as a valuable tool for monitoring other bioterrorism threats that might result in unusual syndromes, vaccine-derived or otherwise.[20]

The loss of the VSD would also undermine other research priorities. CDC officials told my staff that concerns over your subpoena threaten to derail a number of research projects, including some on developmental delay, another topic you have pursued in committee hearings.

Conclusion

I know you are deeply interested in the safety of immunizations. Indeed, I understand that the reason you are threatening to subpoena the VSD data is that you believe the data may contain important information about the risks of vaccines. But in fact, the issuance of a subpoena would have the opposite effect, jeopardizing the VSD system and thereby reducing vaccine safety. I urge you to reconsider your actions.

Sincerely,

Henry A. Waxman
Ranking Minority Member

cc: Members of the Committee on Government Reform

[20]E-mail communication from CDC to minority staff (Apr. 24, 2002).

Studies of exposure to thiomersal (thimerosal) containing vaccines in UK children and developmental outcome

Dr. Elizabeth Miller
Head Immunisation Division
Public Health Laboratory Service
Communicable Disease Surveillance Centre
61, Colindale Avenue
London NW9 5EQ

Thiomersal exposure under the immunisation UK schedule.

The only thiomersal-containing vaccines that have been routinely used in the UK immunisation programme in the last two decades are whole cell diphtheria/tetanus/whole cell pertussis (wDTP), DT vaccine, and any combination vaccine containing wDTP or DT. These vaccines all contain 50μg of thiomersal per dose (25 μg ethyl mercury per dose). Since the UK changed to an accelerated 2/3/4 month DTP immunisation schedule in 1990 (replacing the former 3/5/10 month schedule) and since vaccinations are generally given on time in the UK, there will be a substantial proportion of children in the UK who will have had a cumulative ethyl mercury exposure of 75 μg by 6 months of age, of whom many will have had an exposure of 50–75 μg by 4 months of age.

Hepatitis B vaccine and influenza vaccine also contain thiomersal but are only given to certain high risk children.

Study populations

Two data sets were identified that could be used to test the hypothesis that that there is an increased risk of developmental delay with increasing levels of ethyl mercury given at a younger age.

One is the General Practice Research Database (GPRD) which holds data on all patient consultations, referrals and prescribed medicines including vaccines from 1988 from 500 general practices in the UK. Together these practices provide primary health care for 3.4 million patients (5.7% of the population). Information is available from the GPRD on the dates at which the patient joined and left the practice. One GP provides the entire primary care for a patient while he/she is registered with that practice. Only children who had been registered from birth and who were still registered with the same GP at 2 years of age, and only practices that had met the data quality standards specified by the GPRD data managers were included in the analysis. This yielded a cohort of 116,113 children. The GPRD study therefore has similar power to the US VSD study. The clinical events in the GPRD are coded using Read or Oxmis codes which were mapped to the ICD codes in the VSD study that were in the neurological developmental disability category, this being the only category that contained conditions that showed a positive association with early thiomersal exposure.

The second data set is from the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC). The ALSPAC comprises a cohort of 14,000 children born in

1991 and 1992 in the county of Avon who were recruited prospectively at the time of the mothers' pregnancy. Detailed information was obtained on a variety of prenatal factors that could be potential confounders: such as social and economic conditions, family size, parenting strategies, use of day care, maternal age and level of education. Environmental factors that could also lead to toxic exposures have also been recorded prospectively in pregnancy and throughout infancy and childhood. The ALSPAC children have been followed up regularly since birth and there is detailed information on their developmental progress and behaviour from 4 weeks of age. Data have been collected regarding the behavioural and developmental outcomes of the ALSPAC children based on parentally-completed questionnaires at different time points; data up to 69 months of age were analysed. The information from the questionnaires covers a wide range of behaviours, social achievement, gross and fine motor skills, cognitive skills and communication. Although the size of the ALSPAC cohort is smaller than that in the GPRD and VSD studies, the availability of quantitative outcome measures provides significantly more power than analyses based on the presence or absence of certain conditions (as in the VSD and GPRD studies).

The GPRD and ALSPAC analyses were conducted independently by two different research groups. However, thiomersal exposure in the two studies was expressed in the same way, namely as the amount given by 2, 3 or 4 months of age (maximum cumulative dose of ethyl mercury of 25μg, 50 μg and 75μg respectively). In both data sets around 40% of the cohort had received their third dose by 4 months of age. Only children with a record of having received all three doses of a DTP/DT containing vaccine for primary immunisation were included in the analysis. In both analyses children given Hepatitis B vaccine or influenza vaccine were removed. Premature infants were also removed from the analysis.

Results

The GPRD showed no evidence that receipt of 75μg of ethyl mercury by 124 days or 50 μg by 93 days of age was associated with an increased risk of a developing neurological developmental disability, either overall or for any of the ICD categories that had yielded a significant association when analysed individually in the VSD study. Codes specific for autism were examined and there was no evidence for any association between thiomersal exposure and autism as an outcome. As expected, for some of the conditions there was evidence of a "protective " effect as completion of vaccination on time is likely to be associated with social or economic factors that are themselves associated with a reduced risk of adverse developmental outcomes. Further analyses are planned for preterm infants and for control conditions unrelated to developmental outcomes.

The ALSPAC study also showed no evidence of an association between early thiomersal exposure and specific behaviour problems, speech difficulties, poor motor coordination or tics after controlling for confounders. Before controlling for confounders early thiomersal exposure had a protective effect for some outcomes.

Conclusion

There is no evidence of any adverse developmental effects, including autism, from exposure to a cumulative dose of ethyl mercury of 75μ by 124 days or 50 μg by 93 days of age in UK children.

Mr. BURTON. Regarding the unanimous consent, we would like to review it. We probably have no objection and would like our staff to take a look at that information. So we reserve notation on that. Do we have a copy of that?

Mr. WAXMAN. We will make everything available to you and your staff to put into the record. I would note that the chairman asked for unanimous consent at the beginning of this hearing for all submissions of materials to be part of the record. I would hope you would come to the same conclusion with regard to these.

Mr. BURTON. We probably will. We just want to review it real quickly.

Mr. WAXMAN. I have no problem with that.

Mr. BURTON. Mr. Weldon.

Mr. WELDON. Thank you, Chairman Burton, for calling this hearing.

As a physician who continues to see patients, I have a very, very strong interest in maintaining the safety and integrity of our national immunization program. The response from the CDC and the NIH to the growing concerns over the safety of the measles, mumps, rubella or MMR vaccine continues to baffle me. While this vaccine may be safe for most children, there is growing clinical evidence that a subset of children may be suffering very severe reactions to the MMR.

For too long, public health officials and those with a vested interest in the status quo have engaged in what I perceive to be denial or simply view those who suffer severe adverse reactions as the cost of doing business. We have a moral imperative to look at the clinical evidence to determine why some children may be suffering reactions to MMR. For nearly 3 years, I have been urging the CDC and NIH to more aggressively move to address these concerns and I must say I have been disappointed by the failure of the CDC and NIH since these concerns were first raised in a study published in 1998, and they have not addressed this issue. The CDC in conjunction with public health officials in the United Kingdom have responded to each new clinical study raising safety concerns about the MMR with an epidemiologic study, a statistical study. They did this after the 1998 Wakefield Study, they did it with the study issued in January of this year by Oman et al and they did it again last week in anticipation of the release of a study identifying vaccine strain measles as the strain in the affected children in the Oman study.

These statistical studies have been released with great fanfare to the media and the media thus far have given the expected response of proclaiming the complete safety of the MMR vaccine. Those who have been raising these questions and conducting clinical research in this area have grown to expect the mantra, our statistics say that this cannot be.

I must say, if their purpose is to preserve the status quo and succeed in a public relations campaign, they have been successful, at least to date. However, if their purpose is to directly address the clinical findings of persistent measles infection in seriously affected children, their efforts have been a dismal failure. They have not produced one clinical study to directly address these concerns.

My message to the NIH, particularly to the CDC, is put away your statistics textbooks and get out your microscopes. Failure to do so only breeds speculation and undermines public confidence and ultimately makes the job of clinicians more difficult.

Thank you and I yield back.

[The prepared statement of Hon. Dave Weldon follows:]

News From
DAVE WELDON
Florida's 15th District -- *Serving Brevard, Indian River, Osceola, and Polk Counties*

For Immediate Release:
June 19, 2002

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Researchers Continue to Build Evidence of MMR Safety Concerns Public Health Officials Fail to Address Concerns Head-on

Washington, D.C. -- U.S. Rep. Dave Weldon, a Florida physician, has continued to press public health officials, including the CDC and the NIH, move aggressively to attempt to duplicate the work that has been done raising questions about the safety of the Measles-Mumps-Rubella (MMR) vaccine. At a hearing of the House Government Reform Committee, where additional clinical research raised new questions about this issue, Rep. Weldon issued the following statement:

> "The response from the CDC and NIH to the growing concerns over the safety of Measles-Mumps-Rubella (MMR) vaccine continues to baffle me. While this vaccine may be safe for most children, there is growing clinical evidence that a subset of children may be suffering very severe reactions to the MMR. For too long public health officials at the CDC and those with a vested interest in the status quo, have engaged in denial or simply viewed those who suffer severe adverse reactions as the cost of doing business. We have a moral imperative to look at the clinical evidence and determine why some children may be suffering severe reactions to MMR.
>
> "For nearly three years, I have been urging the CDC and NIH to move aggressively to address these growing concerns. I must say that I have been dumbfounded by the failure of the CDC and NIH, since these concerns were first raised in a study published in 1998, to adequately address this issue. The CDC, in conjunction with public health officials in the United Kingdom, have responded to each new clinical study raising safety concerns about MMR, with an epidemiological study—a statistical study. They did this after the 1998 Wakefield study. They did it with the study issued in January of this year by Ullmann et. al. And, they did this again last week in anticipation of the release of a study identifying vaccine strain measles as the strain in the affected children in the Ullmann study. These statistical studies have been released with great fanfare to the media. The media, thus far, have given the expected response of proclaiming the complete safety of the MMR vaccine. Those who have been raising questions and conducting clinical research in this area have grown to expect the mantra, 'our statistics say this cannot be.'
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> "I must say that if their purpose is to preserve the status quo and succeed in a public relations campaign, they have been very successful – at least to date. However, if their purpose is to directly address the clinical findings of persistent measles infection in seriously affected children, their efforts have been a dismal failure. They have not produced one clinical study to directly address these concerns.
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> "My message to the NIH, but the CDC in particular, is put your statistics textbooks away and get out your microscopes. The failure to do so only breeds speculation and undermines public confidence."

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Mr. HORN [assuming Chair]. Ms. Watson.

Ms. WATSON. Thank you for this opportunity to address some issues that have been of great concern to me for a while.

As you know, I am co-sponsoring, with Congressman Burton, a bill that would require informed consent on the part of patients at a dentist's office when the dentist is getting ready to put in a filling that is an amalgam that contains mercury because over the years there has been a connection between mercury and amalgam and an effect on not only brain cells of the mother but going through the placenta into the fetus.

I will listen very intently in the time that I have to hear from CDC and the other witnesses about the connection of vaccines and autism because we are thinking now that any kind of foreign substance that is toxic that you put into any orifice of the body has an effect and certainly mercury in the teeth.

I have had dentists come to me and argue against our proposition from the standpoint of questioning the research. This morning I put on a ring and I can taste silver on my tongue. This is nickel and there is an effect that metals do have in the body from things that we apply to it and ingest, that are put into these orifices.

I am hoping that CDC will support the work of Dr. Wakefield, make the connection, report back to us. Then I will start looking into the use of nickel and nickel is in most custom jewelry, in the ear rings that we wear, the ring that I have on and so on. It does have an effect on the body.

I want to thank the chairman for having this hearing. There have been hearings before and I am sure there will be hearings and I am listening very closely to see if we can indeed draw that linkage from vaccines to autism and other conditions that face not only children but human beings as a whole.

Thank you, Mr. Chairman.

Forgive me for running out to my next hearing before I can hear all the witnesses.

Mr. HORN. Thank you very much.

The gentleman from Tennessee, Mr. Duncan.

Mr. DUNCAN. Thank you, Mr. Chairman.

I don't have a formal opening statement but I do want to say I want to thank Chairman Burton for calling this hearing and continuing to pay close attention to what I think is a very, very important topic. I mentioned at the last hearing that I became interested in this because I talked to several parents who told me very sad, heartbreaking stories about healthy children they had and just terrible problems that occurred after taking some of these vaccines. I think this is something we really need to look at.

I have been sitting reading the testimony of the witnesses and looking through these outstanding notebooks that the staff has prepared for us. I think this is something that we need to have a hearing about and we need to continue to research and look into this as fully as we possibly can.

I thank you for calling this hearing.

Mr. BURTON [presiding]. Mr. Cummings.

Mr. CUMMINGS. Thank you, Mr. Chairman.

I want to thank you for holding this hearing and I want to thank you for your tremendous interest in health care and for the recent hearing that you held with regard to disparities in health care.

Our committee has held several hearings exploring vaccine safety and the theories on the correlations between vaccinations and autism. Let me say first off that vaccinations have played a very significant role in this country and across the world. When we think of diseases like polio and smallpox and many others, vaccines have certainly allowed many to live who probably would have died and helped them to live the best lives they could as opposed to suffering.

Additionally, the committee initiated investigation into the dramatic rise in autism rates across the country. Autism is a disorder that severely impairs development of a person's ability to communicate, to interact with others and to maintain normal contact with the outside world. One of the most common developmental disabilities, autism affects 2 to 5 out of every 10,000 children and usually appears before the age of 3.

The causes of autism are unknown. There are some effective treatments for some children but there is no cure. In the past, autism was considered a rare disorder. However, today, autism is being diagnosed much more frequently. There have been approximately 2,800 cases of autism reported in my State of Maryland. Additionally, there has been a rise in the number of autism cases in California, New Jersey and other States. Although at this time, it is unclear whether the rise in the number of autism cases is due to increased reporting or demand for services, emerging data appears to support the theory that changes in diagnosis explain the rise in autism cases. Parents everywhere are anxious to learn more about the possible links between common preservatives in childhood vaccinations and developmental problems whose symptoms resemble those of autism. Symptoms of mercury toxicity in young children are extremely similar to those of autism.

There is a growing awareness of the nature of autism and the kinds of approaches to diagnosis, treatment and care that are likely to be effective in meeting the needs of autistic individuals and their families. Diagnosing autism today requires specific training and experience. I would encourage medical schools to offer specialized training for our nursing and medical students for autism.

As I said in past hearings, I applaud the Centers for Disease Control and Prevention, the National Institutes of Health, as well as the Kennedy Kreiger Institute, the Center for Development and Behavioral Learning at the University of Maryland School of Medicine in Baltimore and the many other organizations for their continued research on autism.

Congress should allocate more money for autism research. I offer my support to the families of autistic children. We must continue to look for the cause and cure of autism. I am convinced that with further research a cause and cure will be found. As such, I strongly believe that all theories for the cause of autism must be objectively researched. I look forward to hearing from today's witnesses and learning more about the Vaccine Safety Datalink, a large, linked data base that the CDC uses to research vaccine safety.

Again, I thank you for the hearing and with that, I yield back.

Mr. BURTON. Thank you.

Mr. Horn.

Mr. HORN. I commend you, Mr. Chairman. I have sat through these hearings and we have really looked at this situation. I look forward later in the day, I have to go to Transportation and Infrastructure right now but thank you for putting all this together with the staff.

Mr. BURTON. Mr. Tierney.

Mr. TIERNEY. Thank you for having these hearings.

I would like to get to our witnesses. I am pleased we are going to have testifying today individuals and representatives from the CDC and others who are actually conducting the research into autism's causes. I really believe that affected children and their families obviously can't afford to have us be complacent about this disorder.

I would like to enter my complete remarks in the record and look forward to hearing from the witnesses today.

[The prepared statement of Hon. John F. Tierney follows:]

Statement of Rep. John F. Tierney
House Government Reform Committee Hearing on the Status of Research into Vaccine Safety and Autism
June 19, 2002

Mr. Chairman, today we convene for the latest in a series of hearings you have called on the important subject of Autism. This devastating disease strikes children in their most formative years and robs the child of the ability to develop socially. Autism also leaves its victims with physical ailments that place great strain upon the entire family unit.

There are many theories about the root causes of Autism, none of which have been conclusively proven to be true. However, each of these theories deserves to be thoroughly researched and considered.

For that reason, I am pleased that we have testifying before us today representatives of the CDC and others who are conducting research into Autism and its causes. I strongly believe that we must allow the CDC to conduct its research without Congressional interference.

It is essential that doctor-patient confidentiality be respected and that scientific findings not be discounted because they simply do not support a particular hypothesis.

For the sake of the affected children and their families, we cannot afford to be complacent about this disorder. I welcome our witnesses who are on the front lines of the battle against Autism and look forward to hearing from them.

Mr. BURTON. Thank you.

We would like to have Dr. Bradstreet, Dr. Wakefield, Dr. Stejskal, Dr. Krigsman and Dr. Spitzer come to the table. Let me just say that the purpose of the Government Reform Committee, it is not called oversight anymore but that is still our responsibility, to conduct oversight into every agency of Government where we think there is a problem. The minute the Congress of the United States stops asking questions about very important issues like vaccine safety which affects every single person in this country, then we will be guilty of dereliction of our responsibilities. As long as I am chairman of this committee, I am going to continue to ask these questions.

I want to make one more brief comment and that is we have gone from 1 in 10,000 children who are autistic to 1 in 250. Somebody has to begin explaining why this horrible tragedy is occurring, why we have this epidemic. We are not getting the answers. We have an epidemic here and we can't just close our eyes and stick our heads in the sand. We have to find out why this is going on. The health agencies have not yet given us an adequate answer.

I would now ask the witnesses to rise so that I can swear you in.

[Witnesses sworn.]

Mr. BURTON. Dr. Bradstreet, do you have an opening statement?

STATEMENTS OF DR. JEFF BRADSTREET, MEDICAL DIRECTOR AND FOUNDER, THE INTERNATIONAL CHILD DEVELOPMENT RESOURCE CENTER AND AN AUTISM PARENT; DR. ANDREW WAKEFIELD, RESEARCH DIRECTOR, THE INTERNATIONAL CHILD DEVELOPMENT RESOURCE CENTER; DR. VERA STEJSKAL, ASSOCIATED PROFESSOR OF IMMUNOLOGY, UNIVERSITY OF STOCKHOLM, FOUNDER OF MELISA MEDICA FOUNDATION; DR. ARTHUR KRIGSMAN, PEDIATRIC GASTROINTESTINAL CONSULTANT, LENOX HILL HOSPITAL AND CLINICAL ASSISTANT, PROFESSOR, DEPARTMENT OF PEDIATRICS, NEW YORK UNIVERSITY SCHOOL OF MEDICINE; AND DR. WALTER SPITZER, PROFESSOR OF EPIDEMIOLOGY, EMERITUS, MCGILL UNIVERSITY

Dr. BRADSTREET. Unfortunately, the nature of autism is so complex that to do it in 5 minutes will be challenging, so I have submitted, under Tab 5 a more complete review of the nature of our research. I will try to get through my slides quickly.

Thank you very much for the hearing and for an opportunity to present this. Dr. Weldon and I previously met 2 weeks ago in your office with the Deputy Secretary of Health and Human Services, Claude Allen, to present this data to him. So he has been made aware of it. It was a very encouraging and positive meeting and I look forward to the outcome of that over time.

The prevalence may be both misunderstood and underestimated. Two recent studies, one from England and a CDC study with Brick Township indicated between 57 per 10,000 and 67 per 10,000 children. However, autism is primarily a boy related disorder, four to eight times as many boys suffer with this disorder. That means the prevalence is therefore in the order of 1 percent for boys.

The economic impact: We estimate that there are approximately 420,000 children with autism in this country at this time based on those studies, greatly less than what the Time Magazine article said at 1 million. However, that puts a price tag over the next 50 years to take care of these children in excess of $1 trillion. The lifetime costs could be $3 to $4 trillion for the families and for society with the lost wages and other factors.

The biological evidence for causality is growing significantly and for those members of the committee who may not be familiar with me, I am a physician, I am also a parent of a child with autism and I am a clinical researcher associated with studies currently ongoing at 14 medical schools around the world.

The growing evidence is substantial that measles virus is still the frontrunner with the viral etiology aspects of things and not all children suffer from measles virus related disorders, but we will show you today some examples that are quite impacting.

Additionally, auto-immunity continues to be published by a variety of researchers at multiple medical schools that there is a unique disorder affecting the immunity in these children where they become immune to their gut and their brain, and that is a disaster for them.

Mercury and to a lesser extent lead remain significant toxin burdens, and we presented that data to the Institute of Medicine in July of last year.

I am going to present two cases today and I will try and go through them briefly. Matthew who was born in 1984 from an uncomplicated pregnancy and an easy delivery had a normal early development except he did develop some gait abnormalities that are very consistent with what you might expect from mercury. We will see that data later on. He had a rapid decline after each of two MMRs. He did receive those in combination with other vaccines, however. He developed auto-immunity to myelin basic protein, a critical insulator of the brain. He suffered seizures shortly after the second MMR and he has persistent immune deficiency with protracted low lymphocyte counts.

He has inflammatory bowel disease that has been documented on endoscopy and biopsy. He has persistent measles virus genome in that inflammatory bowel disease. He has persistent measles virus in circulating white blood cells. He has persistent measles virus F gene in his cerebral spinal fluid, which is the fluid that surrounds the brain, implying it is present in the brain as well. He has autoantibodies to measles virus in his spinal fluid. He has autoantibodies to myelin basic protein in his spinal fluid, a very low serum sulfur level, and cysteine level and very high mercury as a result of that.

That is my son—Matthew—who is also the inspiration for our research and the work that we do. He was a very happy, well connected child prior to his MMR at approximately 12 months of age and that is Matthew completely lost about 2 months after his MMR vaccine.

This is a copy of the laboratory results documenting the presence of measles virus in his terminal ileum. This is a copy of the laboratory results from Utah State University where Matthew had his

spinal fluid analyzed which showed antibodies to myelin basic protein and to measles virus in his spinal fluid.

This shows the presence of antibodies in his RBCs, the presence of virus in his red blood cells and also presence in his cerebral spinal fluid.

This is his first mercury titer showing marked elevations of mercury, and you can see for all those essentially the only thing that is truly abnormal is the significant increase in mercury.

The first challenge test to get mercury out of his body resulted in an extremely high titer. That number of dots actually represents 24 mcg per gram. It would take it well off the slide, perhaps into the next room.

This is an interesting correlation. Mark Blaxil presented this to the Institute of Medicine last year and that shows that rising titer of cumulative mercury in the vaccine program in California compared to the prevalence of autism in California.

I want to superimpose on that a very interesting graphic derived from the government Web site on the use of methylphenidate, also known as ritalin or concerta. Look at the time relationship. It is identical. In 1990, the rise in the mercury titer started to go up and in 1990 there is a striking and continuous rise in the use of ritalin in this country which I think is rather telling.

This is the thimerosal versus autism relative risk that was produced in the CDC confidential study which was acquired under the Freedom of Information Act showing that at the time approximately 62 mcg of mercury is administered, there is more than a doubling of the relative risk of autism.

This is a copy of a transcript from the Simpsonwood meetings, page 229 where Dr. Brent, who is not employed by the CDC, but who is a public health official from one of the States, said "The medical legal findings in the study, causal or not, are horrendous. If an allegation was made that a child's behavioral findings were caused by thimerosal containing vaccines, you will not find a scientist with any integrity who would say the reverse with the data that is available. So we are in a bad position from the standpoint of defending the lawsuits if they were initiated and I am concerned." I think that may set part of the tone for what we have seen happen in the last several years.

Additionally, there was a very good documentary on this. Parents are aware and I think it is very important for Congress to be aware that the parents are receiving information from a variety of outlets. This is not your doing or undoing of policy. Parents are well educated, they are hungry for information and they currently don't believe many of the reassurances that are being provided by CDC.

Case two is very similar to my son and I present it so that you will realize that my son was not an isolated case. He had normal developmental milestones. He developmentally arrested shortly after his first MMR at 15 months. He again has antibodies to many things in his brain and persistent measles virus in places that it doesn't belong including his cerebral spinal fluid.

This lab slide indicates he has antibodies to myelin basic protein and to measles in his spinal fluid. He has this unique antibody, this is the presence of MMR antibody which is actually the H protein or the hemogluten protein from the measles virus of a special

antibody titer that was derived using the MMR vaccine, done in Dr. Singh's laboratory at Utah State University, also positive in spinal fluid.

We presented this data, Dr. Singh and myself, at the American Society of Microbiology last month which indicates that 50 percent of children in our study had antibodies to this special measles, mumps, rubella derived protein in their cerebral spinal fluid and also 86 percent have antibodies to myelin basic protein in their spinal fluid, and again a very high percentage, up to 100 percent, had antibodies to myelin basic protein in their blood. This is not present in normal controls. This is a controlled study. We now have significant controls and we do not see these present. This is not an antibody leakage, this is real disease in these children.

Scott has documented measles virus in his terminal ileum and his blood as well as his spinal fluid. These are the laboratory data.

I want to include from Dr. Menkes, his comments, where he concludes that this is related to the MMR vaccine in this particular child. Dr. Menkes wrote the textbook "Child Neurology." He is considered to be one of the foremost experts both on child neurology and on vaccine safety and has concluded that measles, mumps, rubella vaccine is causing this syndrome.

I think it is always important to put a face with this. This is impacting human lives.

I would leave you with some questions. I think there are some important things that we need to ask. These are in the handout but as we work through this, I think we need to ask: what if Dr. Wakefield, myself, Dr. Singh, Dr. O'Leary and Dr. Menkes and others are right, what then? What would be the reaction of public health officials if in fact this data, as we believe, is verifiable? In addition, what is the response to treating these kids? How are we going to get this virus out of these kids and restore them to good health? Have we traded a very rare occurrence of severe side effects to natural measles infection for a very common occurrence of autism?

With that, I will end because I think I have gone past my time.

[The prepared statement of Dr. Bradstreet follows:]

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Written Supplement to Oral Testimony at the Hearing of the
Government Reform Committee,
Congress of the United States
US House of Representatives
by
James Jeffrey Bradstreet, MD, FAAFP, Clinical Director
The International Child Development Resource Center
Palm Bay, Florida 32907
June 19, 2002

Mr. Chairman and Honorable Member of the Committee, much has happened to forward our knowledge of autism spectrum disorders (ASD) since I last spoke to you one year ago. To that end I am encouraged. But there remains so much more to learn, and even more to do for the families whose lives have been permanently altered by this silent epidemic. I want to thank Chairman Burton for his leadership. Your battle to bring the challenging issues of autism before the Congress, poignantly demonstrate the power of a grandfather's love for his family. I am equally impressed by the efforts of Dr Dave Weldon. He remains a trusted friend, fellow physician and Representative for my home district in Florida.

Autism is clearly not any single entity, nor does it have simplistic genetic or epidemiological characteristics. Rather, it represents a rather broad spectrum of clinical disorders which share behavioral and delayed-development features. Autism and its related entities are characterized by: delayed neurodevelopment, lack or inappropriate use of language, stereotypical repetitive behaviors, and social withdrawal. The various clinicians and researchers associated or affiliated with ICDRC have been involved in treating and/or describing this disorder from its biological roots, as opposed to the genetic and psychiatric perspectives. We have medically evaluated and treated over 1500

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children with autism related disorders. Therefore, the insights we have contribute primarily to an understanding of the immunology and toxicology of this condition.

The changes since last year in the level of national attention for autism are well reflected by events in my life during the last few weeks. On June 4th, Congressman Weldon and I met with the Deputy Secretary of HHS, Claude Allen in Chairman Burton's office to discuss both recent clinical findings and the state of the autism epidemic. Then ICDRC entered into collaboration agreements with Robert Wood Johnson Medical Center, Washington University Medical School, and Wake Forrest University to further define the immunological and toxicological disorders common in autism. And last Tuesday an ABC news crew spent the entire day filming at both my office and home. Those segments will air tonight and tomorrow on the ABC evening news.

With this new public and academic awareness of the epidemic in childhood developmental disorders in mind, where has the last year's investigations taken our understanding of both Thimerosal and MMR as they relate to autism? In July of 2001, I presented the ICDRC data on mercury burden and autoimmunity to the IOM (page 47, **Immunization Safety Review: Thimerosal-Containing Vaccines and Neurodevelopmental Disorders**, 2001). It doesn't seem the IOM understood my recommendations based on that data, so it warrants some degree of explanation here.

First, however, there is a fundamental flaw in the analysis process of vaccine safety. The IOM has undertaken the process of drawing conclusions regarding separate pieces of the actual schedule when they are an integrated event in an individual child's life.

I presented 221 children with ASD who showed a significant - 500% - on average greater mercury burden when compared to neurologically normal controls. The study was based on routine heavy metal provocation challenge testing similar to that published in *Environmental Health Perspectives* that same year. I did not try to infer a direct tie to thimerosal. Rather, it was apparent some possible foundational problem in the

metabolism of heavy metals was present in the autistic population. This observation could represent a significant predisposing factor in their vulnerability to mercury when used as a perservative – a point the IOM did not mention. It is also consistent with research regarding sulfur depletion in the presence of persistent viral infections. The literature is replete with reference in the case of HIV* and specific to autism as published by Dr Rosemary Waring. She has found marked renal loss of sulfur in autism.*

But most concerning to me in the Institute's treatment of the mercury problems, was the almost complete absence of regard for the compounding effect of thimerosal on pre-existing mercury levels. The NHANES study from CDC had already established perhaps one in ten children is born to mothers with elevated mercury burden.

Prevalence:

Various studies provide data that there are greater numbers of children with autism than previous suspected. Recently, the Congressional Reform Committee, held hearings where there was broad consensus that autism spectrum disorders (ASD), now represent an epidemic of neurodevelopmental problems for our youth. Various **recent studies place the prevalence at 57 to 67/10,000 children (Scott, 2002 & Bertrand, 2001)**, although older literature places the prevalence at 10/10,000 (1/1,000). However, this deceptively under estimates the problem for males. Boys suffer from autism at a four to 10 fold greater frequency than girls. So the actual problem for the male offspring in this country is more accurately represented as 100/10,000 (or greater). **The 1997 US Census of disability reported 2.4% of children ages five and under suffer from developmental delays** – clearly many of these are ASD related issues. Data from California further reveals the rate of growth in ASD is doubling every four years.

Using simple math – we appear to be on the Titanic of child development:

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1:149 US children according to the CDC, have autism. That is the statistic for Brick NJ, but it was implied by CDC to be consistent with the likely general stats.

> ***Prevalence of autism in a United States population: the Brick Township, New Jersey, investigation.***
> *Pediatrics 2001 Nov;108(5):1155-61*
> *Bertrand J, Mars A, Boyle C, Bove F, Yeargin-Allsopp M, Decoufle P.*
>
> *National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia 30341, USA. jbertrand@cdc.gov*
> *RESULTS: The prevalence of all autism spectrum disorders combined was 6.7 cases per 1000 children (1:149). The prevalence for children whose condition met full diagnostic criteria for autistic disorder was 4.0 cases per 1000 children, and the prevalence for PDD-NOS and Asperger disorder was 2.7 cases per 1000 children. Characteristics of children with autism in this study were similar to those in previous studies of autism. CONCLUSIONS: The prevalence of autism in Brick Township seems to be higher than that in other studies, particularly studies conducted in the United States, but within the range of a few recent studies in smaller populations that used more thorough case-finding methods.*

1:149 = one child per 68 homes (assuming 2.2 children per family)

And form the US Census Bureau
Population, 2001 estimate 284,796,887
Persons under 5 years old, percent, 2000 6.8%
Persons under 18 years old, percent, 2000 25.7%

If the current epidemiology of autism is correct, then it will affect approximately 1% of boys under 18, or an estimated 364,540, and a further approximately 60,000

girls would be affected. This is considerably less than the one million figure reported in the recent Time Magazine cover story, but probably far more accurate.

Economic Impact:

While no precise studies have attempted to look at the cost of correcting the biological problems associated with ASD, at least on report from England places the custodial costs of ASD in the range of $3-4 million per child per lifetime, with a societal cost that would likely be three times the individual cost.

Autism 2001 Mar;5(1):7-22
The economic impact of autism in Britain.
Jarbrink K, Knapp M.
Institute of Psychiatry, London, UK.

Little is known about the economic impact of autism. This study estimated the economic consequences of autism in the United Kingdom, based on published evidence and on the reanalysis of data holdings at the Centre for the Economics of Mental Health (CEMH). With an assumed prevalence of 5 per 10,000 *(a gross underestimate)*, the annual societal cost for the UK was estimated to exceed 11 billion *(likely 110 billion)*. The lifetime cost for a person with autism exceeded £2.4 million. The main costs were for living support and day activities. Family costs account for only 2.3 percent of the total cost, but a lack of relevant information limited our ability to estimate these costs. **Minor improvements in life outcome for people with autism could substantially reduce costs over the lifetime.**

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The cost of education, medical care, and therapies for behavioral and physical symptoms is staggering. Many of our families report having paid $50,000 per year to care for their child. IDEA allows up to $35,000/year for education of children with autism. So much of this burden is already being carried by the Federal and State programs which provide for disabled children. Custodial care for autism can exceed $100,000/year. The public education system is literally swamped with children. Any survey of public educators will quickly reveal the suddenness and magnitude of the ASD problem. They lack the therapists and trained special educators to deal with the problem, so children with severe disorders receive nominal meaningful intervention. The further loss of potential earnings form the ASD children who will likely not be self-supporting are impossibly large to calculate meaningfully. Many parents must quit working to care for the child as well. We, as a nation, are therefore paying and will continue to pay an enormous price for this epidemic.

ICDRC estimates the minimal cost in present value, to care for those 420,000 existing children with autism is $1,260,000,000,000 (based on $3million/lifetime and 420,000 children affected). So a little over a $1 trillion in the next 50 years would be required if we stopped creating new cases today. Because autism is doubling every four years, this is likely an overly conservative estimate. The societal cost could easily be $3-4 trillion.

Biological Evidence of Causality:

The data will show there is sufficient cause for concern and abundant published findings that the causal relationship of MMR to ASD does not represent a narrow view held by radical or renegade physicians. Rather it is sound peer-reviewed science, which, while currently not widely accepted, represents a plausible hypothesis consistent with our observations and the totality of the data. Unfortunately, the present objections to the data are largely based on conclusions drawn from epidemiological studies. The data

must be evaluated in its entirety, rather than critiqued bit by bit as it has been. However, as a clinician treating hundreds of children with specific & measurable biological disorders – I draw very little comfort from the conclusions of epidemiologists. Nor does it help me explain or treat the child's inflammatory bowel disease or the autoimmunity to vital brain components. So what I will present here today is a definable clinical disorder, in which children present with antibodies to a variety of brain components, inflammatory bowel disease, heavy metal burdens, often accompanied by seizures, skeletal maturation delay and a variety of significant biochemical abnormalities. The children I treat have symptoms consistent with encephalopathy with autistic features.

We are in the process of collecting data and analyzing the trends in our patient population. The two cases I will present here represent very early data. We have now accumulated simultaneous autoimmune, immune studies and viral polymerase chain reaction studies on blood, spinal fluid and intestinal biopsies. These are combined with comprehensive biological studies. As yet, there are no controls for the viral spinal fluid data, but the immunological data does have controls. What these two cases mean for the rest of the population of children with autism will have to wait for larger studies, reproducibility and necessary controls.

Case Presentations:

Case 1. Matthew, my son, seems very typical of many children I have examined over the past 5 years. He shares similar historical events and laboratory data with as many as 80% of our 1500 patients. He presently is age 8 and went to term without complication in pregnancy and had an uncomplicated labor and delivery. He presented with an entirely normal first 7 months. At the end of that period he self-weaned and standard formula was tried. This resulted in reflux and vomiting, so he was changed to predigested formulas with significant reduction in symptoms. The pediatrician noted slight delay in ambulation at 12 months, but in line with maternal developmental patterns. He had a protracted otitis media which required tube placement by 10 months and extended courses of antibiotics.

By 11 months he was seen in the ER for an acute febrile event not accompanied by seizures. It responded to IV antibiotics and outpatient treatments. Near 15 months he was seen for routine care and vaccinations. He was noted to be on track and developing normally. He received MMR, HIB and Varicella vaccinations at that visit. Shortly after that he developed tantrums and bizarre behaviors. Then he developed diarrhea and hyperactivity accompanied by a new symptom – night terrors. With the introduction of essential amino acids and taurine these symptoms improved somewhat for about 8 to 12 months. He then began slipping with increased hyperactivity and unusual language and behaviors. By age three he was diagnosed as having pervasive developmental delays and tested at the lowest percentile for function in all areas. He was started in therapies and improved somewhat. On his 4th birthday the original Wakefield paper was published and at nearly the same time, Matt received his MMR booster. (He received the full recommendations of the AAP for vaccinations during the mid to late 1990s). Shortly thereafter we noted staring spells as did the special needs teacher in his title H program. The neurologist diagnosed seizures and tried several medications unsuccessfully. His diarrhea returned and his behavior declined. Several months later we learned about gluten and casein free diets, secretin and IVIG. After a variety of studies confirmed autoimmunity to his brain, Matthew was begun on IVIG at the suggestion of two department chairs of immunology at different medical schools. The results were dramatic, with improvement in behavior and bowel dysfunction which had become explosive bouts with daily soiling past diapers.

The process of regression was not understood by Matthew's pediatrician or any of us in his family. Typically, it was variously dismissed as the result of the terrible two's, having an older sister, being a boy – "they are slower than girls you know", several ear infections, food allergies, or an attention deficit hyperactivity disorder.

If we are to believe the experts from the IOM and Vaccine Safety Committee of CDC, my son's autism was a coincidental event, and these double hit MMR events are of no consequence, because MMR has nothing to do with autism. A few years ago, Dr. Neal

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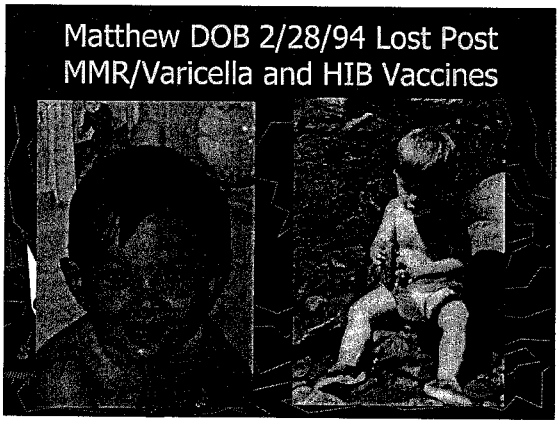
Halsey, the eminent professor of vaccine safety, told the listening audience of CNN that it was natural for me to want to blame something for my son's autism, but MMR was unquestionably not part of either the timing or autoimmune profile observed. I believe, medicine lacks the luxury of such amazing confidence. However, it seems extraordinarily improbable that his autoimmune encephalopathy and seizures are not MMR related. A review of his lab data paints an unmistakable picture, recognizable to any skilled clinician. **I choose to share the details of my son's medical history, so that those who continue the refrain – "there is no data" might know they are wrong – data exist – and it is compelling.**



(Photo set 1. Reflects excellent & happy eye contact at age 12 months but loss of contact at age 18 months where he could only repetitively bang the rock – language lost at this point).

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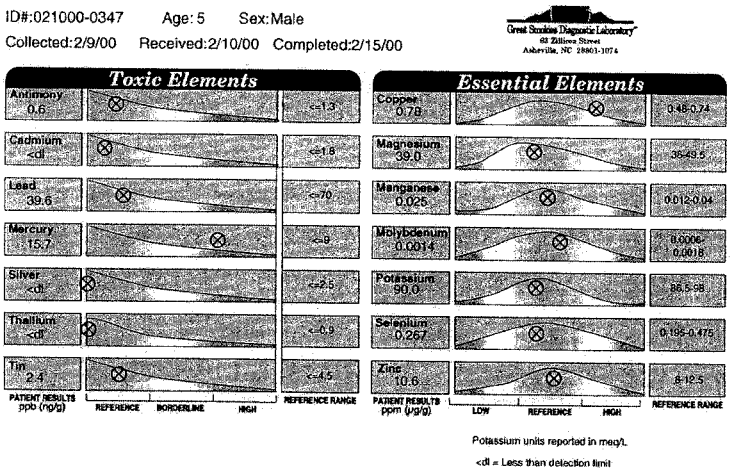
Review of Labs:



(Figure 1. Above) First heavy metal and nutritional mineral study of packed erythrocytes prior to his 5th birthday, at the end of his vaccine schedule.

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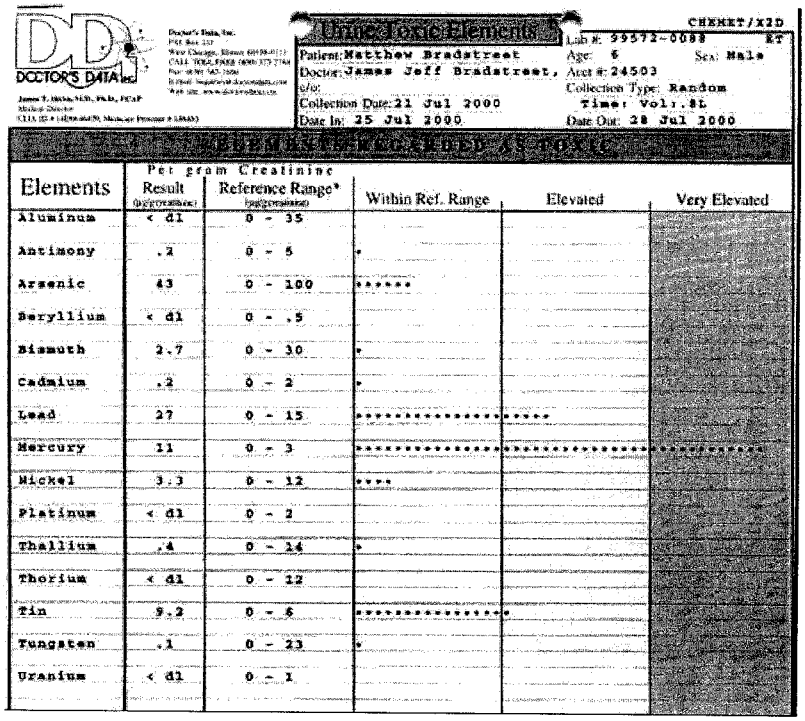

DOCTOR'S DATA inc

Urine Toxic Elements

CHEMET/X2D

Patient: Matthew Bradstreet
Doctor: James Jeff Bradstreet, M.D.
c/o:
Collection Date: 21 Jul 2000
Date In: 25 Jul 2000

Lab #: 99572-0088 ET
Age: 6 Sex: Male
Acct #: 24503
Collection Type: Random
Time: Voi:.8L
Date Out: 28 Jul 2000

Elements	Per gram Creatinine Result	Reference Range*	Within Ref. Range	Elevated	Very Elevated
Aluminum	< dl	0 - 35			
Antimony	.2	0 - 5	*		
Arsenic	43	0 - 100	******		
Beryllium	< dl	0 - .5			
Bismuth	2.7	0 - 30	*		
Cadmium	.2	0 - 2	*		
Lead	27	0 - 15	**********		
Mercury	11	0 - 3	**********		
Nickel	3.3	0 - 12	****		
Platinum	< dl	0 - 2			
Thallium	.4	0 - 14	*		
Thorium	< dl	0 - 12			
Tin	9.2	0 - 6	**********		
Tungsten	.1	0 - 23	*		
Uranium	< dl	0 - 1			

(Figure 2. First chelation challenge for determination of heavy metal burden. For this study 10 mg per kilogram of body weight of DMSA – Chemet-Sanofi were given to three times daily for three days. Urine was collected on the morning of the 4th day. Matthew has no amalgams – mercury filings and ate fish only occasionally. His mother was also tested and had minimally detectable levels of mercury in both red blood cells and after a chelation provocation challenge test.)

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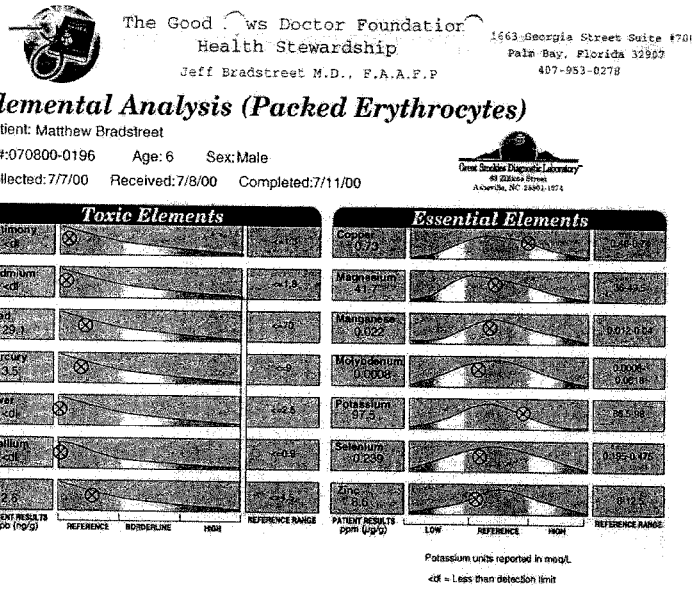

(Figure 3. Repeat packed erythrocyte level after several rounds of DMSA - Chemet, showing significant improvement. The first course of DMSA used the FDA recommendations for lead which is a 19 day course. There were no apparent side-effects during the chelation.)

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DOCTOR'S DATA INC.

Urine Toxic Elements — CHEMET

Lab #: 99635-0075 T

Patient: Matthew Bradstreet — Age: 6 — Sex: Male

Doctor: James Jeff Bradstreet, — Acct #: 24503

c/o: — Collection Type: Random

Collection Date: 25 Sep 2000 — Time:

Date In: 26 Sep 2000 — Date Out: 28 Sep 2000

Elements	Per gram Creatinine Result (µg/g creatinine)	Reference Range* (µg/g creatinine)	Within Ref. Range	Elevated	Very Elevated
Aluminum	< dl	0 - 35			
Antimony	.2	0 - 5	•		
Arsenic	30	0 - 100	••••		
Beryllium	< dl	0 - .5			
Bismuth	1.9	0 - 30	•		
Cadmium	.2	0 - 2	•		
Lead	22	0 - 15	•••••••••••••••	••	
Mercury	24	0 - 3	•••••••••••••••	•••••••••••••••	•••••••••••••••
Nickel	4.7	0 - 12	•••••		
Platinum	< dl	0 - 2			
Thallium	.5	0 - 14	•		
Thorium	< dl	0 - 12			
Tin	9	0 - 6	•••••••••••••••	•	
Tungsten	.2	0 - 23	•		
Uranium	< dl	0 - 1			

(Figure 4. Repeat DMSA urine provoked heavy metal study showing marked increase in mercury excretion despite 6 months of treatment indicating a very significant total body burden of mercury. In this study, we actually see a significantly greater level of mercury. This is presumably secondary to mobilization of Hg and redirection to the kidney where it could be eliminated.)

But intermixed with these studies were investigations for inflammatory bowel disease which did demonstrate grade II nodular hyperplasia of the terminal ileum and eosinophilic colitis and enteritis. He had autoantibodies to MBP detected about a year after his second MMR vaccine.

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Research Laboratory Coombe Women's Hospital,
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Report for Measles Virus Detection

Client information:

Name:	Matthew Bradstreet
Patient Identification	BL5606
Date of Birth:	28/02/1994
Lab Number:	265

TEST - MEASLES VIRUS DETECTION

RNA was extracted from the ileal biopsy and measles virus was detected using a reverse transcriptase quantitative PCR procedure (TaqMan RT-PCR).

The detected measles virus per ng of RNA:F Gene: 1.0 X 10^3 copies/ng total RNA

Result: **Positive for Measles Virus**

Approved by: _____ Date: 02/02/[illegible]

Prof. J. O'Leary

(Figure 5. Represents the results of viral Fusion gene (F gene) investigations of the terminal ileum taken on evaluation at the Royal Free Hospital by Dr Tomson in August of 2000.

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Date: March 20, 2002

Subject Name: **Matthew Bradstreet** DOB/Age: 2/28/94
Address: c/o Jeff Bradstreet, MD
1663 Georgia Street, Suite 700, Palm bay, FL 32907
Referring Physician: Dr. Jeff Bradstreet, MD

LABORATORY RESULTS (For Investigational Use Only)

SPECIMEN: ☐ Serum ☑ CSF ☐ Other Specimen Date: 3/7/02

Test	Result
1. Myelin Basic Protein (MBP) Antibody (Screened at 1:26 dilution of CSF)	**Positive** (weak reaction)
2. Neuron-axon Filament Proteins (NFP) Antibody (Screened at 1:26 dilution of CSF)	Negative
3. Measles Virus (MV) IgG Antibody (Screened at 1:5 dilution of CSF)	0.4 Unit (low level signal)
4. Measles-Mumps-Rubella (MMR) Antibody (Screened at 1:8.5 dilution of CSF)	Negative
5. Human Herpesvirus-6 (HHV-6) IgG (Screened at 1:5 dilution of CSF)	Negative (below detection limit)

Comment:
This child's CSF shows a mild sign of autoimmune reaction to brain myelin sheath. A low level signal for measles virus antibody was also detected.

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Dublin 8, Ireland. Tel. + 353 1 4737142 Fax +353 1 4737144

Report for Measles Virus Detection

Client information:

Name:	Matthew Bradstreet
Patient Identification	BL5606
Date of Birth:	28/02/1994
Lab Number:	265

Sample Information:

Date of Sample Collection: 07/03/2002

Date of Sample Receipt: 13/03/2002

Type of Sample(s) Received: Spinal Fluid with RNA Later

Condition of Sample(s): Satisfactory

TEST - MEASLES VIRUS DETECTION

RNA was extracted from spinal fluid and measles virus was detected using a reverse transcriptase quantitative PCR procedure [TaqMan RT-PCR].

The detected measles virus per ng of RNA: F Gene: 6.16 x 10^6 copies/ng total RNA.

Result: **Positive for Measles Virus.**

Approved by: _____ Date: 12/04/2002
Prof. John O'Leary

Summary of Major Abnormalities in Matthew:

- Milk allergy early in life
- Multiple ear infections
- Transient gait abnormality up until about one year. Was this mercury related?
- Rapid decline after each MMR or combination of vaccines with MMR
- Autoimmunity to Myelin Basic Protein (the insulation of the central nervous system).
- Seizures
- Immune Deficiency with protracted low lymphocyte levels
- Inflammatory Bowel Disease
- Persistent Measles Virus genome in that inflammatory bowel disease
- Persistent Measles Virus in circulating monocytes
- Persistent Measles Virus in genome in spinal fluid
- Antibodies to Measles Virus in spinal fluid
- Autoantibodies to Myelin Basic Protein in spinal fluid
- Elevated ammonia
- Low sulfate with resultant high mercury due to a loss of glutathione and cysteine

So, in my child, what would a reasonable clinician conclude for the medical diagnoses? Autism? Certainly not, unless they believed the hypotheses of Wakefield, Singh and a handful of others who are arguing as I am, that what we have come to call autism – in fact represents a new disorder of immune, viral and toxic origin.

About the only question left to answer is – did the viral persistence cause the condition or did the condition cause the viral persistence? In part, we need to consider the toxicity of thimerosal and Matthew's early gait disorder. Thimerosal becomes a neurotoxin as soon as it dissociates and liberates ethylmercury. The levels of mercury obtained in the vaccine – likely combined with environmental mercury from various sources to precipitate the early motor/coordination/gait problems. Tiddelbaum and colleagues from the University

of Florida have published their findings regarding early movement disorders as a predictor of future risk of autism. This may well be an association with the subtle effects of mercury, although that was not their conclusion. I believe we can the inherent "chicken or egg question", but I want to present another case to establish that my son's condition is not an isolated event.

Case 2. I presented this child to this committee last year. Scott was born 7/25/95. For brevity sake I will comment only that numerous documentations of his early development established no abnormalities at all. Shortly after receiving the MMR vaccine Scott became fussy and lost eye contact and then developed diarrhea and behavioral and developmental regressions. On 2/20/99 we obtained a serum specimen from Scott for evaluation at the University of Michigan, College of Pharmacy, Neuroimmunological Research Laboratory of Dr. V.K. Singh. The 2/20/99 serum underwent testing for autoantibodies to myelin basic protein (a component of the central nervous system), which were found to be positive at a dilution of 1:400 - (Strongly positive range). Scott has had repeated spinal fluid analysis which will be presented here. He has also had intestinal biopsies and blood work for the detection of measles virus F gene – all of which are positive. Scott's parents have filled a claim in the Federal Court of Claims alleging the MMR vaccine precipitated their child's autoimmune encephalopathy – which like my son's – has autistic features. They, as parents, are also not reassured by epidemiological studies or arguments from the public health officials claiming MMR cannot cause the disorder their son has.

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Research Laboratory Coombe Women's Hospital,
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Report for Measles Virus Detection

Client information:

Name:	Franklin Scott
Patient Identification	0001667-484
Date of Birth:	07/02/1995
Lab Number:	476

Sample Information:

Date of Sample Collection: 29/01/2002

Date of Sample Receipt: 01/02/2002

Type of Sample(s) Received: Frozen Whole Blood

Condition of Sample(s): Satisfactory

TEST - MEASLES VIRUS DETECTION

RNA was extracted from whole blood and measles virus was detected using a reverse transcriptase quantitative PCR procedure [TaqMan RT-PCR].

The detected measles virus per ng of RNA: F Gene: 6.21 x 10^0 copies/ng total RNA.

Result: **Positive for Measles Virus.**

Approved by: _____ Date: 12/04/2002
Prof. John O'Leary

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Research Laboratory Coombe Women's Hospital,
Dublin 8, Ireland. Tel. + 353 1 4737142 Fax +353 1 4737144

Report for Measles Virus Detection

Client information:

Name:	Franklin Scott
Patient Identification	0001667-484
Date of Birth:	07/02/1995
Lab Number:	476

Sample Information:

Date of Sample Collection: 29/01/2002

Date of Sample Receipt: 01/02/2002

Type of Sample(s) Received: T-ileum biopsy

Condition of Sample(s): Satisfactory

TEST - MEASLES VIRUS DETECTION

RNA was extracted from the ileal biopsy and measles virus was detected using a reverse transcriptase quantitative PCR procedure [TaqMan RT-PCR].

The detected measles virus per ng of RNA: F Gene: 3.56 x 10^2 copies/ng total RNA.

Result: **Positive for Measles Virus.**

Approved by: _____ Date: 5/04/2002
Prof. John O'Leary

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Date: September 4, 2001

Subject Name: **Scott P. Franklin** DOB/Age: 7/2/95

Address: c/o Dr. Jeff Bradstreet, 1663 Georgia Street, Suite 700, Palm Bay, Florida
Referring Physician: Dr. Jeff Bradstreet, M.D., Palm Bay, FL 32907

LABORATORY RESULTS (For Investigational Use Only)

SPECIMEN: Serum/CSF/Other Date: 3/31/01

Test	Result
1. Measles-Mumps-Rubella (MMR) Antibody (CSF tested at 1:8.5 dilution)	**Positive***

COMMENT:

*This result indicates an inappropriate or abnormal immune reaction to MMR, which appears to be related to brain autoimmunity in autistic children. According to our other research, the MMR antibodies recognize measles subunit, but not the mumps or rubella subunit, of this multivalent vaccine.

Vijendra K. Singh, Ph.D.
Utah State University
Biotechnology Center
4700 Old Main Hill
Logan, UT 84322-4700
Tel: (435) 797-7193 Fax: (435) 797-2766

ICDRC

Date: April 12, 2001

Subject Name: **Scott P. Franklin** DOB/Age: 7/2/95

Address: c/o Dr. Jeff Bradstreet, 1663 Georgia Street, Suite 700, Palm Bay, Florida
Referring Physician: Dr. Jeff Bradstreet, M.D., Palm Bay, FL 32907

LABORATORY RESULTS (For Investigational Use Only)

SPECIMEN: Serum/CSF/Other Date: 3/31/01

Test	Result
1. Myelin Basic Protein (MBP) Antibody (Positive at two dilutions: 1:25 and 1:50 dilution)	Positive*
2. Neuron-axon Filament Proteins (NFP) Antibody (Negative at two dilutions: 1:25 and 1:50 dilution)	Negative
3. Measles Virus (MV) IgG Antibody (Detectable at 1:6 and 1:11 dilutions)	0.8 Units (Positive)**
4. Human Herpesvirus-6 (HHV-6) IgG Antibody (Undetectable at 1:6 and 1:11 dilutions)	0 Units (Negative)

COMMENT:

*This is a sign of autoimmunity to brain myelin proteins but not to neurofilament proteins, suggesting autoantibody specificity for the brain myelin sheath. Note that NFP autoantibodies were tested as a control for MBP autoantibodies.

**Antibodies to measles virus were present but antibodies to human herpesvirus-6 (HHV-6) were absent; this indicates a measles virus infection. Note that HHV-6 antibodies were measured as a control for measles virus antibodies.

To conclude, there is a possibility of an autoimmune reaction to brain myelin sheath, presumably secondary to a measles infection.

Vijendra K. Singh, Ph.D.
Utah State University
Biotechnology Center
4700 Old Main Hill
Logan, UT 84322-4700 Tel: (435) 797-7193 Fax: (435) 797-2766

Conclusions regarding these two cases:

The implications of these findings could have incredible potential impact on public health policy and the future acceptance of voluntary vaccines by parents for their children. We desire safer vaccines and safer administration of vaccines, but we fear a lack of government response to the concerns of researchers and parents will result in lowered overall immunity to numerous preventable disorders, because parents will reject some of the vaccines in their current forms. The request for a safer MMR vaccine was also presented by Imani and colleagues at the Division of Clinical Immunology, Department of Medicine, The Johns Hopkins University School of Medicine, Asthma and Allergy Center (Clin Immunol 2001 Sep;100(3):355-61). So, we do not feel alone in our understanding of the apparent immunological flaws of the current trivalent vaccine.

These data are also public knowledge and have been presented at numerous professional and public forums, as well as through publication in mainstream medical literature, eg *Pediatrics, The Journal of Pediatric, The British Medical Journal – Molecular Pathology, The American Journal of Gastroenterology,* and recently in a press release from *the American Society of Microbiology*. Historically, high titer measles vaccine caused more mortality than expected due to the induction of immune deficiency (Halsey 1993). This caused a reversal of policy and high titer MV vaccines no longer exist. The nature of mass vaccination programs are in effect an ongoing open-label experiment. No study can predict the long-term and subtle effects of a vaccine adequately prior to introduction to a group as large as most of the population of our planet.

Unfortunately, and as true of many new discoveries in medicine, the initial reactions are that of skepticism or rejection. We have seen this historically with *H.pylori* and peptic ulcer disease, as well as during the emerging literature on AIDS and HIV. Eventually, the early observations in these disorders were proven accurate, medicine adapted and acceptance became universal. We believe the same is true for this literature which will be summarized below, despite the present political incorrectness of the findings.

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What do we know so far:

1) MV wild type persists in seemingly normal individuals, although I would have preferred a more in depth study of the histories obtained from autopsy studies.

2) Therefore the mere presence of MV (even vaccine strain) is not enough evidence for us to claim causality, although it is definitely not reassuring to find it in the CSF of children with encephalopathy, or in the intestines of f children with inflammatory bowel disease. MV is known to cause encephalopathy and as found in the study from the Mayo Clinic – it is also a risk factor for inflammatory bowel disease.

3) We have shown - through Dr Singh's efforts that the children are reacting to the virus (immune response) - which are not seen in controls. The response is to Myelin Basic Protein as would be typical in measles viral infections of the CNS. Other viruses are known to do this as well, eg, Japanese Encephalitis, but we have no evidence or history for any of the other candidate infections. So, we see:

- Presence of the virus in 82% of regressed/bowel patients compared to a very low number of controls. This represents a documented unique inflammatory bowel disease in ASD children. (Uhlmann 2002 & Wakefield 2000)
- Autoimmunity in the presence of the virus (gut and brain – published by Singh, et al & the group at Royal Free). Present in cases not controls.
- Antibodies to the virus in the CSF - not seen in controls. (Singh & Bradstreet 2002).
- Virus genome (F gene) in the CSF - no controls yet. High correlation between MV in blood of cases (currently 100% of those with suspected brain MV). (Presented here).
- Frequent seizures (typical of MV in the CNS, but not specific for any one virus).
- Depletion of cysteine and sulfur (Waring et al 2000), consistent with a persistent viral infection, not specific for MV - also seen in HIV patients.

- Resultant 500% higher levels of Hg in cases over controls. (ICDRC – IOM presentation of Bradstreet, 2001).

4) In that last several months, a senior investigator for the Committee and I have conducted an informal poll of numerous pediatricians, neurologists and immunologist. We have provided laboratory results and histories. Then we asked them to give us their best diagnosis for the cases. Every physician was unanimous that the findings represent measles infection in the brain. They differed somewhat on the nature of the infection, but only over whether it represented acute infection or subacute sclerosising panencephalitis (SSPE).

5) In Scott's situation, Dr John Menkes the esteemed professor of pediatric neurology and author of the foundational textbook *Child Neurology,* agrees that the findings can only be interpreted to represent measles infection in the brain. He refers to this as atypical SSPE, since it does not appear to be causing the typical findings in SSPE. That may be somewhat confusing terminology. I would prefer to call it ***autoimmune encephalopathy with measles virus persistence.*** I believe Professor Menkes and I remain in complete agreement about the disease process, and as with this entire problem – just need to come to terms about the nomenclature. Menkes would no doubt have an identical interpretation of my son's case.

So who and what are we to believe. Everyone agrees the epidemiology is not precise enough to detect rare events. But are these two boys rare? Certainly the data of Singh , Uhlmann, Wakefield, Bradstreet and others represent a much larger population than just these two cases. Several hundred children have been studied and published in the various papers. While we need controls and confirmation for this most recent piece of the puzzle (viral genome in the CSF), I think we should be more than concerned about the findings. My impression from carefully examining and investigating 1500 cases of autism is that these boys are not isolated cases. I am terribly concerned they may well represent the majority of cases of regressed autistic encephalopathy children.

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Therefore, we as a society need ask and answer some important questions:

- **What if Wakefield, Singh, Bradstreet and Menkes are right about these data.?**
- **What then?**
- **Have we traded acute measles and occasional SSPE from the wild disease for a 1 in 80 risk for boys to develop this new form of measles disease?**
- **Can that be a justifiable risk/benefit ratio?**
- **Do we have safer vaccines?**
- **If so, why aren't we using them? It appears Dr Bellanti at Georgetown does have a safer measles vaccine that he cannot get licensed.**
- **What has held up the approval of that measles vaccine?**
- **If we do not have safer vaccines, why don't we?**
- **How are we going to treat these two boys, or the potential hundreds of thousands like them?**
- **Why doesn't the epidemiology agree with the biology? Have we asked the right questions in the way the epidemiology studies were constructed? Did they use reliable methods and databases?**
- **Is it only a reaction to MMR or are many things capable of triggering the brain autoimmunity and gut disorders we are seeing?**
- **Do, as I suspect thimerosal, aluminum, and the various vaccine antigens prime the immune system to respond abnormally to live virus injections?**
- **We suspended live polio vaccines for early life because of 9 cases of polio in susceptible individuals. How many persistent measles autistic-like encephalopathies will it take to stop using MMR and find a safer vaccine alternative? Are 10 enough? 100? 1000? Or do we need hundred's of thousands of cases?**
- **In a similar light, how many inflammatory bowel diseases must it cause?**

- **Should live viruses be injected, thereby violating the normal immune mechanisms, or should they always be provided through natural route of infection means?**
- **Should live viruses ever be used, or is this playing with immunological and virological fire?**

I am only asking these questions to stimulate reasoned medical debate and investigation. I am convinced about the nature of our present autism epidemic, but I also recognize changing the course for vaccine policy is like changing the course for a large ocean going vessel, hopefully it will not be like the *Titanic*. Presently, my partner, Dr Kartzinel and I have a waiting list to get on our waiting list. We hear from parents daily with newly diagnosed children. I will once again remind the Congress of the words of our Surgeon General:

> ***"Growing numbers of children are suffering needlessly because their emotional, behavioral, and developmental needs are not being met by those very institutions, which were explicitly created to take care of them."*** Surgeon General Sachet (http://www.surgeongeneral.gov/cmh/childreport.htm)

Epidemiology (with the known flaws in the published studies) has failed to find an association, although the data sources used are suspect. The most difficult piece of data is the continued rise in prevalence despite flat uptake of the vaccine. Our explanation of that observation has to do with other priming events for MMR which are not constant over the time in question.

So how is it the IOM and the various expert bodies looking at this data come away saying there is NO evidence of a link between MMR and ASD? They ignore all of these molecular viral data and immunological findings and rely slavishly upon rather poor epidemiology. Is ASD multi-factorial? It must be - humans are far to complex to be

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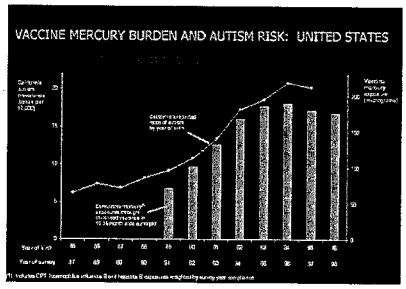
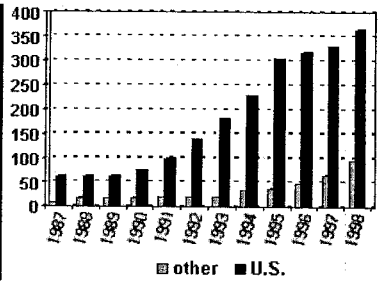
reduced to simplistic & mechanistic processes when brain development is involved. Is it just MMR? I doubt it for most cases.

The better question is this: is it ultimately MMR? I certainly see the evidence for that - again - in most cases. This, I believe is the result of numerous antecedent priming events – including the right genetic predisposition to certain immunological events – such as autoimmunity.

There is even more reason for concern. The CDC was willing to present data that Thimerosal vaccines were associated with a statistically significant increased risk of Attention Deficit Hyperactivity Disorder. Below I compare the chart prepared and presented to the IOM by Mark Blaxil and the US data on stimulant use for ADHD. It seems obvious there is a significant relationship between the two – both start to rise abruptly around 1990.





Cumulative Dose of Mercury from Vaccine Burden and Autism rates in California on the left side and United Nations Data Methylphenidate Consumption (Defined Daily Doses in millions) on the right side.

Source:http://www.ahcpr.gov/clinic/epcsums/adhdsutr.htm

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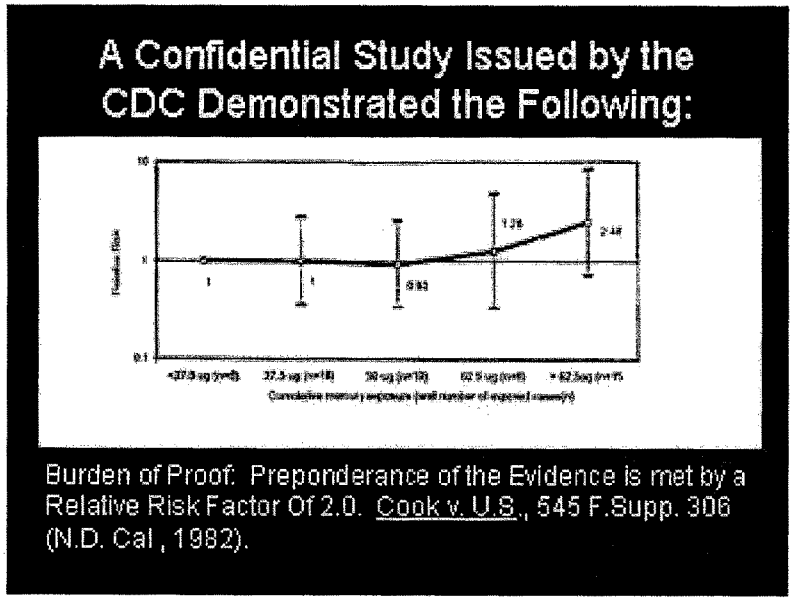
Add these data to the findings of the original CDC study on thimerosal and autism risk. See slide below:



This moves my discussion into: Legal Concerns Congress Must Keep in Mind

Last year I predicted that if there was not immediate action to address the growing understanding of thimerosal toxicity and MMR, that this country would face potentially catastrophic legal consequences. I made several recommendations, some of which are echoed in the proposed amendments to the Vaccine Injury Compensation Fund, (VIC

Fund) supported by both sides of this Committee. But sending parents to the "Fund" for compensation for their child's needs is literal purgatory.

As we search for truth in determining the safety, or lack thereof, for the many vaccine components, we must keep in perspective there exists two separate systems for determining medical truth in this country: 1) the realm scientific purity which is largely impossible to obtain in pediatric research and practice, and 2) the legal or tort system.

The requirements to satisfy the Institute of Medicine, from my personal dealings with them, might be greater than 90% certainty prior to affirming any casual relationship to vaccine components. But the tort system defines things differently. While it will not be my place to offer legal definitions to the committee, it suffices to say that our courts and/or special masters will soon answer the question regarding vaccine linkage to autism.

Having been an expert at several causation hearings for vaccine "Fund" cases, it is clear this system will in no way benefit the children affected by ASD, even if the table were amended. The program is broken beyond repair and the use of the Justice Department to try cases is unwise. They - by the nature of legal practices - take an adversarial position against the parents – whom are already suffer through tremendous financial and emotion hardships. Presently 85% of our ASD families have ended in divorce. Clearly then, a non-adversarial system must be created, or again the thousands of children enrolled in class- action or private suits against vaccine manufacturers and distributors will quickly become hundred's of thousands.

A primer on causality from Attorneys Kenneth S Lewis and Ann-Louise Kleper: *"To the lawyer, "cause" includes not only that which precipitates, initiates or produces, but also that which accelerates, aggravates or worsens some medical condition. In other words, the definition embraces elements which bring about symptoms, disability, damages or death sooner than would have ordinarily been expected in the normal course of the underlying disease. Such a concept is inherently foreign to scientific thinking,*

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which considers the underlying reason for the entire disorder. After considering all of the factors underlying the disorder and their inter-relationships, medicine seeks to ascertain the cause - the single element responsible for the condition of ill-being, the identity of which may be demonstrated clearly and conclusively. ***In law, exclusivity may not be demanded... The evidence necessary to establish causation in medicine must be verifiable by objective diagnostic methods; physicians demand scientific proof. The law is too pressed for time to allow the parties the luxury of such certainty. If disputes are to be resolved and if justice is to be done, a decision cannot be postponed until medical science advances to the point where all questions posed by a particular claim may be unequivocally determined."***

And what ultimately determines "scientific proof" always seems to be debatable amongst the experts themselves. So, while medical types piously discuss the purity of research, the courts grind on. Inaction by Congress and Administrations (current and past) has allowed a tragic epidemic to go unnoticed, except by those directly involved. While there may be some hope based on recent meetings I have had with HHS, government response to the crisis is still painfully slow. As regrettable as our present reality is – it does appear families will be turning to the courts to resolve their grievances in huge numbers. And that will be, to quote the Bard: "A pox on both your Houses."

Regardless of the ultimate legal outcome, everyone will loose something.

- The child with autism will loose irreplaceable time as the cost of required treatment goes unmet by both governmental and insurance providers.
- The vaccine manufacturers will pay vast amounts in legal defense and thereby loose money which might be used to generate safer vaccines. If the courts find against the vaccine industry, the losses could be staggering – beyond any prior tort awards given the nature of ASD and the huge numbers of children affected.
- Parents have already lost their peace of mind regarding public health policy, but the public legal battle will no doubt erode remaining confidence in vaccines even further regardless of the science – doubt will be fostered.

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- Society will continue to loose the productive contribution of parents and children consumed by ASD.

Again I ask Congress and the Administration to address the needs for families and the appropriate funding for ASD treatment, therapy and research. In any other clinical setting the information we have gathered on children would be far more than what would be needed to make a diagnosis. Is it enough evidence? Most certainly! Is it proof? Well, I guess that depends on what you call proof. Is it more than the 50% assurance as would be required in a legal setting? Is it 100%? No, but things rarely are in medicine - especially early in the evolution of knowledge on a new finding.

Respectfully Submitted,

James Jeffrey Bradstreet, MD, Fellow, AAFP
Director, Clinical Services
International Child Development Resource Center

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REFERENCES & ABSTRACTS:

Serological Detection of Measles Virus in Relation to Autoimmunity in Autism

102nd General Meeting of the American Society for Microbiology
May 19-23, 2002, Salt Lake City, Utah, Presentation V-5

V.K. Singh, R.L. Jensen, J. J. Bradstreet
Utah State University and the International Child Development Resource Center

Abstract: Autoimmunity to brain myelin protein (MBP) secondary to a measles infection may cause autistic regression in some children with this neurodevelopmental disorder. We hypothesized that measles-mumps-rubella (MMR) immunization is a source of measles infection; hence the serological link between MMR and MBP antibodies might exist in autistic children. To test the hypothesis, we conducted a serological study of MBP, MMR and neuron-axon filament protein (NAFP) in serum and cerebral spinal fluid (CSF) of autistic children. Antibodies were assayed by immunoblotting with MBP, NAFP and MMR as antigens. We found that a significant number of autistic children had antibodies to MBP (up to 88% positive) and antibodies to MMR (up to 65% positive), but not to NAFP. Normal children did not harbor these antibodies. Moreover, the analysis of paired samples (serum and CSF) from 7 autistic children also revealed a high degree of serological association between MMR and MBP: 50% of CSF had MMR antibodies, 86% of CSF had MBP antibodies, 75% of sera had MMR antibodies and 100% of sera had MBP antibodies. Therefore, as indicated by paired analysis of serum and CSF samples, there is a strong correlation between MMR antibodies and MBP autoantibodies in autism. By using monoclonal antibodies, we characterized that the MMR antibodies are due to the measles subunit, but not due to mumps or rubella subunits, of the polyvalent vaccine. Furthermore, the MMR and MBP antibodies are not cross-reactive because the pre-incubation of MBP with MMR did not block the binding of MBP antibodies. In light of the new evidence presented here, we suggest that the MMR vaccine in some cases of autism might cause autoimmunity and it might do so by bringing on an atypical measles infection that does not produce a typical measles rash but manifests neurological symptoms upon immunization.

Note: The MMR antibody has been previously reported to be the hemagglutin protein of the vaccine measles virus (MV-HA). **"Immunoblotting analysis showed the presence of an unusual MMR antibody in 60% (75 of 125) of autistic children, but <u>none</u> of the 92 normal children had this antibody. Moreover, by using MMR blots and monoclonal antibodies, we found that the specific increase of MV antibodies or "MMR" antibodies was related to**

measles hemagglutinin antigen (MV-HA)," (Singh, VK. Abnormal Measles Serology and Autoimmunity in Autistic Children, *Journal of Allergy Clin Immunol* 109 (1):S232, Jan. 2002.) It is confirmed here (in an additional population) that this antibody is not typically produced during normal immune response to the vaccine.

Molecular Psychiatry (2002) ●●, ●●●–●●●

www.nature.com/mp

ORIGINAL RESEARCH ARTICLE

Small intestinal enteropathy with epithelial IgG and complement deposition in children with regressive autism

F Torrente, P Ashwood, R Day[1], N Machado, RI Furlano, A Anthony[4], SE Davies[4], AJ Wakefield[3], MA Thomson, JA Walker-Smith and SH Murch●<aq1>●

[1]*Centre for Paediatric Gastroenterology, with the Inflammatory Bowel Disease Study Group, Royal Free & University College Medical School, London, UK;* [2]*The IBD Research Unit, St Mark's Hospital, Harrow, London, UK;* [3]*Department of Medicine, Royal Free & University College Medical School, London, UK;* [4]*Department of Histopathology, Royal Free & University College Medical School, London, UK*

We have reported lymphocytic colitis in children with regressive autism, with epithelial damage prominent. We now compare duodenal biopsies in 25 children with regressive autism to 11 with coeliac disease, five with cerebral palsy and mental retardation and 18 histologically normal controls. Immunohistochemistry was performed for lymphocyte and epithelial lineage and functional markers. We determined the density of intraepithelial and lamina propria lymphocyte populations, and studied mucosal immunoglobulin and complement C1q localisation. Standard histopathology showed increased enterocyte and Paneth cell numbers in the autistic children. Immunohistochemistry demonstrated increased lymphocyte infiltration in both epithelium and lamina propria with upregulated crypt cell proliferation, compared to normal and cerebral palsy controls. Intraepithelial lymphocytes and lamina propria plasma cells were lower than in coeliac disease, but lamina propria T cell populations were higher and crypt proliferation similar. Most strikingly, IgG deposition was seen on the basolateral epithelial surface in 23/25 autistic children, co-localising with complement C1q. This was not seen in the other conditions. These findings demonstrate a novel form of enteropathy in autistic children, in which increases in mucosal lymphocyte density and crypt cell proliferation occur with epithelial IgG deposition. The features are suggestive of an autoimmune lesion.
Molecular Psychiatry (2002) ●, 000–000. DOI: 10.1038/sj/mp/4001077

Keywords: autism; small intestine; inflammation; lymphocytes; immunoglobulins; autoimmunity; complement

Mol Psychiatry 2002;7(4):375-82

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ORIGINAL ARTICLE

Potential viral pathogenic mechanism for new variant inflammatory bowel disease

V Uhlmann, C M Martin, I Silva, A Killalea, O Sheils, S B Murch, A J Wakefield, J J O'Leary

J Clin Pathol: Mol Pathol 2002;**55**:0–6

See end of article for authors' affiliations

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Accepted for publication 8 November 2001

Aims: A new form of inflammatory bowel disease (ileocolonic lymphonodular hyperplasia) has been described in a cohort of children with developmental disorder. This study investigates the presence of persistent measles virus infection in the intestinal tissue of these patients (new variant inflammatory bowel disease) and a series of controls by molecular analysis.

Methods: Formalin fixed, paraffin wax embedded and fresh frozen biopsies from the terminal ileum were examined from affected children and histological normal controls. The measles virus Fusion (F) and Haemagglutinin (H) genes were detected by TaqMan reverse transcription polymerase chain reaction (RT-PCR) and the Nucleocapsid (N) gene by RT in situ PCR hybridisation. Localisation of the mRNA signal was performed using a specific follicular dendritic cell antibody.

Results: Seventy five of 91 patients with a histologically confirmed diagnosis of ileal lymphonodular hyperplasia and enterocolitis were positive for measles virus in their intestinal tissue compared with five of 70 control patients. Measles virus was identified within the follicular dendritic cells and some lymphocytes in foci of reactive follicular hyperplasia. The copy number of measles virus ranged from one to 300 000 copies/ng total RNA.

Conclusions: The data confirm an association between the presence of measles virus and gut pathology in children with developmental disorder.

Aliment Pharmacol Ther 2002; 16: 1–12.

Entero-colonic encephalopathy, autism and opioid receptor ligands: an hypothesis

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Accepted for publication ■ ■ 2001

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COMMENTARY

MMR vaccine

New evidence for a viral pathogenic mechanism for new variant inflammatory bowel disease and development disorder?

A Morris, D Aldulaimi

See article by Uhlmann *et al* page XXX

We are all aware of the public unease about a potential link between vaccination with the triple vaccine MMR (mumps, measles, and rubella) and autism or bowel inflammatory conditions, with some hundreds of parents of afflicted children undertaking legal action against the manufacturers. There is no space to go into detail of the controversy over the link here (search the web using keywords "measles, MMR, vaccination, autism")—suffice it to say that reliable epidemiologists are content that there is no significant association between MMR and either autism or bowel inflammatory conditions. However, epidemiology is a pretty blunt tool and the studies done do not rule out the possibility that there may be "at risk" groups where a real link between MMR and autism/bowel inflammatory conditions exists.

> "Epidemiology is a pretty blunt tool and the studies done do not rule out the possibility that there may be at risk groups where a real link between MMR and autism/bowel inflammatory conditions exists"

In 1998, Wakefield and colleagues reported colitis and ileal lymphoid nodular hyperplasia in children with developmental disorders such as autism, and suggested a possible link between MMR vaccination and a chronic enterocolitis associated with neuropsychiatric dysfunction in these children.[1] In 2000, a further study by the same group supported the association of developmental disorders with a distinct form of inflammatory bowel disease—new variant inflammatory bowel disease.[2]

In this present paper,[3] the authors report the association of this condition with the persistence of at least fragments of the measles virus genome within the follicular dendritic cells and lymphocytes of areas of lymphoid nodular hyperplasia. The technique used (reverse transcriptase polymerase chain reaction) could not indicate whether whole virus was present, or whether it was replicating, but for the moment we can go along with the notion that the virus is persisting in some form in these patients.

The interpretation of this finding is difficult. It would be entirely wrong to jump to the conclusion that the measles component of MMR "causes" the colitis or the developmental disorder in these particular (or any other) children. Causation is rarely simple and never pure: most if not all diseases are multifactorial in nature, and the data here could equally well be interpreted as indicating that the colitis or the developmental disorder "cause" the persistence of the measles. The measles virus persistence could reflect the inability of patients with a developmental disorder to clear the virus. The enterocolitis may cause failure of viral clearance. And in no way can the data presented here be used to support the generalisation that MMR causes all autism and/or inflammatory diseases of the bowel.

There is evidence that developmental disorders are associated with a functional disturbance of the brain–gut axis. Neurogenerative disorders such as Parkinson's disease and functional bowel diseases, such as the irritable bowel syndrome, are associated with abdominal pain, bloating, and diarrhoea. Functional magnetic imaging has demonstrated striking differences in cortical activation following colonic distension in patients with irritable bowel syndrome compared with normal controls, suggesting that a disturbance in perception in the absence of obvious pathological changes may lead to abdominal pain, bloating, and diarrhoea. Thus, the symptoms present in the patients with developmental disorders may result from pathological modulation of the functional interface between the immune and sensory motor systems of the gut. Hence, disturbance of the brain–gut axis might lead to alterations in local neurotransmitters and mediators of inflammation—and so failure to clear virus infections efficiently.

> "There is evidence that developmental disorders are associated with a functional disturbance of the brain–gut axis"

The data presented here are unquestionably interesting but beg a string of further questions: Is replicating whole virus present? Is it identical to the vaccine strain? Are other viruses—mumps or rubella—present? What about the nature of immunity to measles and other pathogens in these children? These questions come immediately to mind. Doubtless the present (and other) authors are pursuing these (and many other) questions: we look forward to answers.

J Clin Pathol: Mol Pathol 2002;55:0

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3 **Uhlmann V,** Martin CM, Sheils O, *et al.* Potential viral pathogenic mechanism for new variant inflammatory bowel disease. *J Clin Pathol Mol Pathol* 2002;55:XX–XX.

New Foundation of Biology
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Neuro-immunopathogenesis in Autism

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Infection of Human B Lymphocytes with MMR Vaccine Induces IgE Class Switching

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Circulating immunoglobulin E (IgE) is one of the characteristics of human allergic diseases including allergic asthma. We recently showed that infection of human B cells with chimovirus or measles virus could lead to the initial steps of IgE class switching. Since many viral vaccines are live viruses, we speculated that live virus vaccines may also induce IgE class switching in human B cells. To examine this possibility, we selected the commonly used live attenuated measles mumps rubella (MMR) vaccine. Here, we show that infection of a human IgM[+] B cell line with MMR resulted in the expression of germline ε transcript. In addition, infection of freshly prepared human PBLs with this vaccine resulted in the expression of mature IgE mRNA (transcript. Our data suggest that a potential side effect of vaccination with live attenuated viruses may be an increase in the expression of IgE.

Key Words: vaccine; IgE; asthma; allergy.

INTRODUCTION

A key component in allergic reactions is increased levels of circulating immunoglobulin E (IgE) (1, 2). Mature resting B cells express IgM and subsequently can further differentiate to undergo immunoglobulin class switching and secrete immunoglobulins with IgG, IgA, or IgE isotypes. Upon interaction with allergens and crosslinking of specific IgE molecules bound to the high-affinity surface receptors, mast cells and basophils release several mediators. The release mediators such as histamine and leukotrienes are responsible for many clinical manifestations of allergic responses (3–5).

The incidence rate of allergic reactions such as asthma has increased in the past 20 years. However, the reason for this increase is not yet clear. Since genetic background of the population has not changed in a significant way, several environmental factors have been suggested. One proposed factor is the improvements in home construction leading to an increase in the indoor humidity and temperature resulting in an increase in house dust mite and cockroach allergens (6, 7). Bacterial products such as CpG nucleotides are thought to down-regulate allergic differentiation; therefore, others have suggested that an increase in antibiotic usage and a subsequent reduction in bacterial infections has created an environment that may favor allergic conditions (8, 9). Moreover, a decrease in childhood outdoor activities and an increase in sedentary life styles have been suggested to be contributory to the increase in asthma incidence (6, 10).

Another intriguing mechanism for the increasing incidence of allergic reactions is viral exposure during childhood. Our recent reports have demonstrated that viral infections can modulate IgE class switching in human B cells (11, 12). The induction of class switching was subsequent to activation of protein kinase R (PKR), NF-κB, and STAT-6. This is consistent with targeted disruption studies in mice demonstrating that deletion of the gene encoding the p50 subunit of the NF-κB complex and STAT-6 resulted in a reduction in the level of serum IgE, suggesting a critical role for these nuclear factors in IgE class switching (13–16).

To induce protective immunity against pathogenic viral diseases, live attenuated viruses are used in several childhood vaccines such as polio, MMR (mumps, measles, rubella), and varicella. Based on the previously published data and our recent reports we addressed the hypothesis that live viral vaccines can induce IgE class switching. In this report we provide evidence that infection with MMR vaccine can induce IgE class switching in a human B cell line and freshly prepared peripheral blood lymphocytes (PBLs).

MATERIALS AND METHODS

Cell culture conditions, vaccine infections, and reagents. The human Burkitt's lymphoma Ramos B cell line of 1×10^5–1×10^6 cells/ml was grown in RPMI 1640 supplemented with 10% fetal calf serum, 0.1 mM nonessential amino acids, and 1 mM sodium pyruvate

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1521-6616/01 $35.00

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"Vaccination provides great protection against the mortality and morbidity associated with many childhood diseases and should not be discouraged, **but it is possible that a side effect of viral vaccination constitutes an increase in the incidence of IgE-mediated disorders. A better understanding of the mechanism underlying this event may yield improved vaccines in the future." Imani and Kehoe, page 360.**

J Bone Miner Res 1996 Nov;11(11):1602-7
Detection of measles virus nucleocapsid transcripts in circulating blood cells from patients with Paget disease.
Reddy SV, Singer FR, Mallette L, Roodman GD.

Dig Dis Sci 2000 Apr;45(4):723-9
Detection and sequencing of measles virus from peripheral mononuclear cells from patients with inflammatory bowel disease and autism.
Kawashima H, Mori T, Kashiwagi Y, Takekuma K, Hoshika A, Wakefield A.

J Med Virol 2001 Oct;65(2):381-7
Detection of measles virus genome in lymphocytes from asymptomatic healthy children.
Sonoda S, Nakayama T.
Department Pediatrics, School of Medicine, Keio University, Shinjyuku-ku, Tokyo, Japan.

A total of 342 samples of peripheral blood mononuclear cells (PBMC) were obtained from 145 healthy individuals, which we examined for the presence of measles virus genome RNA by reverse transcription-polymerase chain reaction (RT-PCR), to identify whether asymptomatic infection of measles virus has occurred in healthy children. Measles virus genome was detected in 11 (23.4%) of 47 nonimmunized individuals; all positives for RT-PCR were infants who experienced measles exposure. No genome was detected in those without measles exposure. In 83 individuals immunized with measles vaccine, the vaccine strain genome was detected in 10 (71.4%) of 14 recipients whose PBMC were obtained within 2 months of vaccination. Measles wild-type genome was detected in 36 (46.2%) of 78 individuals, 40 (25.2%) of 159 samples, who had been immunized more than 2 months before. The wild-type measles genome was also detected in 6 (46.2%) of 13 individuals who had been infected with measles in the distant past. The measles PCR-positive rate was not related to the period since immunization or natural infection. Sequence analysis of PCR products demonstrated they were all in the same cluster of D5 lineage, which was the circulating strain during the study period. We obtained 13 samples of nasopharyngeal secretion (NPS) simultaneously from individuals whose PBMC were positive for measles PCR but did not detect virus genome. Measles genome was, however, detected from NPS in cases of acute infection. We conclude that asymptomatic measles infection is common but would rarely become a source of transmission because of negative PCR in NPS. Copyright 2001 Wiley-Liss, Inc.

J Med Virol 1998 Oct;56(2):174-7
Partial amplification of the measles virus nucleocapsid gene from stored sera and cerebrospinal fluids for molecular epidemiological studies.
Kreis S, Schoub BD.
National Institute for Virology, Johannesburg, South Africa. Stephk@niv.ac.za

The analysis of stored sera for retrospective molecular epidemiological studies provides a powerful tool to investigate strain variation in measles viruses that had circulated up to 20 years ago. For this purpose, a

rapid and simple method for extraction of RNA from stored sera and cerebrospinal fluids (CSF) was developed. When used on sera and CSFs that have been frozen for as long as 20 years, this method proved to be more efficient than established techniques. The extracted RNA was reverse transcribed into cDNA by using random hexamer primers. The PCR amplification of the 3' terminus of the nucleocapsid gene (N) was divided into two overlapping fragments of 375 and 384 bp length, covering the entire region of interest. This region is thought to have the highest variability within the MV genome and has previously been shown to be suitable for strain characterization. The resulting PCR fragments were sequenced manually by using standard methods without the need of further clean-up steps.

Brain Dev 1996 May-Jun;18(3):220-3
A case of intractable epilepsy positive for the detection of measles virus genome in the cerebrospinal fluid and peripheral mononuclear cells using reverse transcriptase-polymerase chain reaction.
Kawashima H, Miyajima T, Mori T, Yuan L, Ogihara M, Kinoue K, Takekuma K, Hoshika A.
Department of Pediatrics, Tokyo Medical College, Japan.

We report a rare case of intractable frontal lobe epilepsy with mental deterioration, in which the measles virus gene was detected from the cerebrospinal fluid (CSF) and peripheral mononuclear cells (PBMC) obtained 9 years after the first epileptic episode using reverse transcriptase-polymerase chain reaction (RT-PCR). The patient had been immunized with an attenuated measles vaccine and had no history of clinically apparent acute measles infection. However the analysis of the sequence of the PCR product from CSF showed the circulating wild strain genotype at the time when the patient complained of his first epileptic episode.

Psychiatry Clin Neurosci 1995 Jun;49(3):S294-5
A case of intractable epilepsy with mental deterioration: detection of measles virus genome in cerebrospinal fluid and peripheral mononuclear cells using reverse transcriptase-polymerase chain reaction.
Miyajima T, Kawashima H, Hoshika A, Ogihara M, Yamada N, Wang CY, Kinoue K, Takekuma K.

Virus Res 1995 Jan;35(1):1-16
Detection of measles virus genome directly from clinical samples by reverse transcriptase-polymerase chain reaction and genetic variability.
Nakayama T, Mori T, Yamaguchi S, Sonoda S, Asamura S, Yamashita R, Takeuchi Y, Urano T.

A simple and sensitive method for the detection of measles virus genome was developed, amplifying the regions encoding the nucleocapsid (N) protein and hemagglutinin (H) protein of measles virus by reverse transcriptase-polymerase chain reaction (RT-PCR). We examined a variety of measles patients: 28 patients with natural infection, 4 with measles encephalitis and 1 with subacute sclerosing panencephalitis (SSPE). In 28 patients with natural measles infection a single step PCR amplifying the N region resulted in a high detection rate for all plasma samples (28/28) within 3 days of the onset of rash and 80% (20/25) even on day 7 of the onset of rash and later. Within 3 days of the onset of rash, 24/25 (96.0%) of nasopharyngeal secretions (NPS) and 27/28 (96.4%) of peripheral blood mononuclear cells (PBMC) were positive for the N region PCR and the positivity rate of PCR decreased in NPS and PBMC after 7 days of the rash. In acute measles infection, measles genome was detected in all cell fractions, CD4, CD8, B cells, and monocytes/macrophages by the H gene nested PCR. Measles genome was also detected from cerebrospinal fluids (CSF) in patients with measles encephalitis, SSPE, and acute measles by the H gene nested PCR. PCR products of the N and H regions were sequenced and we confirmed the presence of measles genome. Based on the sequence data, chronological sequence differences were observed over the past 10 years. The sequences obtained from the SSPE patient were closely related to those of the wild viruses that were circulating at the time when the patient initially acquired measles. RT-PCR for NPS, PBMC, CSF, and plasma provides a useful method for the diagnosis of measles and molecular epidemiological study in addition to virus isolation.

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Ann Neurol 1994 Jul;36(1):103-8

Subacute sclerosing panencephalitis in an infant: diagnostic role of viral genome analysis.

Baram TZ, Gonzalez-Gomez I, Xie ZD, Yao D, Gilles FH, Nelson MD Jr, Nguyen HT, Peters J.
Department of Neurology, University of Southern California, Los Angeles.

Subacute sclerosing panencephalitis (SSPE) is related to "defective" measles virus or vaccination, though an association with parainfluenza viruses has been reported. SSPE is characterized by a slow, erratic course and elevated cerebrospinal fluid measles titers. An immunocompetent, vaccinated infant, with onset of symptoms in parainfluenza virus season and a catastrophic course is described. Cerebrospinal fluid titers were negative, but postmortem brain had typical SSPE lesions. Patient brain-derived RNA, subjected to reverse transcription followed by polymerase chain reaction yielded polymerase chain reaction products with measles virus but not parainfluenza virus genes. The sequenced fragment revealed multiple mutations, typical for SSPE. SSPE can thus present in infants, with short latency and no cerebrospinal fluid antibodies. Viral genomic analysis may be diagnostic, permitting early therapy.

J Med Virol 1990 Apr;30(4):237-44

Detection of measles virus genomic sequences in SSPE brain tissue by the polymerase chain reaction.

Godec MS, Asher DM, Swoveland PT, Eldadah ZA, Feinstone SM, Goldfarb LG, Gibbs CJ Jr, Gajdusek DC.
Laboratory of Central Nervous System Studies, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20892.

The polymerase chain reaction (PCR) was modified to detect RNA genomic sequences by generating cDNA copies of these sequences as a preliminary step. Oligonucleotide primer pairs complementary to sequences in each of the five major structural protein genes of the measles virus (nucleocapsid protein, phosphoprotein, matrix protein, fusion protein, and hemagglutinin protein) were synthesized. PCR products were tentatively identified by visualization of bands of the appropriate size by ethidium bromide staining after gel electrophoresis, and identity was confirmed by subsequent restriction enzyme cleavage of the products at predetermined sites to yield fragments of predicted size. This method successfully amplified 400-500 base regions from each of these five genes in RNA extracts of wild measles virus cultured in Vero cells and in RNA extracted from most of the SSPE brain tissues tested, but not in RNA from any control brain tissues. Measles virus genome was detected in SSPE brain tissues stored frozen for as long as 27 years and formalin-fixed paraffin-embedded subacute sclerosing panencephalitis (SSPE) brain tissues as old as 9 years. This method provides a simple, rapid and highly sensitive means of detecting and identifying sequences of RNA genomes by PCR. The success of this method in detecting measles virus in SSPE brain tissue suggests that PCR is appropriate to investigate the possible presence of RNA viruses in other neurological disorders of unknown etiology.

Infection of human B lymphocytes with MMR vaccine induces IgE class switching.

Clin Immunol 2001 Sep;100(3):355-61

Imani F, Kehoe KE.

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Circulating immunoglobulin E (IgE) is one of the characteristics of human allergic diseases including allergic asthma. We recently showed that infection of human B cells with rhinovirus or measles virus could lead to the initial steps of IgE class switching. Since many viral vaccines are live viruses, we speculated that live virus vaccines may also induce IgE class switching in human B cells. To examine this possibility, we selected the commonly used live attenuated measles mumps rubella (MMR) vaccine. Here, we show

that infection of a human IgM(+) B cell line with MMR resulted in the expression of germline epsilon transcript. In addition, infection of freshly prepared human PBLs with this vaccine resulted in the expression of mature IgE mRNA transcript. **Our data suggest that a potential side effect of vaccination with live attenuated viruses may be an increase in the expression of IgE.**

Mr. BURTON. That is all right. I think it was very informative. Dr. Wakefield.

Dr. WAKEFIELD. It is a great pleasure to be back here again.

Before bringing you up to date with the research linking MMR vaccine to autism, I would like to put the record straight with respect to Dr. Gershon's testimony last year on the molecular detection of measles virus in the laboratory of Professor O'Leary. Dr. Gershon's was false in relation to a number of assertions, whether or not his testimony constituted perjury or simply sloppy science. It is not my wish to take up valuable time in this hearing with the details of Dr. Gershon's unacceptable errors or correspondence relating to this. All raw data have been provided to both the ranking majority and minority members.

Merely by way of illustration, he stated that tissues from experimental animals and others infected with measles virus were positive in Professor O'Leary's lab. In fact, they were all entirely and consistently negative on repeat testing in blinded studies.

Scientifically, Dr. Gershon's behavior was a disgrace and I stand by that. I would level the same charge at anyone who relies on or has relied on in any way upon his testimony. The disgrace is that he did not check the raw data before impugning the reputation of a fellow scientist before the eyes of the world. I am not surprised that Dr. Gershon has turned down on two occasions the offer to appear before this committee.

Let me turn now to the current state of the science. The association between MMR vaccine autism and intestinal inflammation was first suggested by my group on the inspiration of parents from the Royal Free Hospital Medical School in 1998 in a paper published in the Lancet. This is well known to you.

The same research team in collaboration with Professor John O'Leary and Dr. Simon Murch, a pediatric gastroenterologist from the Royal Free Hospital have since shown in a comprehensive series of what were 8 and now 10 peer reviewed scientific studies that the major findings of our original study were indeed correct. These papers are listed in the appendix. The papers are here and I will make them available to anyone who wishes to read them.

The sum of the research of my group and our collaborators taken together with additional work by independent physicians and scientists in the United States has now confirmed the following facts. Children with regressive autism and intestinal symptoms have a novel and characteristic inflammatory bowel disease. This disease is not found in developmentally normal control children. This disease is entirely consistent with a viral cause. This disease may be the source of a toxic or immune insult to the brain. The measles virus has been identified in the diseased intestine in the majority of children with regressive autism studied, precisely where it would be expected if it were the cause of the intestinal disease.

These children who suffer the same pattern of regressive autism and intestinal inflammation come from many countries, including the United States and Ireland where they have been investigated and biopsied independently. These biopsies have been no where near my laboratory.

Measles virus has been found in only a small minority of developmentally normal control children. The measles virus in the dis-

eased intestine of autistic children is from the vaccine. Children with regressive autism appear to have an abnormal immunal response to measles virus, as you have heard from Dr. Bradstreet, and these findings are entirely consistent with parental reports that their normally developing child regressed into autism following exposure to the MMR vaccine. As you will hear from my colleague on my left, Dr. Stejskal, these findings are also entirely consistent with an immune mediated damage to the developing child by thimerosal.

Confirmation of the intestinal findings, other researchers in the United States have confirmed the presence of intestinal inflammation in children with regressive autism and we will hear testimony from Dr. Krigsman to this effect independently, the link between measles virus and children who were given the MMR vaccine and abnormal immune responses.

Measles virus sequencing has been performed, most significantly a study due to be presented at the Pathological Society of Great Britain and Ireland in Dublin at the beginning of July has confirmed that the measles vaccine virus is present in the diseased intestinal tissues of these children. The Dublin researchers, headed by Dr. John O'Leary, professor of pathology at Trinity College, Dublin, examined viral genetic material from intestinal biopsies taken from 12 children with gastrointestinal disease and autistic spectrum disorder.

The viral genetic material had already been identified as coming from measles virus in a study published in January in Molecular Pathology. Using state-of-the-art molecular science, the samples from these 12 children have now been characterized as from the vaccine strain virus. This investigation continues. These data constitute a key piece of evidence in the examination of the relationship between MMR vaccine and regressive autism.

We heard last year about rechallenge phenomena, children who had received more than one dose of the vaccine. A further key piece of evidence comes from the examination of these rechallenge cases and biological gradient effects. I will explain what I mean by that.

Rechallenge refers to a situation where exposure of an individual to an agent, for example a vaccine elicits a similar adverse reaction to vaccine following the initial exposure. The secondary reaction associated with rechallenge may either reproduce the feature associated with the primary challenge or lead to worsening of the condition that was initially induced. In other words, Mr. Chairman, I give you a drug, you develop a rash. That could be coincidence. I give you the same drug again, you develop the same rash, that is not coincidence until proven otherwise.

During the course of our clinical investigations, we have observed some children who received a second dose of MMR or in the UK, boosting with the combined measles rubella vaccine experience further deterioration in their physical and/or behavioral symptoms as explained in Dr. Bradstreet's trial.

In a report of April 2001, the Vaccine Safety Committee of the Institute of Medicine said that in the context of MMR vaccine as a possible cause of this syndrome, challenge, rechallenge would constitute strong evidence of an association. In the context of ad-

verse reactions, a biological gradient refers to an increasing severity of the disease upon repeated exposure.

We have undertaken a systematic evaluation of rechallenge and biological gradient effects in children with regressive autism who have undergone investigation at the Royal Free Hospital. We have compared exposed children, those who have received more than one dose with those who have only received one dose to ask is there a sequential deterioration in their behavior and development compared with the group who only received one dose and is there worsening of the intestine or inflammation.

In analysis based upon the exposed and unexposed children, we find that secondary regression on the basis of three independent analyses including parental history alone, excluding those children whose secondary deterioration appeared after the publication of our first paper in 1998, or inclusion of only those children for whom we can find independent corroborative evidence in their records there is a highly significant effect in terms of secondary deterioration in the children who had two doses compared to those who only had one.

Secondary physical symptoms, for example, deterioration in their bowel disease, their bowel symptoms is present. Severe lymphoid hyperplasia, you will remember the swelling of the lymph glands in the intestine is significantly worse in the children who have had two doses, and to me as a pathologist, the most significant finding is the intestinal inflammation, a blinded observation made independently of any knowledge of the child's deterioration or their vaccination status shows that it is much worse, worse in those children who have received two doses than one.

This is something you cannot confabulate. The quality of records might not be good enough to make didactic decisions about deterioration but you cannot fake the state of a child's intestine in terms of inflammation.

These data identify rechallenge effects upon symptoms and the biological gradient effect upon severity of intestinal inflammation but provide evidence of a causal association between MMR and regressive autism.

What about the political aspects of this? I have repeatedly requested a meeting with the Sir Liam Donaldson, the UK's Chief Medical Officer, in order to discuss this situation. His response has been to refuse to meet but instead to demand that we send him the children's samples. He has provided absolutely no indication in terms of scientific protocol how he would proceed to analyze these samples. He may have a PCR machine in his kitchen for all I know. I do not know how he intends to analyze them.

He has, as far as I am aware, no ethical approval for analyzing these samples but he may be reassured to know that independent testing is being conducted and that as part of the litigation process in the UK, the defendants are being provided with identical samples for entirely independent analysis.

The last 7 days have seen a report in the journal Clinical Evidence from the UK publicized as new research, disproving any links between autism and the MMR vaccines. The author specifically excluded clinical research into the bowel disease, in other words, everything that has been performed in my laboratory.

They do not cite any of our publications beyond the initial study of 12 children in 1998. In fact, this paper does no more than review the epidemiological studies that have already been deemed irrelevant by the members of the IOM committee.

In closing, Mr. Chairman, Dr. Bradstreet's data somewhat underestimate the size of the problem. A recent study published by the National Autistic Society in the UK shows that in primary school children, those between 4 and 11, autism now affects 1 in 86 children, not 1 in 86 boys but 1 in 86 children. This is a staggering level of a disease. It is unacceptable and no society can afford to sustain this attrition of its children. Something has to be done. We have to depoliticize this process and conduct the science that is necessary to answer the questions. Thank you.

[The prepared statement of Mr. Wakefield follows:]

Testimony of Dr Andrew J Wakefield MB MS FRCS FRCPath
Oversight Committee on Government Reform
June 2002

Mr Chairman and members of the Committee,

Before bringing you up to date with the research linking MMR vaccine to regressive autism I will put the record straight with respect to Dr Gershon's testimony last year on the molecular detection of measles virus in the laboratory of Professor O'Leary. Dr Gershon's testimony was false in relation to a number of assertions, whether or not his testimony constituted perjury or simply sloppy science. It is not my wish to take up valuable time in this hearing with the details of Dr Gershon's unacceptable errors. All correspondence and raw data have been provided to the ranking majority and minority members. Merely by way of illustration, he stated that tissues from experimental animals not infected with measles virus were positive in Professor O'Leary's lab. In fact they were all entirely and consistently negative on repeat testing. Dr Gershon's behaviour was a disgrace. I would level the same charge at anyone who relies or has relied in any way upon this testimony. I am not surprised that Dr Gershon turned down the offer to appear before this committee. Had he done so, I am sure he would have enlightened the Committee, somewhat belatedly, as to any proprietary rights his wife might have in the Merck chickenpox vaccine patent.

The current sate of the science:

The association between MMR vaccine, autism and intestinal inflammation was first suggested by my group from the Royal Free Medical School in 1998 in a paper published in the Lancet. The same research team, in collaboration with Professor John O'Leary and Dr Simon Murch from the Royal Free Hospital, has since shown in a comprehensive series of eight peer-reviewed scientific studies that the major findings of our original study were correct. These papers are listed as an appendix.

The sum of the research by my group and our collaborators, taken together with additional work by independent physicians and scientists in the United States has now confirmed the following facts.

- Children with regressive autism and intestinal symptoms have a novel and characteristic inflammatory disease of their intestine (1-4).
- This disease is not found in developmentally normal control children (2-4).
- This disease is entirely consistent with a viral cause (5-8).
- This disease may be the source of toxic damage to the brain (9).
- Measles virus has been identified in the diseased intestine in the majority of children with regressive autism studied, precisely where it would be expected if were the cause of the intestinal disease (5,8).
- These children, who suffer the same pattern of regressive autism and intestinal inflammation, come from many countries including the US and Ireland where they have been investigated and biopsied independently.
- Measles virus has been found in only a small minority of developmentally normal children (5).
- The measles virus in the diseased intestine of autistic children is from the vaccine (11).
- Children with regressive autism appear to have an abnormal immune response to measles virus (1a,2a)
- These findings are entirely consistent with parental reports that their normally developing child regressed into autism following exposure to MMR vaccine (1,11).

Confirmation of intestinal findings

Other researchers in the US have confirmed the presence of intestinal inflammation in children with regressive autism (3a & see testimony of Dr A.

Krigsman MD) and, independently, the link with measles virus in children who were given the MMR vaccine (12,13).

Measles virus sequencing

Most significantly, a study due to be presented at the *Pathological Society of Great Britain and Ireland*, in Dublin at the beginning of July has confirmed that the measles vaccine virus is present in the diseased intestinal tissues of children with regressive autism.

The Dublin researchers headed by Dr John O'Leary, Professor of Pathology at Trinity College Dublin, examined viral genetic material from intestinal biopsies taken from 12 children with gastro-intestinal disease and an autistic spectrum disorder. The viral genetic material had already been identified as measles in a study published in January in Molecular Pathology. Using state of the art molecular science the samples from these twelve children have now been characterised as from vaccine strain measles virus. This investigation continues. These data constitute a key piece of evidence in the examination of the relationship between MMR vaccine and regressive autism.

Re-challenge and biological gradient effects for MMR/MR vaccines

A further key piece of evidence comes from examination of "re-challenge" and "biological gradient" effects for possible vaccine-related adverse events.

Re-challenge refers to a situation where re-exposure of an individual to an agent (e.g. vaccine) elicits a similar adverse reaction to that seen following the initial exposure. The secondary reaction associated with re-challenge may either reproduce the features associated with the primary challenge, or may lead to worsening of the condition that was provoked or induced by the initial exposure.

During the course of our clinical investigation we have observed that some children who received a second dose of MMR, or boosting with the combined

measles rubella (MR) vaccine, experienced further deterioration in their physical and/or behavioural symptoms following re-exposure. In a report of April 2001, the Vaccine Safety Committee of the US Institute of Medicine (IOM) stated that, in the context of MMR vaccine as a possible cause of this syndrome, "*challenge re-challenge exposed would constitute strong evidence of an association*"[1].

In the context of adverse vaccine reactions, a biological gradient refers to an increasing severity of, or increased risk of developing, a particular disease outcome. More severe bowel disease in children with regressive autism who had received more than one MMR/MR would be an example of this.

We have undertaken systematic evaluation of re-challenge and biological gradient effects in children with regressive autism who have undergone investigation at the Royal Free Hospital.

"*Exposed*" – children with normal early development & regressive autism who had received more than one MMR/MR - were compared with age and sex matched "*unexposed*" – children with normal early development & with regressive autism who had received only one MMR but otherwise similar baseline characteristics to the exposed group. Comparisons included: secondary (2^o) developmental/behavioural regression; 2^o physical deterioration, prospective, observer-blinded scores of endoscopic & microscopic disease severity.

In a preliminary analysis *exposed* children scored significantly higher than *unexposed* children for:

(i) secondary regression on the basis of analyses performed at the different levels, including :
   - parental history

[1] Stratton K., Gable A., Shetty P., McCormick M. Immunization Safety Review: Measles-Mumps-Rubella Vaccine and Autism. National Academy Press. Washington DC. 2001. www.iom.edu/imsafety

- excluding those whose secondary regression occurred following publication of the 1st suggested MMR-autism link in 1998; and,
- inclusion of only those for whom independent corroborative evidence of secondary regression was obtained from the records;

(ii) secondary physical symptoms;

(iii) presence of severe ileal lymphoid hyperplasia; and,

(iii) presence and severity of acute mucosal inflammation.

No measures of disease were worse in *unexposed* than *exposed* children.

These data identify a re-challenge effect on symptoms and a biological gradient effect on severity of intestinal inflammation that provide evidence of a causal association between MMR and regressive autism in these children.

I have repeatedly requested a meeting with Sir Liam Donaldson the UK's Chief Medical Officer to discuss the situation. His response has been to refuse to meet, but instead to demand that we send him the children's samples. He has provided absolutely no indication, in terms of scientific protocol, how he would proceed to analyse these samples. He has, as far as I am aware, no ethical approval for analysing these samples. He may be reassured to know that independent testing is being conducted and that as part of the litigation process in the UK, the Defendants are being provided with identical samples for independent analysis.

The last seven days have seen a report, in the journal Clinical Evidence, publicised as "new research" disproving any links between autism and the MMR vaccine. The authors specifically excluded clinical research into bowel disease, immune disorders and other documented features of autism that may relate to a viral cause. They do not cite any of our publications beyond the initial study of 12 children in 1998. In fact, the Clinical Evidence paper was no

more than a review of the epidemiological studies, including the Davis study that will be critically reviewed during this hearing, that have already been dismissed as irrelevant by an independent review commissioned by the Institute of Medicine in the US.

Key Publications by Wakefield/O'Leary groups

1. Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, et al. Ileal LNH, non-specific colitis and pervasive developmental disorder in children. Lancet 1997; 351: 637-641.
2. Wakefield AJ, Anthony A, Murch SH, Thomson M, Montgomery SM, Davies S, et al. Enterocolitis in children with developmental disorder. American Journal of Gastroenterology 2000; 95:2285-2295
3. Furlano RI, Anthony A, Day R, Brown A, McGavery L, Thomson MA, et al. Colonic CD8 and γδ T cell infiltration with epithelial damage in children with autism. Journal of Pediatrics 2001;138:366-372
4. Torrente F, Machado N, Ashwood P, et al. Enteropathy with T cell infiltration and epithelial IgG deposition in autism. Molecular Psychiatry 2002;7:375-382
5. Uhlmann V., Martin CM., Shiels O., Pilkington L., Silva I., Lillalea A. Murch SH., Wakefield AJ., O'Leary JJ. Potential viral pathogenic mechanism for new variant inflammatory bowel disease. Molecular Pathology. 2002;55:1-6
6. Kawashima H., Takayuki M., Kashiwagi Y., Takekuma K., Hoshika A., Wakefield AJ. Detection and sequencing of measles virus from peripheral blood mononuclear cells from patients with inflammatory bowel disease and autism. Digestive Diseases and Sciences. 2000;45:723-729
7. Wakefield AJ and Montgomery SM. Measles, mumps, rubella vaccine: through a glass, darkly. Adverse Drug Reactions & Toxicological Reviews 2000;19:265-283.

8. Wakefield AJ and Montgomery SM. Autism, viral infection and measles mumps rubella vaccination. Israeli Medical Association Journal 1999;1:183-187

9. Wakefield AJ, Puleston J., Montgomery SM., Anthony A., O'Leary JJ., Murch SH. Review article: the concept of entero-colonic encephalopathy, autism and opioid receptor ligands. Alimentary Pharmacology and Therapeutics 2002; 16: 663-674

10. Shiels O., Smyth P., Martin C., O'Leary JJ. Development of an allelic discrimination type assay to differentiate between strain origins of measles virus detected in intestinal tissue of children with ileocolonic lymphonodular hyperplasia and concomitant developmental disorder. Pathological Society of Great Britain and Ireland. Journal of Pathology. 2002 .A20

11. Wakefield AJ, Anthony A. Clinical characteristics of children with autism and entero-colitis comparing recipients of one and more than one measles-containing vaccine (submitted).

Publications by others

1. a. Singh V., Lin S., Yang V. Serological association of measles virus and human herpesvirus-6 with brain autoantibodies in autism. Clinical Immunology and Immunopathology. 1998:89;105-108

2. a. Singh VK. Neuro-immunopathogenesis in Autism. 2001. New Foundations of Biology. Berczi I & Gorczynski RM (eds) Elsevier Science B.V. pp447-458

3. a. Horvath K, Papadimitriou JC, Rabsztyn A, Drachenberg C, Tildon JT. Gastrointestinal abnormalities in children with autism. Journal of Pediatrics 1999; 135: 559-563

Mr. BURTON. Before we go to the next witness, I believe other scientists who have differed with the prevailing opinions have suffered similar castigation as you have. You may rest assured that eventually the truth will out. Louis Pasteur found that out after 17 years when he was knighted, so eventually the truth will come out and those who criticize and continue to denigrate what you have done will be eating a heck of a lot of humble pie.

Dr. Stejskal.

Dr. STEJSKAL. I am honored to be here and this is my first testimony. In this limited time, I am going to tell you why I am here and what are my credentials.

I have been working for 20 years in pharmaceutical industry directing a group of clinical immunotoxicologists so I have been working with allergy to simple chemicals like mercury for 20 years.

What I am going to tell you is the fact which has not been mentioned here before, to my big surprise, and this is that thimerosal in clinical setting is a strong allergen. You can learn about it more by looking on our Web site which I will show later where I compiled the studies from all over the world telling us that thimerosal obviously due to vaccination is No. 1 childhood allergen, meaning that if you are getting a special testing, which I will tell, 10, 20, 30 percent of the children are allergic.

I will tell you why this is risky to be allergic if you don't know this and I will also tell you how it goes together, opening ways to autoimmunity and at the end to be constructive. I will tell you how to diagnose the causes which are leading to autism and what studies should be conducted.

I been also asked to see if it is plausible that there is a synergistic reaction between thimerosal and MMR and yes, it is and I will tell you why.

You are well acquainted with the fact that mercury, not organic mercury only but also inorganic mercury, will damage the brain, especially organic mercury because it is lyophilic, it will easily go to the brain. There are some ways we call retrograde transport. If someone wants, it is on our Web site. So in addition to toxicity, which is very important which can damage, you also have to worry about allergy.

Allergy is a thing which explains to us why not every child is affected by vaccination. This is something which is very important. As you know, some children cannot eat eggs, some others cannot ride a horse because they are allergic to horses, and some don't eat fish, people don't either, which is also very important. Allergy affects the brain. As you know, in spring when there is pollen around, people become sleepy, they cannot concentrate. This is due to the chronic inflammation which is affecting the brain. This may be part of the answer why Dr. Wakefield sees inflammation in the stomach affecting the brain. This is another reason why we can see that in certain children, especially the autistic ones, also other types of allergies like food allergy, increased denigration of the immune system.

This is very simply showing you that we are not equal. Genetics determines our detox capacity. This will explain to us that we have a subgroup of children and subgroup of adults which will not properly handle the overload of toxins and allergens.

Thimerosal as an allergen, it is worldwide known for years since 1970's that if you are doing special testing for a special type of allergy which is lymphocyte mediated allergy, so-called delay type sensitivity or cellular hypersensitivity, you find that actually thimerosal is superseding nickel in the frequency of sensitization worldwide.

If you look at a few studies which have been done comparing East and West Germany, you see that the East Germany allergy was very low and it started to rise after those two merged. You wonder why that is so. It may be that the most strict regime of vaccination couldn't do something against this.

How do you test for this important allergy to thimerosal and other things? You do it by so-called patch testing. In patch testing, you put your putative allergen, the things you would like to see if you are allergic, on the skin in the back. I have to say again I read some witnesses from CDC and others claiming that thimerosal is perfectly safe because the only thing we could see is its local reaction on the skin. These people do not remember from the years it is cool that allergy is never a local phenomena. Allergy is a systemic phenomena, governed by special types of white blood cells which are circulating in the body.

If somebody tells you that there is only local reaction, this is a lie or incompetence but this is not true. Allergy is a systemic reaction and anywhere in the body where there is foreign agents, for example, thimerosal, the reaction will occur and this is inflammatory reaction.

We are doing patch testing. You read on my Web site there are thousands and thousands and thousands of people patch testing telling you that especially children are very strongly sensitized. I think the data from Germany shows that children 8 years or less have actually sensitization rate in those which are tested, people with skin problems, 20 to 30 percent which is quite amazing.

The other test which can be used, especially should be used in children because it is not so good to put the allergen on the skin because you become resensitized, is so-called blood test or lymphocyte transformation test. This test has been used for years in America for detection of people who are sensitized to different occupational allergens, for example beryllium. Beryllium specific stimulation tests is used as a golden standard in America to detect latent sensitization to beryllium prior the clinical outcome.

So pharmacologic factories and those who are using beryllium in industry have realized you can save a lot of suffering like long term sickness and sarcoidosis to detect by bio markers because now we are looking at the markers of susceptibility, the people or children which are susceptible to the agents which others tolerate.

So with Melisa, you take a blood test, the Melisa stands for optimized lymphocyte proliferation test and memory lymphocytes. You take a blood sample and you ask if the body has stored the information of allergy to certain circumstances. If it is yes, there is a sensitization, then you can see it objectively by increase in the volume of lymphocytes and you can measure it objectively. If there is no such allergy, that means the person is genetically not able to respond, there is no difference. I will in the end show some cases of this.

If you forget everything, you remember this. Thimerosal and autoimmunity are the two sides of the one coin. That means you can never separate. Why is this? This is because mercury, not only mercury, nickel and other metals, will strongly bind to a certain immunoacid in our body which contain SH groups. These groups are everywhere. They are in two aminoacids which are called methionine and cystine and are especially rich in fat tissues. As you know, the brain is full of fat, so that is why mercury will go into the brain and it will find there, for example, in so-called myelin protein. This is the reason why Dr. Singh can measure increased antibodies, again myelin, in many of those children.

Since there are physical chemical properties which are undisputable, mercury will bind in the brain and elsewhere, where do we find these things? It will go there, it will bind there and then your genetic susceptibility if you can make it or not make it will explain why some will be ill while others will not.

MMR and thimerosal, there is no way I can comprehend that there is a concern about synergistic adverse effects upon the immune system of susceptible children if you put those things together. So you can buy immunosuppression, which is the other way mercury works, you can lower the threshold of protection against the virus, meaning in this time there will be persistent viral infection instead of the limited one.

There is a fact which you may or may not know. This is that in my country in Sweden, thimerosal has been removed from vaccines since 1998. One of the reasons for it is a report on the pharmaco working party of the European Agency for Medical Products. They basically say that alteration of the immune system due to mercury could have consequences on the ability of the host to withstand viral attack.

So Swedish people made a lecture and since I have been working in toxicology laboratories for 20 years, I know there is always risk assessment and they decided they don't want to take the risk.

The conclusion for this general part is yes. I really believe there is a connection between synergistic effect of thimerosal and MMR and there is a group of susceptible individuals which we may detect even prior and they will be affected and will be ill.

Some were published and some were not. Just to show you how we work with this, the big guys, lymphocytes, which are now stimulated, in culture outside the body, this test is a blood test, and the big guys are lympoblasts and the small ones are the ones which are not affected.

Since I was talking about patch testing as an instrument or device to look on the special type of hypersensitivity which has no counterpart in the serum, we studied these in 1992, we have taken which have positive patch tests and looked for the lymphocytes just to prove this is not only back reactions, it is a systemic reaction driven by lymphocytes.

This woman has a muscle inflammation and she also has been susceptible to infections and chronic fatigue. She was patch tested in 1991 and positive to thimerosal. I am looking on different mercuries because this part goes together, everything I say now can be actually applied to dental fillings and you can look on our Web site.

In 1991, she had thimerosal positive patch test, in 1992 we did Melisa test. This is exposure. We are always looking into the exposure. From this point of view, she had occupationally exposed to inorganic mercury, had 17 amalgam fillings, she was exposed to ointment which contained thimerosal and she received gamma globulin and other vaccines at least 16 times.

You can see now a diagram of her lymphocyte reactivity to different metal salts. This can be difficult for you to follow but the horizontal line shows the line of positivity and the rest is very, very strongly positive. This is from a published paper which you can download on the Internet.

This patient has been treated by mercurochrome another organic mercury. You can see the huge red staples showing extreme sensitization to mercurochrome but not at all sensitization to other mercury compounds meaning that both in patch testing and in lymphocyte testing you an actually see no cursory activity between inorganic and organic mercury but there is one cursory activity and this is between ethyl mercury and methyl mercury, meaning we are very much afraid that any sort of sensitization to one may cross react and deteriorate and heighten the response to other ones. They are patch test results.

Mr. BURTON. Doctor, could we submit the rest of your testimony for the record. We will have questions for you and you can elaborate then.

Dr. STEJSKAL. I just would like to finish with the data on autistic children two of them. This study is done together with scientists from Center for Pediatric Health in Belgium, Antwerp from a group of Austrian researchers, from some American scientists and from some Swedish scientists. The study is still continuing. I am just showing some case reports.

This is an Austrian guy, 14 years old with mild autism, lactose intolerance and vaccinations. There is a causal relationship of vaccines to his deterioration.

The next one shows you the nonresponsiveness to inorganic mercury, strong reactivity thimerosal, cross reaction to methyl mercury and no reaction to nickel and cadmium.

This is a Belgian boy, 5 years old, from John Cronenberg a pediatrician in Antwerp. He was healthy at birth, got first instance of autism as a baby, strong aggravation of symptoms at 15 to 18 months. He was diagnosed with autism at 11 months of age. He has digestive problems, food sensitivity, dairy products, skin lesions, eczema, rashes and irritation from metallic contact. Mother had dental work during pregnancy.

This is the schedule of vaccination in Belgium. They don't vaccinate at birth. You are the only ones who do. At 3 months, 4 months, 5 months, 7 months, at 2 years, several vaccines at once. This is his reactivity. In this case, there is thimerosal and methyl mercury.

In conclusion, I would like to say that preliminary data show the theory that thimerosal containing vaccine may be a co-factor in the development of autism in genetically susceptible children. I would like to tell you what I would like to have for future studies because there is no sense you give millions and millions to waste the time for nothing.

What we learned about the allergic reactivity to simple compounds, for example, mercury, regardless if it is inorganic or organic is that rats and mice are not suitable. One of the reasons is that they produce their own cyton. It is not a man and we don't do it. Cyton will protect against metals.

The second thing is you have to do a biomarker screening for susceptible children and there is a notion from a paper on our Web site published by my daughter which says the increased knowledge about individual sensitivity based on genotype and phenotype variability together with the markers for the diagnosis of individual susceptibility seems to be the key in elucidation of operative mechanisms of any autoimmune disease and also autism.

Thank you.

[The prepared statement of Dr. Stejskal follows:]

Testimony for Committee on Government Reform June 19, 2002

Vera Stejskal
Associate Professor of Immunology
University of Stockholm
President of MELISA MEDICA Foundation
Danderyd, Stockholm, Sweden

Central Question

Thimerosal ⟹ Autism

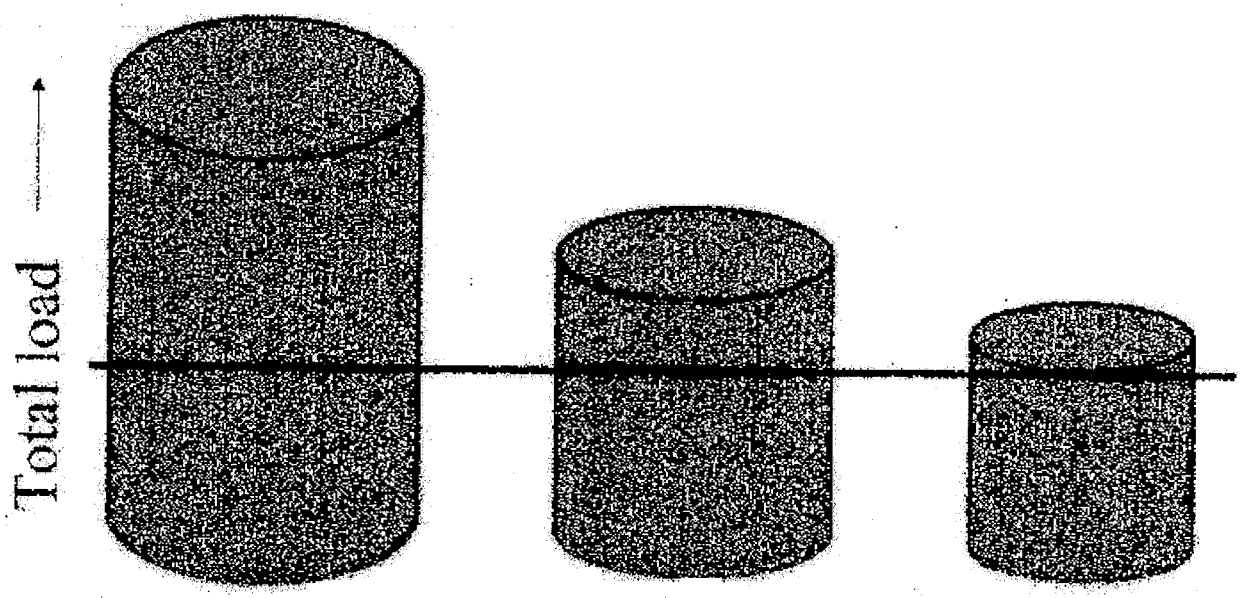
MMR ⟹ Autism

- Are the two hypotheses compatible?

Mercury and the immune system

- Organic mercury damages the developing immune system in three ways:
  - Toxicity
  - Allergy
  - Autoimmunity

Genetics determines detox capacity



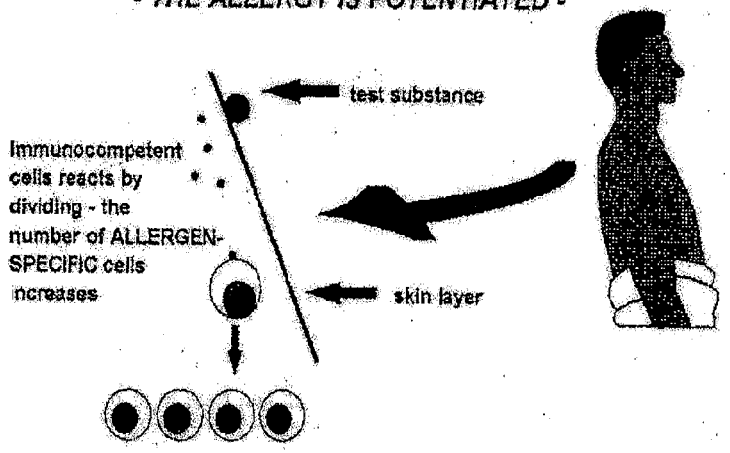
Thimerosal as an allergen

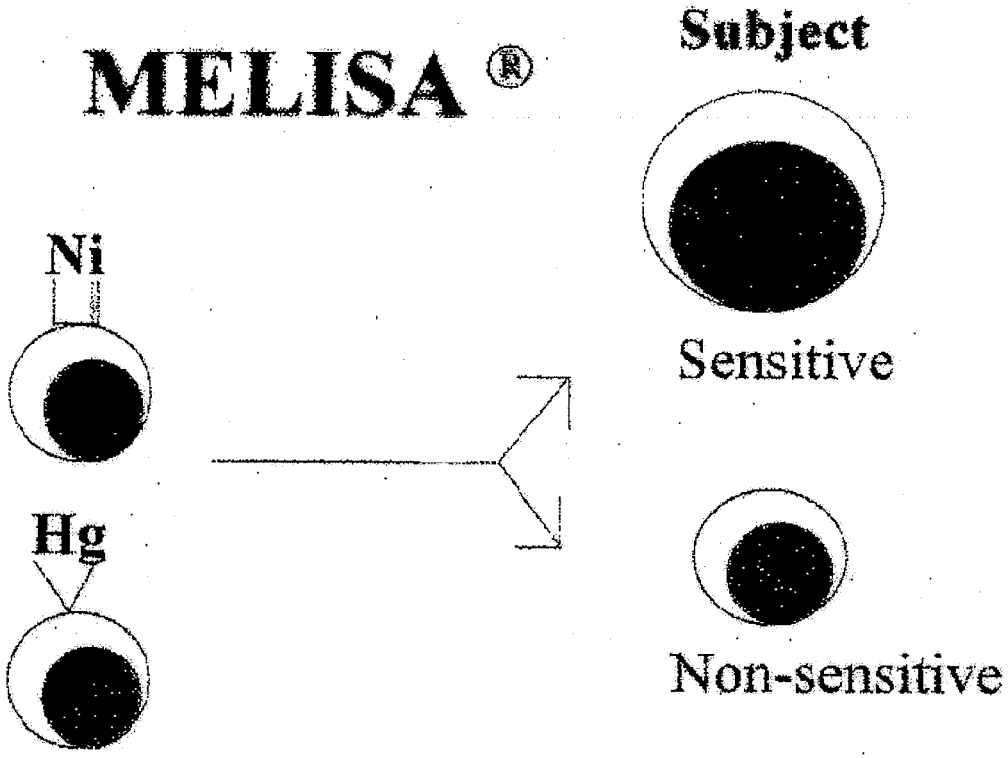
- Thimerosal is among the strongest allergic sensitizers in children
- Diagnosed by "patch testing" or blood test

Patch Testing

BY USING SKIN-TEST AN ALREADY SENSITIZED INDIVIDUAL IS EXPOSED TO THE ALLERGY-CAUSING AGENT

- THE ALLERGY IS POTENTIATED -





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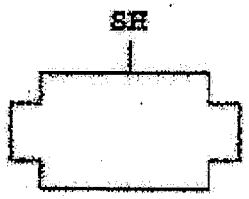
Thimerosal and autoimmunity

- Allergy and autoimmunity – two sides of the same coin

METALS HAVE AFFINITY FOR SH-GROUPS IN PROTEINS..

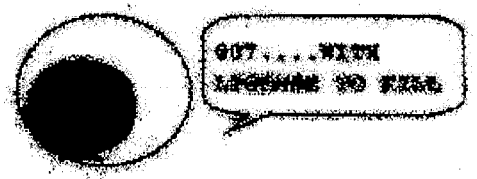
AUTOLOGOUS PROTEIN



DOES NOT STIMULATE THE IMMUNE SYSTEM

CHANGED AUTOLOGOUS PROTEIN

STIMULATES THE IMMUNE SYSTEM = AUTOIMMUNITY !



MMR and Thimerosal

- Synergistic adverse effects upon the immune system of susceptible children
- Triggering allergy and autoimmunity
- Autism

Mercury and viruses

- Mercury weakens the immune system making a child less able to handle a virus or a live viral vaccine
  - Viral persistence
  - EMEA statement

Conclusion

- Yes, the Thimerosal-MMR hypotheses **are** compatible

Future studies

- Primates and humans – not mice
- Biomarker screening for susceptible children
- Longitudinal rather than case control studies

Mr. BURTON. Thank you, Doctor. We will have questions for you later.

Dr. Krigsman.

Dr. KRIGSMAN. Thank you for having me today.

The purpose of my appearance today is to report to the committee the status of my findings regarding my research into the intestinal inflammation in autistic children.

We have done a retrospective survey and collected intestinal biopsy specimens from 43 patients. These 43 patients were mostly referred from private practitioners who were caring for their overall autistic medical issues, among them their GI symptoms. After chronic frustration and inability to control mainly symptoms of diarrhea and constipation, these patients were referred to me. Other patients came on their own after often years of frustration with these symptoms.

Of the GI symptoms that these children have been seen for mostly it is diarrhea. Many also have constipation. A large number have both diarrhea and constipation alternating. The stools are severely malodorous, one of the most common things we hear parents talk about is the entire house smelling when these children have a bowel movement in the basement.

Abdominal pain is a very, very common symptom. Most of the kids are noncommunicative and when they have pain they either just scream and wail and fall to the floor having tantrums, unexplainable crying, which could last for half a hour to an hour.

There are problems sleeping at night, waking up in the middle of the night screaming. Parents intuitively feel that these symptoms are due to pain. Sometimes there is an objective observation as such, holding their belly but more often than not it is just unexplainable crying.

Abdominal distention is another symptom and poor growth. The growth is a very interesting issue. I have seen that most of the children with regressive autism fall in the bottom 10 percentile on the growth charts and weight for age. We have not found that their height for age is similarly affected. I don't have an explanation for that but their weight for age, most of these kids are skinny kids.

The male to female ratio of these 43 patients is 7 to 1. Who said that these kids are autistic? The diagnosis was made either by a pediatric neurologist, a developmental pediatrician and for the most part parents have gone to both and even a third opinion. In no patient was the diagnosis in dispute.

When I first meet with these patients, we do a routine evaluation for what is often diarrhea, constipation, we get a complete blood count, sedimentation rate, chemistry. To most of you these tests are meaningless; to a gastroenterologist or parents they are very, very meaningful.

These tests look for specific reasons, specific diagnoses that can cause these GI symptoms these kids complain of. We do stool cultures, we look for parasites, we look for occult blood in the stool. We go over their diet, make major revisions in their diet, remove carbohydrates, remove sorbitol from their diet, take them off gluten and casein and pretty much without exception, none of these interventions help and none of these tests show anything that would explain why these kids have chronic diarrhea, constipation and pain.

At that point, I perform a colonoscopy, along with biopsy. We will look at the entire colon and not just the colon but more importantly the very end of the small bowel which is the terminal ileum the area that Dr. Wakefield had described as involved in these diseases.

I should mention that as recently as 2 years ago, I would never have put a colonoscope in any of these children. I didn't feel it was justified or appropriate. I didn't know what I would be looking for, and I wouldn't do it even though I had seen quite a number of them. It wasn't until I read Dr. Wakefield's article of September 2000, American Journal of Enterology where he described the biopsy findings in over 60 patients and he described a pattern of colonic inflammation that could explain their symptoms. It wasn't until I read that article—I read it about seven times actually in one night because I just couldn't believe it. After reading it over and over, I decided that I could not find any valid criticism to the article. I felt justified at that point to perform these colonoscopies myself.

At the outset, I will say that our findings, which are independent of Dr. Wakefield's findings, completely support his explanation and his observations of the abnormalities that are found in the bowels of these children.

I also performed an upper endoscopy looking at the esophagus and stomach. I performed that test in those children who based upon the histories as related by the parent. If those histories contained abdominal pain, a story of pain, then we needed to rule out any esophageal or esophagus problems, stomach problems, intestinal inflammation, infection, and so forth.

I am showing now a series of slides, actual photographs that are taken during the colonoscopies to give you a visual idea of the extent of abnormality that we find. As you will see, these are not normal.

This first slide is normal. This is a terminal ileum, the area at the end of the small bowel in a normal patient. What you can see in the photo on the right, if you look carefully you will see very small bumps, almost indiscernible. Those are enlarged lymph nodes but those aren't normally enlarged lymph nodes. Those are the kind of lymph node enlargements you see in normal small bowel.

In contrast, the upper row of photographs—can you dim the lights?

Mr. BURTON. She said it would not be good.

Dr. KRIGSMAN. It is a pity because I think the effect would be greater.

Mr. BURTON. You said we cannot dim the lights? The TV cameras then can't pick up what you are doing and I think that is important that the American people get a chance to review all this.

Dr. KRIGSMAN. Absolutely.

The upper row, three across, show marked nodularity, marked abnormality, numerous small lumps and bumps.

Another patient, same exact finding.

Another patient, you are looking down the tube of the small bowel, along the right side on the wall those large nodular bumps. This is not normal.

I call your attention to the upper left and those large bumpy nodules are the ileal tissue that Dr. Wakefield first described. On the right side, same patient, a view from a bit further away, upper right corner.

Another patient, same finding.

Same finding, upper right corner in both those pictures.

Upper right corner on both pictures, those large nodular bumps.

Same thing, lower left half of the slide.

Same thing from another patient, all over the mucosa of the ileum there is nodularity.

This particular patient didn't have as much nodularity as they have swelling. The medial term is edema and is one of the byproducts of ongoing inflammation.

Same thing. Next patient.

This is a very dramatic photograph. If you look in the middle downwards in both of those pictures, there is actually normal mucosa but on both sides of the mid line you see marked nodularity.

Same thing.

Again.

These are all different patients.

Same thing once again and again.

This patient I included because the lower two photographs show the same modularity. The upper two photographs are of the colon and if you look carefully, you will see very small minute nodules scattered around the mucosa. Not only are these nodules present in the ileum of these patients, they are also present scattered throughout the colon.

Same thing.

Same thing.

This patient, the inflammation was so bad in the colon that he formed what is called a pseudopolyp and the polyp is recognizable to all. It actually is not really a polyp. What has happened in this patient is the surrounding tissue is so inflamed and eroded that what is left is the polyp. Everything else has eroded around it.

This patient I just saw yesterday. This is the final patient I will be showing you. This is the oldest patient that I have done a colonoscopy on. He is 13 years old, autistic. The regression history is not clear, it has been many years with a chronic history of one to two bowel movements a day, always very loose, dismissed by the pediatrician. Over the last 3 months, this child's diarrhea has become uncontrollable, 10 to 15 times per day. He is incontinent all of a sudden. He never was incontinent. His behavior has been intolerable, aggressive, throwing tables over and his parents are at the verge of institutionalizing him because of this recent worsening over the last 3 or 4 months.

His mother found me out and I did the colonoscopy just yesterday. This child has the absolute worse colitis I have ever seen. Most of these kids, when you put the scope up the colon, the colon appears normal and it is only on biopsy that you find the abnormalities. In this particular child, the inflammation was so bad, it has obtained the characteristics of classic inflammatory bowel disease. If you saw this colon, you would think this patient has ultrative colitis or Crohn's disease.

What is interesting about this patient, and Dr. Wakefield might be interested particularly in this slide, is that the photo on the left is the bottom of the esophagus and in the area of about 3 o'clock, you see a white little nodule. That is an abscess ulcer which is something you see in classic inflammatory bowel disease. You find those ulcers anywhere in the GI tract. The photo on the right is the upper esophagus, the upper esophageal sphincter and you can see there are two nodules there as well, two more abscess ulcerations as well. I am wondering if this patient doesn't have just autistic enterocolitis but actual inflammatory bowel disease. The biopsies are still pending.

I am going to bypass these slides because I want to point out that the area of the round ball on the right is the microscopic view of those big nodules that you saw grossly.

The circle in the middle you see here is the crypt in the intestine and on the left side of the crypt you see there seems to be small little black dots. This is a cryptitis, this is one of the classic findings of bowel inflammation which we have seen over and over and over in these patients exactly as described by Dr. Wakefield.

The is the same view. The crypt in the middle in particular is being invaded by inflammatory cells. It is a very heavy inflammatory throughout the mucosa.

Same thing here. One more slide.

So looking at our 43 patients, what are our cumulative results? The percent of patients who had colitis, 65 percent, meaning either active colitis or chronic colitis, there is a difference, active colitis, 51 percent of the patients had that, chronic colitis, 40 percent. Most patients had both which is why the overall colitis indicator is 65 percent.

A third type of colitis is the cosinophilic colitis, also described by Dr. Wakefield. We have a 7 percent number, very similar to his number.

The percentage of patients that had the large nodularities of the ileum we found to be 90 percent, also very similar to Dr. Wakefield.

Thirty-five percent of our patients had no form of colitis. However, even though they did not have colitis or inflammation on biopsy, all of them without exception had abnormal lymphnodes so they are not normal even though there is no colitis.

This is my last slide. I would like to conclude that our study is ongoing. We have a control group in place. We are waiting for our formal IRB approval to sit down with one designated pathologist, the gastrointestinal pathologist specialist on preagreed-upon pro forma to define the grade of colitis, types of colitis and with one definition to give you all the slides we have done from all 43 patients plus our control group and publish our results and make them known.

The question I would like to explore in our publication is if you compare regressive autistic children with non-regressive autistic children, is the incidence of colitis the same or will it be different? I would like to go over the growth of these children and compare the growth of children both in regressive groups and non-regressive groups and see if we find a percentile difference when we compare the two groups.

Finally, because it is our hypothesis that children with regressive autism will be those who are most likely to exhibit growth failure, and also that if we trace back their growth charts to early infancy, I suspect we will find for the first year of life, they were growing normally, closer to the median and somewhere near the onset of their autistic symptoms, I suspect we are going to find that they began to show evidence of growth failure along with their autism which suggests that their autistic symptoms and their GI symptoms are related.

Thank you very much for having me.

[The prepared statement of Dr. Krigsman follows:]

Testimony before Congressional Oversight Committee on Autism and Immunization by Arthur Krigsman MD

Mr. Chairman and members of the committee:

This testimony represents the scientific findings of data accumulated over the past year and a half from autistic children during the course of standard evaluations of their gastrointestinal symptoms. This testimony should in no way be taken as anti-vaccine. Children in my pediatric practice continue to receive all vaccinations in accordance with the guidelines set forth by the American Academy of Pediatrics. The observations expressed herein are my own, and do not represent the opinions of any institution, organization, clinic, or medical practice with which I may be associated.

My involvement with autistic children began approximately one and a half years ago. At that time, I was approached by a colleague who was caring for a large number of autistic patients. He observed that a large proportion of these patients suffered from chronic, unexplained gastrointestinal symptoms and that these symptoms were a source of great anxiety to the parents. I agreed to evaluate them, and my findings are detailed below. The evaluations undertaken were standard "textbook" evaluations of children with chronic diarrhea, constipation, and abdominal pain, uninfluenced by the fact that these children were autistic.

Patient Population

Our experience consists of a total of 43 consecutive children aged 2-10 years of age. Most were referred by private practitioners but many were self referred after much frustration with their children's ongoing discomfort. 42 patients had received a diagnosis of either autistic disorder or autistic spectrum disorder by a pediatric neurologist or developmental pediatrician. Many children had received independent confirmation from a second or even a third pediatric specialist. In no instance was the diagnosis disputed by a second specialist. The remaining patient carried a diagnosis of Aspergers syndrome.

The majority of patients had a clear history of developmental regression. Specifically, these children developed in an entirely normal fashion for the first 12-18 months. They typically had a vocabulary of 15-25 words,

maintained normal eye contact, were playful and interactive, and were not overly irritable. At some point during this age interval of 12-18 months, they had either a precipitous or gradual decline in all the above mentioned developmental markers, and this was accompanied by the appearance of typical autistic behaviors, "stimming", and bouts of unexplained irritability. In some patients, verbal stagnation, but not regression occurred. However, in these patients, clear regression was seen in the interactive and social skills of the children.

The majority of patients are from the northeastern United States. The ratio of males to females was 7:1.

Symptomatology

The most common gastrointestinal symptom noted by the parents was diarrhea. In some children, the diarrhea took the form of a soupy liquid that occurred 4 to 7 times per day and would frequently leak from the child's diaper. However, the majority of parents reported a stool frequency of 1-3 per day with a consistency of mashed potatoes. The stool is particularly malodorous, and usually contains pieces of undigested foods. Irritability is often noted just prior to the bowel movement.

Constipation is another frequent complaint, consisting of bowel movements every 3-6 days and typically accompanied by great irritability upon passage of the stool. The consistency of the passed stool was not overly hard, suggesting that these children are actually withholding stool and not truly constipated in the strict sense of the term. This constipation is often accompanied by abdominal distension and flatulence. Most patients experienced periods of diarrhea alternating with periods of constipation.

Abdominal pain is another frequent complaint. Most of these children are poorly communicative, and parents often rely on body language cues in determining that their child is experiencing abdominal pain. Children often drop unexpectedly to the floor howling and screaming. This often lasts for up to half an hour. Many children clutch their abdomen and bend over. Some assume a fetal position on the bed or floor, and others take the parents hand and rub their abdomen.

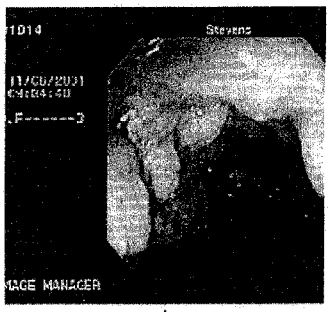
Finally, we have noticed that most regressive autistic children show poor growth, with the majority falling in the lower 10^{th} %tile weight for age. Interestingly, there does not seem to be a concomitant percentile deficit in height for age.

Evaluation

All children underwent initial evaluation of their gastrointestinal symptoms. This included a thorough history and physical exam, complete blood count with platelets, erythrocyte sedimentation rate, serum chemistries, celiac antibody panel with serum IgA, inflammatory bowel disease serology, and stool examination for ova and parasites, culture, and occult blood. The patients diet was thoroughly reviewed to assure that it did not contain excessive nonabsorbed carbohydrates or fruit juices. Therapeutic alterations in the diet were undertaken, including the removal of all gluten and casein containing foods. Medications and supplements were reviewed to assure that they did not contribute to the symptoms.

The evaluation above invariably did not lead to a diagnosis and patients then underwent colonoscopy. Upper endoscopy was performed only if pain was a predominant complaint or if celiac disease was strongly suspected.

Findings



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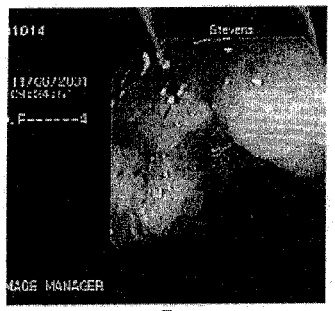

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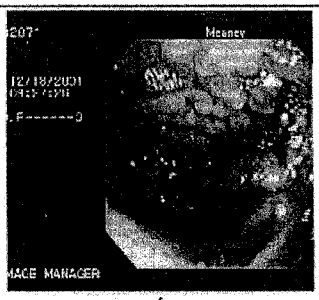
M.D.
Patient ID: 1654674 **Referring Phys**
Exam Date: 12/18/2001



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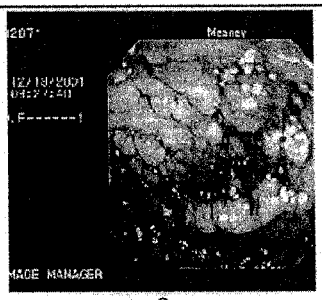

2

The above images depict the terminal ileum in two patients. They are representative of the gross endoscopic findings of 90% of these patients in whom the lymphoid nodules of the terminal ileum were found to be markedly enlarged. This is in agreement with the previously published findings of Dr. Wakefield in which a similar proportion of patients were found to have abnormal lymphonodular hyperplasia of the terminal ileum.

The second significant finding in our series was on histologic evaluation of the biopsy specimens. The results are summarized below.

% patients with colitis	28/43	65%
% patients with active colitis	22/43	51%
% patients with chronic colitis	17/43	40%
% patients with eosinophilic colitis	3/43	7%
% LNH (macro) of terminal ileum	36/40	90%
% neither active, chronic, nor eosinophilic	15/43	35%

Colitis was determined as per the report of the institutional pathologist. The interpretation of whether the degree of inflammation represented true pathologic inflammation versus a normal variant was subject to the personal experience of the individual pathologist and was not subjected to a uniform rating system.

The patterns of inflammation were patchy and unpredictable in any given patient, but overall were noted in all parts of the colon and terminal ileum. Although the table above lists chronic and active colitis separately, most patients with colitis had both chronic and active inflammation. Most patients had at least 3-4 distinct areas of histologic inflammation, with an equal number of biopsies that were histologically normal. The intensity of the inflammatory lesions varied as well, with many being subtle and somewhat focal, and others being more marked and diffuse. The latter included areas of cryptitis, crypt abscess, ulcerations, and dense inflammatory infiltration. One patient was found to have an inflammatory polyp. Most significantly, these findings were consistent and seen repeatedly amongst the majority of patients.

In regards to the last group of patients in the table above, it should be noted that although the histology did not reveal pathologic colonic inflammation, the majority of these patients were found to have a heavy and diffuse lymphoid hyperplasia of the colon (macroscopic and microscopic), signifying an activation of the colon's internal immune system.

Conclusion

In a series of 43 autistic children, mostly regressive, with chronic gastrointestinal symptoms, the majority were found to have pathologic inflammation of the colon and terminal ileum. 90% had pathologic lymphonodular hyperplasia of the terminal ileum. Moreover, the findings were similar and consistent from patient to patient within the affected group.

Questions

1) Does autistic colitis occur equally in regressive vs. non-regressive autism?
2) Do differences in growth exist between the colitis and non-colitis group?
3) Do differences in growth exist between the regressive vs. non-regressive group?
4) In a retrospective analysis of growth, will onset of growth failure coincide with the onset of regressive behaviors?

Dr. WELDON [presiding]. Thank you very much, Dr. Krigsman. You essentially did what I have been asking the NIH to do for several years.

Dr. Spitzer, you are recognized for 5 minutes.

Dr. SPITZER. I would like to start by saying my presentation will attempt to be as objective and as neutral as I can. I would like in particular to say that despite disagreement on a narrow set of issues, the CDC, in my experience of 35 years in epidemiology, has been a great institution, I am honored that some of my students have been hired by them, that we have been able to recruit their colleagues, graduates and people with work experience.

I do not know Dr. Davis or any of the colleagues. I am looking at the paper and what I find and I would like that accepted.

The focus of what I am going to talk about is measles containing vaccines and the risk of inflammatory bowel disease as published by Dr. Robert Davis and others in the publication cited in the slide.

The purpose of the study published was to examine the risk of inflammatory bowel disease following exposure to a measles containing vaccine. Unfortunately, as implied by my other colleagues at the table, the use of the results to demonstrate no link between MMR and autism is what I respectfully consider to be a misuse of the study and I shall try to explain why.

The fatal flaw of the study is that it is grossly underpowered. With conventional programs of power calculation, the calculation of power is somewhat complex but not controversial and we all do it similarly in various institutions. The power we calculate is 12 percent where normally accepted power is on the order of 80 percent and when you are looking at trying to demonstrate no difference, you want the power to be higher to avoid what is called a Type II error as opposed to a Type I error which is what we worry about in clinical research.

As I say there in what I try to make non-jargon English, a power of 12 percent means that one has a chance of 88 percent of declaring no increase in risk if indeed there was a twofold increase. Just to explain that in a somewhat different way to a non-statistical or non-epidemiologic audience and to colleagues in the world of politics, if you mandate a poll and say as you are facing reelection and so on and you get a poll with a point estimate that 55 percent in your jurisdiction are in favor of reelection, in the ones published in newspapers, Time Magazine and so on, you will see the error is about 3 percent, so whether you are on the low side, 52 percent or 58 percent, you will probably get elected.

If it were 40 percent, your estimates go down to the 20's and up to the 80's and 90's and you have no way from that poll which had insufficient numbers to predict whether you are going to get elected or not. It is an underpowered poll as I am giving the example from this paper.

So the low power results in the wide confidence intervals you see if not in every estimate of the paper we are talking about, and in this case 6 percent of the exposed to measles containing vaccines in the population from which the sample was drawn, were among the controls they picked. I think their choice of controls was reasonable and that is what determines the low power. It is an imbal-

ance, a maldistribution with exposed and non-exposed in the controls. That low 6 percent is what demonstrates the low power.

Let me turn to another issue. We can expand with questions, Mr. Chairman.

A hallmark of science as I have always taught, my colleagues teach, is replication and/or verification. I think the replication that Dr. Krigsman has done or the British work is an enormous contribution to our understanding of the validity of what went on before and it must be part of the practice in an evolving challenge like this or other challenges.

These temples of secrecy, it is more in academia in fact, I would say, than in organizations like the CDC where this is our data and false issues such as confidentiality are brought up. We worked that out decades ago. Ten years ago, I went through the data base in Saskatchewan and in 4 months we sorted out the controversy of beta agonists and death in children due to asthma. It took 4 months, it took $4 million; it would have taken 5 years and $25 million to do it out in the field. You can protect the identity of the patients easily in our state of science today in computer skills and so on.

We should avoid adversarial challenges. There were those who didn't believe this. We worked together on that. I just hope we can get past that in these controversies. As I say, temples of secrecy and adversarial approaches have no room in population science and most other clinical and related sciences.

I would agree with what the chairman said earlier, that the Datalink Data base should be opened to train scientists with reasonable safeguards. I don't believe in fishing expeditions. I am sure the colleagues in the CDC worry about that. These at random searches to see if you can find some dirt if you wish has no place. This is done seriously in a scientific way but access must be given to the legitimate concerned academic population, governmental organization that needs to look, especially if they are funded through public funds like the Saskatchewan data base in Canada.

I conclude that the Davis case control study from the Vaccine Safety Datalink Project cannot determine whether measles containing vaccines do or do not increase the risk that we are concerned about. In the 3-years I have been looking at epidemiologic literature from the entire world, scarcely any of it allows you to rule out MMR, nor can it rule it in. Part of the reason is in most jurisdictions where this has been done, you can't get high power. That is why in a case control study, my colleagues and I have designed to zero out this problem, we can't do it in the United States. and in the UK. The population has been penetrated too much of a degree. It has to be done in eight other countries just like the NIH supported the WHO studies in oral contraceptives for exactly the same reasons, an appropriately so.

Last, this study does not contribute to our understanding of the relationships between MMR and MCV and autism.

Thank you for your attention.

[The prepared statement of Dr. Spitzer follows:]

EVALUATION OF THE RELATIONSHIP BETWEEN MEASLES-CONTAINING VACCINES AND INCRESED RISK OF INFLAMMATORY BOWEL DISEASE

The Davis et al Paper (Arch Ped Adolesc Med 2001; 155: 354-359)

Submitted by Walter O. Spitzer, M.D., M.P.H., F.R.C.P.C., Emeritus Professor of Epidemiology, McGill University, Montreal

This scope of this opinion is limited to the Davis paper, to the extent that it is relevant to the objectives of the 06/19/02 congressional hearing at Washington D.C. (as summarized in Chairman Burton's letter of invitation).

*The Davis paper cannot evaluate the relationship between Measles-Mumps-Rubella vaccine and/or Measles-Containing Vaccine (MCV) and an increased risk of Inflammatory Bowel Disease (IBD). The paper is flawed.

*The fatal flaw that negates the ability of the study to reach conclusions about the explored association is that it is grossly underpowered.

*The power for the key results (Table 2) is 12%. It was not reported in the paper. We (methodologists at the Royal Victoria Hospital clinical epidemiology unit and I) calculated power from the data in the paper. In non-jargon English, a power of 12% means that one has a chance of 88% of declaring no increase in risk if indeed there was a two-fold increase in the risk. In Table 3 of the Davis paper all power calculations for each cell demarcated by vaccination ages are similarly very low. Providing confidence intervals (CIs) is correct. But that is insufficient for the intelligent layman, the clinician, the patient and the policy-maker to detect how much power is lacking and to understand that such low power does not allow conclusions or decisions.

*It would appear that the Davis group reached their decision about necessary sample size based on advance assumptions of exposure of 70% (from their projection overheads) compared to 30% unexposed. In fact, the published paper reports exposure of 94% among the controls, compared to only 6% unexposed. It is this small 6% unexposed group that reduces the power. This should have alerted the investigators, early during the field work, that the proposed sample size would be inadequate, resulting in the serious underpowering.

*Given controls with exposure of 95 %, the sample sizes that would have been needed to detect a two-fold risk increase:

- For a power of 80% (conventional): cases 730, controls 2215;
- For a power of 90%: cases 930, controls 2820.

*As an epidemiologist focused on direct or indirect potential associations of vaccines, particularly MMR, with autism, and, by extension, IBD in autistic persons, I find the choice of outcomes strange. Restricting the outcomes studied to Crohn's Disease and ulcerative colitis reduces the relevance of Davis' work to current hypotheses about vaccine-IBD associations emerging from laboratory and clinical research.

*A hallmark of valid science is that it is verifiable and replicable. When a research project is done with governmental funds for equipment, material, space, etc. by investigators also supported with public funds, ethics and social responsibility dictate that resources be made available to replicate the project. In epidemiology, the size of typical undertakings is large. Usually, databases created are also large. The time for total replication would often be prohibitively long. Thus, such databases should be available to competent legitimate investigators with valid concerns also on grounds of ethics and social responsibility. "Fishing expeditions" by verifiers should be prevented with *a priori* research plans. If necessary, the plans should be reviewed by entities other than the database owners or funders. Controversial or inconclusive findings by honest investigators can be expected to benefit from verification and/or replication. Issues dealing with confidentiality of patients, doctors and other providers have been worked out for many years. Reasonable time should elapse from original creation of data and release of initial conclusions to verification. Neutral monitoring committees are generally important in such situations.

*All of the foregoing in the previous paragraph also applies to privately funded research with few exceptions such as patents and legitimate commercial considerations.

*I believe that the Vaccine Safety Datalink Project data should be made available to academic, governmental and competent private research groups for all the reasons given above. In this particular case, the VSDP, a public, publicly funded resource should be open with reasonable safeguards unless matters such as national security or an epidemic justified closing access. Temples of secrecy have no place in science. Secrecy always suggests the question, "What do they have to hide?"

***I reiterate that the case control study from the Vaccine Safety Datalink project cannot determine whether measles-containing vaccines do or do not increase the risk for inflammatory bowel disease.**

I do not have any conflicts of interest. I have no nuclear or extended family members with any relevant disease, notably an autistic syndrome.. I have not had any grants for research or for any other purpose from US or other national sources since December 2000. As required by age, I retired this year I advise families of autistic persons in the UK *pro bono*. I do not know Dr R.L Davis personally nor any co-author of the paper commented upon. I do not further any view on association or causation with respect to MMR as a potential determinant of autistic syndromes. I am a worried agnostic, I do not know. I strongly believe we need to rule in or rule out a relationship. As an epidemiologist and public health doctor, my bias, if any, is that I would like to see MMR exonerated on safety, given its efficacy. Long and short versions of my CV have been submitted separately.

Walter O. Spitzer, M.D., M.P.H., F.R.C.P.C.

Emeritus Professor of Epidemiology, McGill University

Emeritus Editor, Journal of Clinical Epidemiology

Member, Institute of Medicine, U.S.A

Focus
Measles-containing vaccines and the risk for inflammatory bowel disease

Robert L. Davis and others

Arch Pediatr Adolesc Med 2001;155:354-359

Purpose of Study

- To examine the risk of inflammatory bowel disease following exposure to a measles containing vaccine

Use and misuse of the study

- Use of results to demonstrate no link between MMR and autism

Fatal flaw of study

- **Grossly underpowered** **12%**

(Accepted power 80%)

(Desirable power 90%)

In English

- "A power of 12% means that one has a chance of 88% of declaring no increase in risk if indeed there was a two-fold increase in risk"
- Low power results in wide confidence intervals
- In this case 6% of exposed to MCV among controls determines the low power

A Hallmark of Science

Replication and/or verification

Temples of Secrecy

Adversarial Strategies

Have no room in population science

The Vaccine Safety Data Link should be opened with reasonable safeguards

Conclusion

- The Davis case control study from the Vaccine Safety Data Link project cannot determine whether measles-containing vaccines DO or DO NOT increase the risk for inflammatory bowel disease
- This study does not contribute to evolving research on autism and gastrointestinal sequelae

Mr. BURTON. Thank you.

I am going to yield to Dr. Weldon because he is a physician and has some scientific background. I thought I would let him start off the questions and then I will chime in as we go through this.

Dr. WELDON. I want to thank all of our witnesses. You have provided us with a tremendous amount of information. I want to focus on a couple of important points initially.

If I understand you correctly, Dr. Bradstreet, you have two cases where you have identified measles virus in the cerebral spinal fluid in two children with regressive autism?

Dr. BRADSTREET. We presented two cases out of the ongoing investigation.

Dr. WELDON. So you have other cases?

Dr. BRADSTREET. Yes, sir, we do.

Dr. WELDON. Have you submitted this for peer review and publication?

Dr. BRADSTREET. No. At this point in time, the data is preliminary. We are in the process of developing a control base and replicating the science at which time we will submit it for peer review. We intend to have, based on the current rate of acquisition of cases, at least 30 cases to submit.

Dr. WELDON. This is fairly significant, what you presented. Has anybody done this type of research where they have looked at kids with regressive autism and done a spinal tap on them and checked their spinal fluid for evidence of the antibodies to myelin and basic protein as you described, but more importantly, viral particles in their cerebral spinal fluid?

Dr. BRADSTREET. I believe we are the only people so far who have done that research.

Dr. WELDON. So you did a research of the medical literature and you didn't find any evidence that this has been looked at previously?

Dr. BRADSTREET. Not at any point in time in the creation of the vaccine and the introduction of the vaccine, development of the safety issues of the vaccine or subsequent to that has anyone looked for persistence of the measles virus from the vaccine or autoimmunity in the sense of the brain as it relates to the vaccine strain. I am not aware of any data to that effect.

Dr. WELDON. My understanding of pathophysiology for them to have measles particles in their cerebral spinal fluid suggests an ongoing encephalitis basically in these kids? Is that what you are implying to the committee?

Dr. BRADSTREET. I think it is very early in terms of drawing conclusions. There is clearly a persistence of a detectable viral genome in the brain in these children. There is the autoimmunity to myelin basic protein and the presence of abnormal antibodies to measles virus only in the children with autism. We do not see that in controls.

Before we draw further conclusions, we would love to have those control spinal fluids looking for the virus. We should have that within 2 months.

Dr. WELDON. One of these children is your own child.

Dr. BRADSTREET. Correct.

Dr. WELDON. Have you tried antiviral therapy in treating these kids?

Dr. BRADSTREET. We have and I would say at this point in time, it is unpredictable and clearly we need a lot more research. There is a risk of developing hemolytic anemia in autism that seems to greatly exceed the risk of hemolytic anemia from antivirals as published in the literature. I have been in contact with the manufacturers of various antivirals and there is something unusual going on in autism that makes them more susceptible to side effects of antivirals. So it would not be a way to proceed generally speaking at this time without some very carefully observed research.

Dr. WELDON. I understand the strain of measles that is in the vaccine has certain genetic markers that enable researchers to distinguish it from so-called wild type measles. Are you making an attempt to do the genetic mapping to see whether this is wild type measles or the vaccine strain?

Dr. BRADSTREET. Certainly that wouldn't be my place, but the collaborators for us at the various laboratories that are analyzing the spinal fluid are going to be looking at strain specificity. The history is very consistent with this being vaccine onset as opposed to a vaccine failure where wild virus is getting in and causing these persistent symptoms. Again, we should know that within 1 to 2 months.

Dr. WELDON. Do these kids have seizures also?

Dr. BRADSTREET. A very high percentage have seizures. Again, this is a select group of children with autism. I am not trying to extend these conclusions to the entire population. These are children that have a very well established history that is very consistent with looking at measles virus or MMR as a cause of their symptoms.

Dr. WELDON. Thank you, Dr. Bradstreet.

Dr. Krigsman, Dr. Wakefield came under a lot of criticism when he published his findings, a lot of professional derogatory statements were made, I believe his credentials as a research professor have been threatened. Have you encountered anything like this in your research at all? You are at Mt. Sinai, correct?

Dr. KRIGSMAN. Lenox Hill Hospital.

Dr. WELDON. By the way, what is your background? Where did you do your training?

Dr. KRIGSMAN. I trained at Mt. Sinai. I did my pediatric residency downstate in Brooklyn and my fellowship in pediatric gastroenterology at Mt. Sinai in Manhattan.

Dr. WELDON. You have published research articles previously?

Dr. KRIGSMAN. Yes.

Dr. WELDON. And you are a professor of medicine?

Dr. KRIGSMAN. No. I have a position at NYU which is the academic affiliate of Lenox Hill Hospital.

Dr. WELDON. Have you come under any of the criticism that Dr. Wakefield encountered?

Dr. KRIGSMAN. Not yet.

Dr. WELDON. Dr. Wakefield, I am curious about this issue of Dr. Gershon. The ranking member brought it up and I just want to clarify my understanding of this issue because I was here when Dr. Gershon testified.

According to Dr. Gershon's statement that measles virus particles are detectable in the controls in Dr. O'Leary's lab, do I have that correct?

Dr. WAKEFIELD. That is correct.

Dr. WELDON. And you are contending that there was no evidence to support the statement made by Dr. Gershon, that Dr. Gershon didn't look at the data, he made that statement based on essentially hearsay, what he had heard from somebody else?

Dr. WAKEFIELD. That is my understanding. In fact, the written data show quite the opposite, that there is substantial evidence that there was no contamination or no presence of measles virus in those tissues.

Dr. WELDON. The reason I am bringing up this issue, and I don't want to get too bogged down in the controversies between you and Dr. Gershon, but as I understand it, Dr. O'Leary, who is a well respected viral pathologist, I think he was the gentleman who first identified Herpes Simplex Type A as the causative agent for Kaposi's Sarcoma, that he came under a certain amount of criticism within the British Isles, Great Britain, England, Ireland and he actually lost some credibility and some research grants, correct, based on that testimony?

Dr. WAKEFIELD. Yes. Within a week of that testimony, he lost five grants from the Irish Cancer Society.

Dr. WELDON. From the Irish Cancer Society. I assume that was very costly to him and his research lab, correct?

Dr. WAKEFIELD. Extremely, both in terms of staff, research and professional reputation.

Dr. WELDON. Is Dr. O'Leary litigating this issue?

Dr. WAKEFIELD. No. Here, I simply want to put the record straight and we do not wish to pursue it beyond that. Let us get on with the science.

Mr. BURTON. I just wanted to add I talked to Dr. O'Leary on the phone and he would have been here today to testify but he is having some health problems of his own and couldn't be with us. He stands by what Dr. Wakefield said.

Dr. WELDON. Dr. Spitzer, I get the Archives of Internal Medicine and I, like a lot of busy doctors, just read the abstracts and I move on. In the case of the Davis Study, I want to make sure I understand this correctly.

I took medical statistics in medical school and I also took it in college. I have looked at this study and do you have the study?

Dr. SPITZER. Yes, I have it right in front of me, Dr. Weldon.

Dr. WELDON. I want to get at this issue of the power. Table III on page 357 in the study reports all inflammatory bowel disease, the fourth column, broken down by age. They have these ranges for children who receive the MMR before age 12 months, a 0.61 with a range of 0.15 to 2.45 and then they have all the others.

As I understand it, 1 basically means it is neutral, correct?

Dr. SPITZER. Yes.

Dr. WELDON. And then the range, let us take less than 12 months, what they are saying is 0.61 so I guess there is a suggestion there is a reduction in risk of inflammatory bowel disease but the range is as low as 0.15 which would be a dramatic reduction in risk up to almost a two and a halffold increase?

Dr. SPITZER. Yes.

Dr. WELDON. That tells me this is garbage. I hate to say that but that is like my pollster telling me your chance of being reelected is 55 percent with a range of 10 percent to 90 percent.

Dr. SPITZER. I prefer not to use the word but you can't rule failure to reelect versus reelection in or out on the basis of the poll.

Dr. WELDON. I think my time has expired and I am sure the coauthors of the study will take issue with some of this when they have their opportunity to testify. I yield back.

Thank you.

Mr. BURTON. If the gentleman would like, we will come back for some more questions for this panel.

Mr. Waxman.

Mr. WAXMAN. I want to point out to the witnesses and the audience that I have a conflict in schedule because at the same time of this hearing, there is a Commerce Committee mark up, a vote on Medicare and Medicaid, so I am trying to go back and forth.

I wanted to get on the record some points about Dr. Wakefield's testimony. Dr. Wakefield today testified about an upcoming scientific presentation in Ireland by Dr. O'Leary. In this presentation, which is going to take place in July, scientists are presumably going to claim to have found vaccine strain measles in the intestines of children with development disorders. I have a copy of the abstract and want to make it a part of the record.

[The information referred to follows:]

Abstract for meeting of Pathological Society, 2 – 5 Ju

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Development of an 'allelic discrimination' type assay to differentiate between the strain origins of measles virus detected in intestinal tissue of children with ileocolonic lymphonodular hyperplasia and concomitant developmental disorder.

O. Sheils, P. Smyth, C. Martin, J.J. O'Leary.
Department of Histopathology, Trinity College Dublin, Ireland.

In a recent study, our group described the presence of measles virus RNA genes in a new form of inflammatory bowel disease with concomitant developmental disorder[1]. One of the many questions raised by this study asked if measles virus detected was wild or vaccine type in origin. The objective of this pilot study was to address this point.

Several conserved amino acid coding changes have been identified in measles virus strains in the Edmonston Vaccine lineage, and it has been suggested these represent a vaccine 'strain signature'[2]. One such site (nucleic acid position 7901, amino acid position 211) displays a consistent A-G mutation in Edmonston derived vaccines compared with wild type strains. This site is located in the H gene region of the measles genome and is associated with cellular CD46 interaction.

This single base mutation was used as the basis for the design of an allelic discrimination assay using TaqMan MGB probes (FAM labeled for wild type, and VIC labeled for Vaccine Type). The assay was run on an ABI 7000 sequence detection system using total RNA extracted from intestinal biopsies amplified with TaqMan one step RT-PCR kit.

Synthetic oligonucleotides representing wild and vaccine strains were designed using published sequences from the NCBI database, and used as controls in the assay system.

The assay identified wild type measles in three brain blocks from an SSPE patient, while 12 gut biopsies from affected children were deemed to have vaccine strain present. This pilot study further corroborates our previous findings of an association between the presence of measles virus and gut abnormalities in children with developmental disorder, and indicates the origins of the virus to be vaccine strain.

1. Potential viral pathogenic mechanism for new variant inflammatory bowel disease.
Uhlmann V, Martin C, Sheils O et al. J Clin Pathol Mol Pathol 2002;55: 84-90.
2. Comparison of predicted amino acid sequences of measles virus strains in the Edmonston Vaccine Lineage.
Parks CL, Lerch RA, Walpita P et al. J Virol 2001;(75)2;910-920.

Comments on abstract submission

'Development of an 'allele discrimination' type assay to differentiate between the strain origins of measles virus detected in intestinal tissue of children with ileocolonic lymphonodular hyperplasia and concomitant developmental disorder'

Sheils O, Smyth P, Martin C, O'Leary JJ. Department of Histopathology, Trinity College Dublin, Ireland.

The authors describe an established technique for discriminating between two closely related genome sequences (it is widely used for screening the human genome and is also known as an SNP - single nucleotide polymorphism assay). (www.pathsoc.org.uk/meet/docs2002/dublinabstract.pdf) The technique detects a difference at a single nucleotide site and is therefore dependant on there being a consistent difference between vaccine and 'wild' measles virus strains at that site. The assumption underlying this technique is based upon a recent paper which investigated sequence differences between several vaccine strains and a single 'wild' strain – the original strain from which all current vaccines are derived (known as the Edmonston strain).[1] The latter paper found a number of differences between the wild Edmonston parent strain and the vaccine strains.[1] The site chosen and described in this abstract is nucleotide position 7901 which is a guanidine (G) in all vaccine strains and adenosine (A) in the Edmonston parent strain.

Review of the measles database (www.ncbi.nlm.nih.gov) shows that there are several 'wild' measles strains which have G at site 7901 and therefore would be, based upon the authors assumptions, incorrectly classified as vaccine 'strains. These strains include recent isolates from Africa and earlier strains from Eastern Europe. Consequently the technique described does not reliably discriminate between 'wild' and vaccine strains of measles virus.

On the basis of the information presented, this abstract does not provide any convincing evidence of the presence measles vaccine virus genome in these samples. The definitive technique to characterise measles strains is sequencing and it is surprising that this technique was not used in this study.

1. Comparison of predicted amino acid sequences of measles virus strains in the Edmonston Vaccine Lineage.
Parks CL, Lerch RA, Walpita P et al J Virol 2001;(75):2,910-920.

Dr David W G Brown, Laboratory Director
Dr L Jin, Clinical Scientist
Enteric, Respiratory & Neurological Virus Laboratory
Dr Mary Ramsay,
Communicable Disease Surveillance Centre

June 2002

Partial List of Measles Strains that Have a G at Position 7901*

* Loss88
* AJ239139-B3I/H-1
* AJ239171-B3I/H-1
* AJ239174-B3II/H-1
* AJ239149-B3II/H-1
* AJ239189-D4/H-1
* AJ239185-D4-1
* Lec/US70sspe
* S(A)/Germ80s/sspe
* S(B)Astria80s-sspe
* AJ239150
* AJ239151

*Source: Dr. David Brown, head of the World Health Organization collaborating center for measles in the United Kingdom

Statement of Rep. Henry A. Waxman Regarding Vaccine Allegations

June 19, 2002

During today's testimony, Dr. Andrew Wakefield testified about data to be presented at an upcoming scientific conference in Ireland. He characterized this research as evidence that vaccine strain measles has been identified in the intestines of some children with developmental disorders. He believes that this finding is consistent with his theory that the measles-mumps-rubella vaccine causes autism.

An abstract of the study has been submitted for the conference in Ireland. According to this abstract, the authors studied 12 children with developmental disorders. Strains of measles virus recovered from their intestines were identified as vaccine strain on the basis of the specific chemical found at position 7901 of the genetic code of the measles virus.

Other scientists believe, however, that the research cited by Dr. Wakefield today has a serious error. These experts say that the strain of virus identified by the researchers could have been natural measles virus, not the vaccine strain. According to Dr. David Brown, head of the World Health Organization collaborating center for measles in the United Kingdom, position 7901 cannot distinguish between vaccine and natural measles strains. Dr. Brown justifies this conclusion on the basis of a search of the NIH gene database on the internet at www.ncbi.nlm.nih.gov/nucleotide.

This matter obviously requires more scientific study. It may yet be proven that some children have vaccine strain measles virus in their intestines. According to experts, this is just one of many issues that must be addressed before the safety of the MMR vaccine is called into question by Dr. Wakefield's theory. The important point for today is that the evidence cited by Dr. Wakefield should not be taken at face value without further scientific evaluation.

National Network for
Immunization Information

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June 17, 2002

Dear Representative Waxman,

In preparation for the Committee on Government Reform's June 19 hearing, "The Status of Research into Vaccine Safety and Autism," I am writing to introduce you to the National Network for Immunization Information (NNii) and guide you toward scientifically credible resources that physicians and nurses look to for guidance on these important issues and can be trusted for their accuracy and reliability. NNii is co-chaired by Dr. Louis W. Sullivan, former U.S. Secretary of Health and Human Services and current president of Morehouse School of Medicine; and Dr. Samuel Katz, professor emeritus of pediatrics at Duke University Medical Center. NNii is funded entirely by private foundations and accepts no support from government agencies or vaccine manufacturers.

NNii, a partnership of medical and nursing professional organizations* was created in 1999 by infectious disease experts, pediatricians, nurses and other health professionals committed to promoting better understanding of—and restoring the declining public confidence in—immunizations. Since its establishment, NNii has become a leading independent, scientifically sound, organization devoted to addressing questions about the effectiveness, value, and safety of vaccines and immunization policies and practices.

Recent NNii research that has guided our efforts in developing information resources and education materials has demonstrated that while the majority of parents support current immunization policies, their understanding of immunizations and the diseases they prevent is limited. Of great concern to us is that a significant percentage of parents have serious misconceptions that may adversely affect their decisions about immunization. For example, NNii's research, "Do Parents Understand Immunizations?: A National Telephone Survey," which was published in the peer-reviewed journal *Pediatrics* in November 2000, revealed that in this nationally representative sample of parents of children < 6 years of age, 25% mistakenly feared that their child's immune system could be *weakened* by too many immunizations. In addition, 19% of parents were not aware that vaccines are evaluated for safety before they are licensed and recommended.

We worry that when "informed" medical decision-making is misinformed, the results can be dangerous. Furthermore, because immunizations impact the control of vaccine-preventable diseases in the individual and in the community at large, decisions about immunizations made by individuals have implications for the health of the public. These decisions must be made on the basis of the best available scientific evidence.

Some of the current concerns about vaccines are, ironically, a result of their effectiveness and success. Since young parents often are unfamiliar with the severity of vaccine-preventable diseases, they question whether the benefits continue to outweigh risks. Driven by concerns appearing in the media, on the Internet and elsewhere, parents and families increasingly worry that vaccines are causing more harm than good and may be responsible for a long list of chronic diseases including asthma, autism, diabetes, learning disabilities, multiple sclerosis, and sudden infant death syndrome.

While we know that no pharmaceutical product is 100% effective or 100% safe and that there are rare but serious side effects following some vaccines, we also know that there is a large body of scientific and epidemiologic information that guides vaccine policy. Before a vaccine can be used in the United States, it must be shown to be safe and effective. Moreover, because healthy children are typically the recipients of vaccines, safety requirements are especially stringent. Once a vaccine is licensed by the Food and Drug Administration (FDA) and recommendations are made by the Advisory Committee on Immunization Practices (ACIP), additional studies conducted by the Centers for Disease Control and Prevention (CDC) and others continue to monitor its effectiveness and safety to assure that it performs in a way that is consistent with the clinical trial and other data that led to its licensure.

We also recognize the appropriate and important role of government oversight, such as that performed by your Committee, in assuring that our immunization policies and practices provide our communities with protection from vaccine-preventable diseases while balancing the risk that may come with this benefit. To this end, we want you to be sure that you are aware of the most up-to-date and scientifically accurate information about two of the issues that are likely to be the focus of the June 19th hearing.

1) The possible link between thimerosal (a mercury-containing preservative in some vaccines) and autism; and,
2) The hypothesis that the MMR vaccine (measles, mumps and rubella) is linked to the development of autism.

The possible link between thimerosal (a mercury-containing preservative in some vaccines) and autism.

As stated on CDC's website (http://www.cdc.gov/nip/vacsafe/concerns/thimerosal/default.htm), "Thimerosal is a mercury-containing preservative used in some vaccines and other products since the 1930's. No harmful effects have been reported from thimerosal at doses used in vaccines, except for minor reactions like redness and swelling at the injection site. However, in July 1999, the Public Health Service (PHS) agencies, the American Academy of Pediatrics (AAP), and vaccine manufacturers agreed that thimerosal should be reduced or eliminated in vaccines as a precautionary measure. Today, all routinely recommended pediatric vaccines manufactured for the U.S. market contain no thimerosal or only trace amounts."

Because some have theorized that the development of autism and other neurodevelopmental disorders may have resulted from exposure to mercury from the thimerosal that was contained in some vaccines, this issue has recently been reviewed by the Institute of

Medicine's Immunization Safety Review Committee. This Committee was formed at the request of CDC and NIH in response to a number of concerns raised about the safety of and the need for certain immunizations. The 15 Committee members have expertise in pediatrics, internal medicine, immunology, neurology, infectious diseases, epidemiology, biostatistics, public health, risk perception, decision analysis, nursing, genetics, ethics, and health communications. To address concerns about the perception that conflicts of interest would have on the acceptance of their reviews and reports, all committee members are free of financial ties to vaccine manufacturers, previous service on vaccine-advisory committees, or prior expert testimony or publications on issues of vaccine safety.

As stated in the IOM's press release that accompanied the release of this report on October 1, 2001, "The committee's comprehensive assessment of the scientific literature on thimerosal included analyses of published and unpublished studies proposing an association with disorders such as autism, and it found them to be inconclusive. No evidence currently exists that proves a link between thimerosal-containing vaccines and autism, attention deficit-hyperactivity disorder, speech or language delays, or other neurodevelopmental disorders."

The Committee went on to state that while the available scientific data do not establish that these neurodevelopmental disorders are caused by thimerosal, at the same time, they do not establish that these neurodevelopmental disorders are not caused by thimerosal. Therefore, the Committee concluded that the hypothesis that exposure to thimerosal-containing vaccines could be associated with neurodevelopmental disorders was "biologically plausible."

In coming to this conclusion, the Committee balanced the following factors. On the one hand they note that the hypothesis that thimerosal exposure through the recommended childhood immunization schedule has caused neurodevelopmental disorders is *not* supported by clinical or experimental evidence because:

a) Low-dose thimerosal exposure in humans has not been demonstrated to be associated with effects on the nervous system.
b) Neurodevelopmental effects have been demonstrated for prenatal but not postnatal exposures to low doses of methylmercury.
c) The toxicological information regarding ethlymercury, particularly at low doses, is limited.
d) Thimerosal exposure from vaccines has not been proven to result in mercury levels associated with toxic responses.
e) Signs and symptoms of mercury poisonings are not identical to autism, ADHD, or speech or language delay.
f) Autism is thought primarily to originate from prenatal injury.
g) There is no evidence that ethylmercury causes any of the pathophysiological changes known to be associated with autism, such as genetic defects, and there are no well-developed pathological markers of ADHA or delay of speech or language that could be compared to effects of ethlymercury on the nervous system.

On the other hand, the Committee noted that information related to their conclusion of biological plausibility is *indirect* because:

a) High-dose thimerosal exposures are associated with neurological damage.

b) An extensive toxicological and epidemiological literature establishes methlymercury, a close chemical relative, as a toxicant to the developing nervous system.
c) Some children who received the maximum number of thimerosal-containing vaccines on the recommended childhood immunization schedule had exposures to ethylmercury that exceeded some estimated limits of exposure based on federal guidelines for methlymercury intake.
d) Some children could be particularly vulnerable or susceptible to mercury exposures due to genetic or other differences.

Since the release of the IOM report last year, research supported by NIH's National Institute of Allergy and Infectious Diseases (NIH) demonstrated that mercury derived from thimerosal in vaccines is eliminated in the stool of infants and that mercury levels in children receiving thimerosal-containing vaccines did not exceed, at any time, the blood levels that correspond to the EPA's guidelines for exposure. In addition, an ongoing study of the pharmacokinetics and tissue distribution of thimerosal, ethyl mercury, and methyl mercury in animals supported by NIH and NIEHS will address whether exposure levels established as safe for methylmercury are also appropriate for exposure limits on thimerosal or ethylmercury.

The hypothesis that the MMR vaccine (measles, mumps and rubella) is linked to the development of autism.

This is a topic that is familiar to your Committee, given past hearings. The IOM's Immunization Safety Review Committee, the American Academy of Pediatrics and the British Medical Research Council have reviewed this hypothesis. Each of these independent reviews of both published and unpublished literature has concluded that while there may often be the perception of a temporal link between the administration of the MMR vaccine and the development of signs and symptoms of autism, a causal relationship has not been established.

More specifically, the IOM Committee noted:

a) A consistent body of epidemiological evidence shows no association at a population level between MMR vaccine and autistic spectrum disorders (ASD).
b) The original case series of children with ASD and bowel symptoms and other available case report are uninformative with respect to causality.
c) There is no relevant animal model linking MMR vaccine and ASD.
d) Biological models linking MMR vaccine and ASD are fragmentary.

Regarding the "fragmentary" nature of this hypothesis, the IOM Committee examined the full range of theories that include immunological mechanisms, the opioid excess hypothesis, theories of autoimmunity, and findings by some investigators of the presence of measles virus in the gut of some affected individuals. The full details of this analysis can be found on pages 27-32 of their report, however, the final paragraph of this section further elaborates their conclusion:

"Thus, with the exception of the results from two [research] groups, there is no evidence to support persistent infection with vaccine-strain measles virus except for individuals with compromised immunity. The extant evidence is internally inconsistent; supporting the need for carefully controlled studies to explore these inconsistencies. In the absence of such

studies, the evidence does not demonstrate persistent vaccine-strain measles virus infection in ASD, inflammatory bowel disease, or ASD with bowel inflammation. Furthermore, it is not possible with the available evidence to describe the direction of any relationship among vaccine-strain measles virus infection, autism, and enterocolitis – i.e., is it possible that autism creates greater susceptibility to enterocolitis following a viral insult?"

Vaccines are one of medicine's greatest achievements. Without vaccinations, millions of children and adults would contract serious diseases that are now prevented by vaccines, and many would have long-lasting effects or even die.

Yet, the message that the public is hearing through the media and over the Internet is often the opposite: that the risks of immunization may now outweigh their benefits. Unfortunately, we are concerned that this same message may emerge from the June 19 Committee hearing if these issues are not put in the context of the value that vaccines have had and continue to have for individuals, communities and the health of the public. To paraphrase a comment once made by former Secretary of Defense and Secretary of Energy James Schlesinger, "Everyone is entitled to their own opinion...but no one is entitled to their own facts."

We look forward to the work of your Committee regarding issues of vaccine safety and stand ready to do what we can to help you to learn the facts about the many important topics that you will be discussing.

Yours sincerely,

Bruce G. Gellin, MD, MPH
Executive Director
National Network for Immunization Information

Associate Professor of Medicine (Preventive Medicine)
Vanderbilt University School of Medicine

Associate Professor of Nursing (Preventive Medicine)
Vanderbilt University School of Nursing

Cc: Dr. Louis Sullivan, Dr. Samuel Katz,

NNii partners:
Infectious Diseases Society of America, Pediatric Infectious Diseases Society, American Academy of Pediatrics, American Nurses Association, American Academy of Family Physicians, National Association of Pediatric Nurse Practitioners, American College of Obstetricians and Gynecologists.

Additional information about thimerosal in vaccines, can be found at the following web sites:

Thimerosal:

Institute of Medicine/National Academy of Sciences

IOM's report on thimerosol in vaccines
http://www.nap.edu/catalog/10208.html?onpi_newsdoc100101

IOM Vaccine Safety Committee's public meeting on Thimerosal-Containing Vaccines and Neurodevelopmental Outcomes held on July 16, 2001 in Cambridge, Massachusetts.
www.iom.edu/iom/iomhome.nsf/pages/thimerosal+agenda

Centers for Disease Control and Prevention

http://www.cdc.gov/nip/vacsafe/concerns/thimerosal/faqs-mercury.htm
http://www.cdc.gov/nip/vacsafe/concerns/thimerosal/faqs-thimerosal.htm

Food and Drug Administration

http://www.fda.gov/cber/vaccine/thimerosal.htm#intro
http://www.fda.gov/cber/vaccine/thimfaq.htm

MMR vaccine and Autism:

Institute of Medicine/National Academy of Sciences

IOM's report on MMR and Autism:
www.iom.edu/iom/iomhome.nsf/pages/mmr+and+autism

Centers for Disease Control and Prevention

CDC: Vaccines and Autism Theory website:
www.cdc.gov/nip/vacsafe/concerns/autism/default.htm

American Academy of Pediatrics

http://www.aap.org/advocacy/archives/mayautmmr.htm

National Alliance for Autism Research
www.naar.org
http://www.naar.org/naarative3/naarrative3.pdf

Medical Research Council (United Kingdom)
http://www.mrc.ac.uk/index/public_interest/public-press_office/public-press_releases_2000/public-mrc-18-00.htm

General background information on vaccines and immunization:

National Network for Immunization Information:)
www.immunizationinfo.org

Institute of Medicine's (IOM) Immunization Safety Review Committee:
www.iom.edu/iom/iomhome.nsf/pages/immunization+safety+review

Centers for Disease Control and Prevention's National Immunization Program:
www.cdc.gov/nip

Allied Vaccine Group:
This is a web "portal" that provides access to information provided by the American Academy of Pediatrics, the Children's Vaccine Program at PATH, Parents of Kids with Infectious Diseases (PKIDS), the National Network for Immunization Information, the Immunization Action Coalition, the Vaccine Page, and the Vaccine Education Center at the Children's Hospital of Philadelphia.
http://vaccine.org

John's Hopkins Institute for Vaccine Safety
http://www.vaccinesafety.edu/

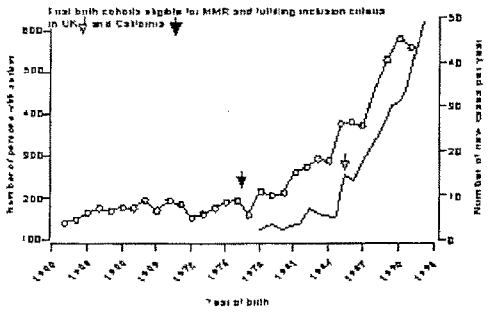
World Health Organization
www.who.int

Case Study No 4: The Graph behind the MMR-Autism Controversy

In an article under the heading "False Alarm: Autism isn't really running riot. It's all in how you interpret the figures," the magazine *New Scientist* printed the following:

> "In particular, Frombonne says, many people have misinterpreted a graph that appears to show a sudden rise in the cases of autism during the 1980s. The graph in fact shows the number of people known to have autism in a single year, 1991, plotted against the year of their birth. The rise in cases for birth dates nearer the present could reflect the rising population and improved diagnosis among young children. Portraying the data in this way is very misleading, Frombonne says. 'Trying to link this with MMR is complete nonsense.' "

Apparently, a link was suspected by some between the combined measles, mumps, rubella vaccine (MMR) and autism. Critics of the idea were blaming misinterpretation of a graph. Naturally, we were interested in how a graph could be so bad that it would be widely misinterpreted. The quotation above appeared *New Scientist* 17 February 2001 (page 17). Backtracking in the pages of the magazine, we found the name Andrew Wakefield, a London gastroenterologist, and a citation in *The Lancet.* There we found the following figure[1] and caption:



Temporal trends for autism in the USA (California*) and the UK (north-west London)
In 1998 the expected numbers of newly diagnosed autistic children in California should have been 105–263 cases, according to DSM-IV; the actual figure was 1685 new cases. The temporal trend in north-west London is almost identical, although the rise is delayed by about 10 years. The two countries use the same dignostic criteria. The sequential trends are consistent with the timing of introduction of MMR to both regions.
*Data from Department of Developmental Services, Sacramento, 1987–98 (www.dds.ca.gov)

We tracked down the link to the California Department of Developmental Services. Here we found

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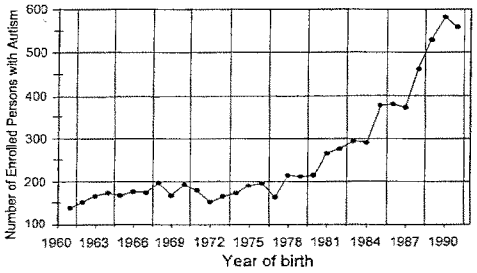
[1] *The Lancet* seems to have trouble with graphics, at least in the version available over the web. The text is very crisp and sharp. The graphics, for the most part, appear to be 75 dpi gif files. Our extract is from Vol 354, September 11, 1999, page 950.

Wakefield's source, in a report to the California legislature[2]:

Figure 1 - Distribution of Birth Dates of Regional Center Eligible Persons with Autism



Now, the authors of this diagram are at pains to point out (right above the diagram) that "data points in Figure 1 do not show how many persons entered the system in a given year, but how many already in the system were born in a given year." In the report's Conclusions they state (our quote starts at the second paragraph):

> "The quality and type of information examined in this report were not suitable for measuring incidence in the population of persons with autism. Ascertaining the incidence for autism and the other PDDs will require carefully controlled research. Furthermore, it is far beyond the capability of this Department to undertake such studies. . . .
>
> "The cause(s) of the increase in the population of persons with autism served by the regional center over the past 10 years is unknown. The sheer complexity of the this phenomenon prevents any clear conclusions about the exact determinants of the increase. Speculation about the rise in numbers is abundant, but such speculation is not based on scientific research and typically leads to debate and controversy when offered as a cause. . . .
>
> "What we do know is that the number of young children coming into the system each year is significantly greater than in the past, and that the demand for services to meet the needs of this special population will continue to grow. . . "

In other words, they acknowledge an increase in demand for the Department's services, and they are trying to help the State of California figure its future needs. They are concerned with their system and the numbers it must serve, not with causes. This is a report to the legislature, not a scientific paper. That is why the vertical axis of the California graph is labeled "Number of *Enrolled* Persons with Autism." (Our italics.)

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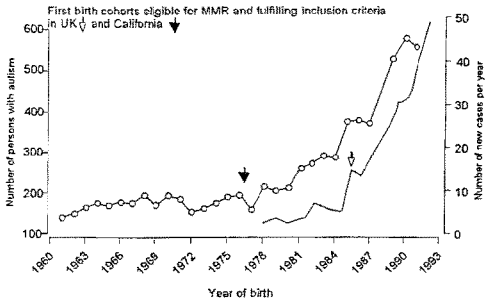
[2] "Changes in the Population of Persons with Autism and Pervasive Developmental Disorders in California's Developmental Services System: 1987 through 1998." A Report to the Legislature, March 1, 1999.

We re-drew the *Lancet* graph to make it more legible, and obtained the following:



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*Data from Department of Developmental Services, Sacramento,1987–98 (www.dds.ca.gov)

Let's see what has changed from the California version.

1. There are now 2 vertical scales. The new one on the right, to be used with the London data, is labeled "Number of new cases per year."

2. The word "enrolled" was deleted from the label on the left, so it reads "Number of persons with autism." This omission is significant: it considerably broadens the meaning from the scope of the original. Presumably, this change was made to give the impression that it was fair to compare the California data with the data from London representing "Number of new cases per year."

3. Note that the new scale on the right starts at zero, and that the suppressed zero of the original left scale has been retained. Even so, the bottoms of the two axes have been aligned.

4. The old figure caption, with its words about "Distribution of Birth Dates" is gone. The new words at the top of the graph, by giving the arrows on both curves the same descriptive label, evidently represent a further attempt to have the reader consider the curves as representing the same kind of entity. The arrows purport to indicate the "First birth cohorts [that were] eligible for MMR . . ." even though MMR is not mentioned in the California report. (In fact, the arrow at 1977 for California is wrong: American children became eligible for the MMR injection in 1971, so the first eligible birth cohorts would have been those born a year or two before that.)

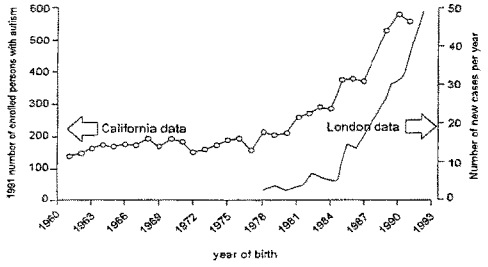
5. New words at the bottom of the graph reinforce this notion of similarity. The new title for the graph, in boldface, is "Temporal trends for autism in the USA (California) and the UK (north-west London)." This flies in the face of what the authors of the original graph said (quoted above) about their graph *not* showing the incidence of autism in a given year.

In fact, there is a good reason the data in this graph do not show the number of cases of autism arising in a given year: *for half the period covered, the Department of Developmental Services Regional Centers System did not even exist, or was not yet admitting cases of autism.*

The legislation (AB 225, the Lanterman Developmental Disabilities Services Act) that created the Department of Developmental Services in California was signed in 1969. This fact is stated in the report. One may imagine that it took a few years for the Department to staff up, and create its network of regional centers. So few patients would have been enrolled before the early 1970s. Further, on the website of at least one of the regional centers (the Alta-California Regional Center, http://www.altaregional.org/history/Lanterman.htm), we read that "In 1974, the additional legislation (AB 846-Lanterman) went into effect which expanded the clientele served by the regional centers to include persons with cerebral palsy, epilepsy, autism, and other significantly handicapping conditions found to be closely related to mental retardation."

Evidently, it wasn't until the mid 1970s that the Department even started to offer services to people with autism.

Suppose we correct some of the graphical errors: put back a zero for the left scale; line up the two zeroes? (It is very easy to adjust the graph this way in most graphics packages.) Suppose, at the same time, we fix a few labels, and make the vertical size of the two curves the same?



Now the correlation apparent in the original graph is starting to look weaker. This is because the California numbers do not have a very large dynamic range compared to the London results. The maximum value is only perhaps 3 or 4 times the "pre-Department" value. In London, there is a change of about 20 to 1, over a much shorter time.

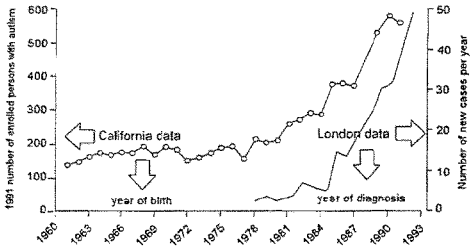
Wakefield's words, in his letter accompanying the *Lancet* diagram, are

> "Can the dramatic increase in autism be ascribed to change in diagnostic practice? Data from the recent California report from the Office (*sic*) of Developmental Services belie this contention. The figure juxtaposes the data from California with those from north-west London. Identical temporal trends are shown, with the rise in autism from a steady baseline value, coinciding with the introduction of MMR vaccine as the single strategy in both countries that use the same diagnostic criteria for autism."

The figure does "juxtapose data." but the data cannot be construed as showing "identical temporal trends." Take the 1990 and 1991 data (the last numbers available from California), for example. In 1991 about 560 children who had not yet celebrated their first birthday were admitted into the system. The same year, there were perhaps 580 children in the system who were between their first and second birthdays. We do not know when they entered the system: it might have been either year.

The London figures are actually rather ambiguous. In 1991 there were 38 new cases (according to the ordinate label) in the system (apparently all born in 1991, according to the abscissa label) and in 1990 there were 32 new cases, all evidently born in 1990. In fact, one suspects that the data are as the vertical axis label says, *New Cases*, and that the abscissa label *Year of Birth* is simply retained from the California graph. The horizontal axis for the London data should have been modified to read *Year of Diagnosis* or something similar. It follows that we do not know how old the new London patients were: some could even have been adults.

The comparison graph should have been more like this:



If our assumption about the London data is correct, it is now apparent that we are comparing apples and oranges. In the California case, we know the age of the patient in 1991, but not the year of admission. In the London case, we know the year of diagnosis or admission, but not the age of the patient.

We could go further. Frombonne says, in the original *New Scientist* article, that we can reasonably expect the size of the California population to have changed over the period shown. Fortunately for those of us wishing to check this idea, population data are available from the US Bureau of the

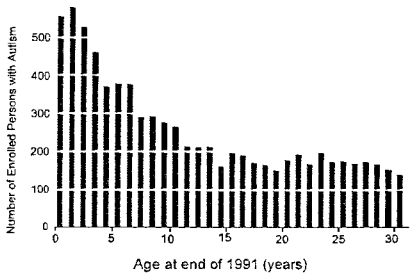
Census. In the summer of 1961, the population of California was 16.5M. By 1991, the number had risen to 30.5M. The population grew by very nearly a factor of 2. Might not this account for a rise in the number of autism cases? As word of the new DDS spread in the late 1970s and the early '80s, might there not be an increase in enrollments due to a growing population that was becoming increasingly aware of the services offered by the Department?

In concluding, it is only fair to point out that the *first* mistake in this whole graphics business was made in California. The California data were represented as a time-series graph, and this apparently invited the misleading comparison. The authors of the California report should have used a scatter plot or a histogram. The use of a histogram, instead of a graph, is justified by the fact that the distribution of birth dates of people enrolled in a growing program is not a time-series trend. The authors are not plotting the time-evolution of a function, or even the sampled values of a variable, they are showing recorded independent statistics.

This topic is discussed in Chapter 6, where a test for whether a histogram or a scatter plot should be used is given. The points that represent the data in the graph area should not have been joined, *because the values of the ordinate change if the sampling frequency is changed.* For example, had the California data been presented on a basis of month of birth rather than year, the numbers would have been about 12 times smaller. The interpolation implied by "joining the dots" is simply not valid.

To conclude the case study, we drew a histogram that contains the data from original the DDS graphic.

Figure 1 - 1991 Distribution of Ages of Regional Center Eligible Persons with Autism



In this figure, the first vertical bar can be interpreted as the number of people "in the system" between zero and one year old; the second bar people between one and two years, and so on. Perhaps this kind of presentation would not have lent itself to quite so much misinterpretation.

The debate over MMR and autism has exercised a number of people in the last few years. In all probability, the debate will last as long as funding can be obtained for researchers to pursue the supposed connection. One cannot help feel, however, that a better job of presenting and understanding the graphics would have avoided a lot of wasted effort.

For the graphic user, the lessons to be learned are:

(1) Choose carefully the kind of graph you use to show your data. Even if (in contrast to Carl Sagan's graph discussed in the previous case study) you select an apparently normal kind of graph, be sure your selection is appropriate.

(2) If you are going to quote someone, do it accurately. That applies both to verbal and graphical statements. If you are going to the trouble of tracing and re-drawing a graph because you do not have the original file, be sure you make no changes.

Even a small change can give the impression you are trying to mislead. Instead of supporting it, that can undermine your case.

Clarification on Measles' Strains in Dr. O'Leary's Research

While the doctor from WHO correctly points out that it is possible for several wild strains of measles virus to contain the H gene SNP 7901 as discussed in his correspondence to Congressman Waxman, he fails to note that Dr. O'Leary's laboratory has created a two step algorithm to safeguard against false affiliation with vaccine strain measles in these samples. The first step of the algorithm was to looking at the H gene 7901 which is found in the vaccine strain of the measles and only a few wild strains (1 found in China, 1 found in Toyashima, Japan in 1959, 1 found in Philadelphia in 1999, 3 found in Banemex in 1990, and 1 lab mutation not found in the wild and not in Dr. O'Leary's lab.). None of the individuals evaluated had been exposed to any of these strains. However, to further determine whether this was a vaccine strain or a wild strain, the researchers looked for another gene that would be in the vaccine strain but not in any of the wild strains to which the H gene 7901 has been identified. This gene was the F gene 6547. It is not found in any of the wild strains which have the H gene but has been found in the samples.

If samples have both the H gene, SNP 7901 and F gene 6547, it is highly probably that the measles DNA found in the samples taken from autistic children who suffer chronic bowel conditions is from the MMR vaccine. Research continues to further clarify these issues.

Mr. WAXMAN. The abstract states that the conclusion that the virus was vaccine strain, which means caused by the vaccine, is based on one nucleic acid position, No. 7901. According to the abstract, if the chemical at Position 7901 is adonine, then the strain is natural measles virus. But if the chemical is quanine, then the strain is from the vaccine. According to this abstract, this difference can perfectly distinguish between natural and vaccine strains of measles. However, according to the Gene Bank Web site run by the National Institutes of Health, this isn't true. So what we see in this abstract, from what we hear from Dr. Wakefield, there is a real question.

Measles experts have told us that more than 10 natural measles strains have a quanine at position 7901, even though the abstract says that only happens in the vaccine strain. If there are 10 natural measles strains that have that particular chemical positioning, then this theory doesn't hold up. I have the names of some of those strains and I expect to even receive other names which I want to add to the record later on.

I want to ask Dr. Wakefield, are you aware if Dr. O'Leary has checked the NIH Web site thoroughly before writing his abstract? If it is true that position 7901 does not distinguish between natural and vaccine strain measles, would it be fair to say that the conclusion of the abstract remains unproven?

Dr. WAKEFIELD. The work was based upon a recent publication by Parkes and colleagues which may well supersede what is published on the Web site. In that study, they make a clear distinction between vaccine and wild type strains based upon that mutation. Other questions on this will have to be referred to Professor O'Leary himself who can't be here.

Mr. WAXMAN. I want to ask you whether you know if Dr. O'Leary checked the NIH Web site thoroughly before writing his abstract?

Dr. WAKEFIELD. I know for sure that he has checked the Gene Bank Web site.

Mr. WAXMAN. If it is true that this position 7901 does not distinguish between natural and vaccine strain measles, would it be fair to say that the conclusion of the abstract remains unproven?

Dr. WAKEFIELD. Yes, it would.

Mr. WAXMAN. I want to point out that we have been in contact with Dr. David W.G. Brown, the laboratory director, and Dr. L. Chen, clinical scientist. They are the head of the World Health Organization Collaborating Center for Measles in the United Kingdom. According to Dr. Brown, he says "The data presented suggesting the presence of fragments of measles vaccine in these tissue samples is not scientifically valid. The author should have reviewed the measles data base fully" and there are a number of questions he believes should have been evaluated.

I guess we will have to hear from Dr. O'Leary whether he did the work that was required in order to come up with the conclusion beyond a doubt, or whether it is a conclusion that remains to be unproven. Dr. Brown says "The approach described is scientifically flawed and will not reliably discriminate between wild and vaccine strains." He didn't know why the authors did not review available data or discuss with other measles groups with experience in this field. "Sequencing is a definitive technique to discriminate between

wild and vaccine strains of measles" and he doesn't know why that wasn't used.

I want to just make the point here in the time I have available to me that what has now been presented to us is another conclusion that has been made, but is based on some unproven information from an abstract that Dr. O'Leary is going to be submitting, which Dr. Wakefield submits to us as establishing the point he wants to make.

According to the World Health Organization Collaborator Center head, Dr. Brown, it is another unproven theory and we need to have a lot more questions answered about that particular scientific evaluation.

Mr. BURTON. Before you leave, Mr. Waxman, I think we have some later information on that and we will yield to Dr. Weldon and maybe he can bring us up to date.

Dr. WELDON. I just want to clarify this issue with Mr. Waxman.

The abstracts that we are talking about is 12 biopsies, is that correct, or you haven't seen it? It is not your publication, is that right? So you are being asked to identify something you didn't do.

Let me say for the record, I know a little bit about this issue of single mutation of a single amino acid using it as a discriminator in determining whether a population, in this case it was 12 biopsies, are wild type versus their vaccine type. You get into the statistics of this and maybe Dr. Spitzer may want to comment on this.

The statistical probability of all 12 happening to get wild type is extremely low, whereas if that is indeed a marker that is used for the vaccine type, then the statistical probability is much, much higher. Yes, you could say that some in that sample may have acquired it through a wild type but nonetheless, the statistically higher probability is that this is vaccine-related measles.

Mr. BURTON. Would any of the witnesses care to comment on that?

Dr. SPITZER. I would really have to look at the specifics of the study, would have to look at comparison groups, especially with the low sample of 12 of that sort and have a bit better understanding than you obviously have Dr. Weldon of the biology under that. Off the top of my head, I would prefer not to give an opinion and have to look at the basic data and the design and some of the biological issues before giving an opinion.

Dr. WELDON. Just for the record, so the ranking member understands, when I was an undergraduate, I did molecular genetics research and specifically we were looking at these kinds of issues in the research I did, so I am somewhat familiar with the issue they are publishing on.

Mr. WAXMAN. Would the gentleman yield?

Dr. WELDON. Yes, I would be happy to yield.

Mr. WAXMAN. It seems to me the question is either the test reliably distinguishes vaccine and natural strain or it doesn't. That really goes to the very heart of this abstract because if the test does establish that the measles in the gut of the bowel came from the natural strain or it came from the vaccine strain, we want to know whether that is established.

I think what Dr. David W.G. Brown, the head of the World Health Organization Collaborating Center for Measles in the

United Kingdom, is pointing out to us is that he thinks the conclusion that they distinguish the strain from the vaccine from other natural sources of strain is not proven by this abstract because that position of those genes can be the result of other strains not from the vaccine itself. That is the essential point that I think remains unsettled. Either it is or it isn't. Dr. Brown believes it hasn't been established. If in fact the chemical at position 7901 is from a natural measle virus or from the strain from the vaccine is the question I think needs to be established and addressed. I think we have enough questions here to really feel that we don't have the conclusion in place.

Mr. BURTON. We have to leave for a vote we are not through with this panel yet. I would just like to say we have gone from 1 in 10,000 children who are autistic and have all these kinds of variables and complications to 1 in 250 and in some cases, more than that. Something is causing it and we have to find out what it is. CDC and FDA and HHS had better get on the ball or else in 10 years, it may be 1 in 25. Something has to be done. We have to get to the bottom of this. To sit here and argue back and forth about one case study or another begs the issue. The issue is, there is a problem and it has to be solved.

We stand in recess until the call of the gavel. We will be back in 15 or 20 minutes.

[Recess.]

Mr. BURTON. Dr. Stejskal, how many people do you estimate are allergic to mercury?

Dr. STEJSKAL. What sort of mercury do you mean? Because there is a distinction when you talk about allergy, if you talk about thimerosal or other mercury?

Mr. BURTON. Something like thimerosal?

Dr. STEJSKAL. Then we have to go for patch testing which has been mostly looked at and I can tell you the numbers are not insignificant. In children, it seems to be especially often they do react to thimerosal.

Mr. BURTON. Ten percent, 20 percent, 30 percent?

Dr. STEJSKAL. No, 20 to 30 percent of those which are tested. In unselected population, that means not coming to dermatology clinics, but the number which I remember from Mueller in Sweden, it is about 15 percent.

Mr. BURTON. Fifteen percent. So anywhere from 15 to 30 percent in the children are allergic to thimerosal?

Dr. STEJSKAL. Yes.

Mr. BURTON. Dr. Krigsman, you did how many colonoscopies on those children?

Dr. KRIGSMAN. We have 43 results back from 43 patients. One patient had to be colonoscoped twice because of unexplainable worsening of symptoms. In addition to the 43 patients we have seen, 5 have been scoped already and those biopsy results are still pending.

Mr. BURTON. I know you can't make a categorical statement about this but in your opinion, do you think this was caused by just regular measles virus or do you think it was caused by the vaccines? What is your theory on this?

Dr. KRIGSMAN. I read the same papers everyone else has read and what I would like to do and what we plan on doing is attempt to replicate what Dr. Wakefield's group has published. We have everything in place, we have our lab, we have been in contact with the laboratories that have performed this test, we have the details of the assay, we have the patients. All we are waiting for now is the hospital's IRB approval. The day after we get that, we start.

Mr. BURTON. So you prefer not to theorize until you get the actual study?

Dr. KRIGSMAN. Until I do it myself, I don't know.

Mr. BURTON. We would like to have that. If you would send that to me for the record when you get it, we think that would be not insignificant. I think what you have done today by showing your results so far is very significant. I think finding the measles virus in the spinal fluid is also a very significant finding. If I were over at CDC or FDA, I think I would want to start replicating those studies right away over there before the private sector does it and they are proven wrong.

It seems to me that our health agencies ought to be ahead of the game instead of standing around waiting for the basketball game to be over and then say, oh, well, we had better do something about that.

I don't think Dr. Weldon had anymore questions for this panel, did he? I think we have pretty much covered everything with you. You have been a very good panel, you have been very patient and we appreciate your being with us. We have one more question.

Do you believe the CDC statistical studies can dismiss the clinical findings? That is what the Associated Press has said and what Reuters News Service has said. Do you believe that the CDC statistical studies can dismiss the clinical findings?

Dr. BRADSTREET. If I might take that up as a clinician treating about 1,500 children with autism between myself and my partner, a pediatrician. One of the disturbing things for me in the way this has been handled by the media is I have a patient, and I only take care of one patient at a time, even though I have 1,500 in my practice, who has a definable, biological problem. I can measuer it. I can get a laboratory test and measure autoimmunity to brain, I can find excessive amounts of mercury and I can send off biopsies and find measles virus.

We could debate whether that is the vaccine strain or the wild strain but we don't seem to be debating the fact that it is measles virus that is persisting in these children. So we have a definable biological problem that must be addressed as a clinician. The problem is that medicine has not yet given me as a clinician the tools to deal with most of these problems. So we need a lot more data that would allow me to treat.

Do the statistics somehow magically erase the laboratory results and the clinical findings and the abdominal pain and the history and the chronic diarrhea that my patients are experiencing? Absolutely not.

Mr. BURTON. Anyone else want to comment? Dr. Wakefield.

Dr. WAKEFIELD. Just to say the statistical studies of the CDC and others have actually tested the wrong hypothesis and this point was made in the paper that was commissioned by the Insti-

tute of Medicine for the review on MMR last year. Until they set about testing the correct hypothesis for a relationship between vaccines, be they thimerosal or MMR or both and autism, then they will continue to come up with ambiguous or negative conclusions.

Mr. BURTON. Anyone else?

Dr. STEJSKAL. I would like you to put up the overhead and I would stress again that I am sure case control studies when you just pull up all autistic children against all controls which may be asymptomatic, will have us power to tell you anything. The effect of risk factor may be diluted. So if we are now talking about mercury sensitization or weak mercury detoxification as a factor in these, normal case control study will not catch this. This paper is saying the effect of risk factor may be diluted in heterogeneous population. Analysis has to be based on the clinical markers of susceptibility either for toxicity or biology but on the biomarkers. These biomarkers can be enzymes for detoxification. You have to select patients, autistic children, for this and then you have to do allergy studies. So analysis based on clinical markers of susceptibility which are phenotype markers but also genetic markers if they are available and this may be one way to separate causes and identify specific and environmental risk factors.

I think this is very important that the new studies which should be set up would be done so we can really measure and find the causes.

Dr. WELDON. I just have one quick followup question. One of the issues I have had a bit of a problem with over the years we have looked at this issue is we hear about mercury and MMR and it is hard to take some of this credibly with people talking about various different causes of autism related to vaccines.

If I understand correctly, Dr. Stejskal, and you two gentlemen talked about this as well, there may be a population of kids out there that are at some sort of genetic predisposition and mercury is somehow like an enhancing agent to allow the measles component of the MMR to cause this abnormal reaction that we are describing as autistic colitis, regressive autism, correct?

Dr. STEJSKAL. Yes. There is evidence from animal studies, as I told you, which are quoted in this paper of the Working Party of the European Agency who says in studies this is the case. Mercury will compromise the immune system.

Dr. WELDON. The reason ethyl mercury or thimerosal was removed first from topical agents by FDA and then later ordered to be removed from all vaccines is because it was causing a hypersensitivity reaction?

Dr. STEJSKAL. That is right. The same with penicillin and sulfur drugs, that was the same thing. A topical application is always the most frequent one for produce of sensitization which doesn't mean that other applications don't.

Dr. BRADSTREET. If I might add, the data is quite compelling that in autism we see autoantibodies to myelin basic protein. We have been able to verify Dr. Singh's work with multiple different commercial clinical laboratories and it is clearly reproducible. So we know we have a very large percentage of children with autism who make antibodies to myelin basic protein. Interestingly enough, one

of the well documented biomarkers for mercury toxicity, also a biomarker for lead toxicity, are antibodies to myelin basic protein.

The intriguing thing for me is the way that mercury alters the immune response, changing it. So rather than a normal, let us get rid of the virus response, ut changes to an autoimmune response and allows for viral persistence. A response which is exactly what we have measured and presented at the American Society of Microbiology meeting, where there is evidence for viral persistence and evidence for autoimmunity in the presence of viral persistence. That I think is quite compelling that there is, in fact, a priming event where thimerosal, the mercury containing component, and we haven't talked about aluminum but I think aluminum in the vaccines is a very important part of that priming event as well, as are other vaccine constituents, set up the child's immune system so when the live virus is provided, and I think the route of administration, jabbing the kid as opposed to natural barrier mechanisms of administration is important too, clearly makes a difference in the child's response. I think the child then is set up for viral persistence and the host of complications we see as a result of that.

Dr. WELDON. It is safe to say that the work in this area is very, very preliminary?

Dr. BRADSTREET. Indeed.

Mr. BURTON. I think that covers the first panel. Thank you very much once again. You are welcome to stay around and listen to the testimony of the people from the health agencies if you so choose.

We will now welcome the second panel: Dr. Roger Bernier of the Centers for Disease Control and Prevention and those accompanying you, Dr. Robert Chen, Dr. Frank DeStefano, Dr. Stephen Foote from NIH and Dr. William Egan from the FDA. Would you please come forward?

Can I ask you to please rise to be sworn, please?

[Witnesses sworn.]

Mr. BURTON. I understand some of you have an opening statement? Dr. Bernier, you have an opening statement?

Dr. BERNIER. Yes, Mr. Chairman.

Mr. BURTON. Proceed.

STATEMENT OF DR. ROGER BERNIER, ASSOCIATE DIRECTOR FOR SCIENCE, OFFICE OF DIRECTOR, CENTERS FOR DISEASE CONTROL AND PREVENTION, ACCOMPANIED BY DR. WILLIAM EGAN, FOOD AND DRUG ADMINISTRATION; DR. STEPHEN FOOTE, NATIONAL INSTITUTES OF HEALTH; AND DR. FRANK DESTEFANO AND DR. ROBERT CHEN, CDC

Dr. BERNIER. Good afternoon, Mr. Chairman and other members of the committee.

I am Dr. Roger Bernier from the Centers for Disease Control and Prevention. Thank you for the opportunity to testify today on CDC's activities on vaccine safety research. I am accompanied today by Dr. William Egan of the Food and Drug Administration, Dr. Stephen Foote from the National Institutes of Health; and at your request, Dr. Robert Chen and Dr. Frank DeStefano from CDC are also here to respond to questions.

Autism spectrum disorders are a group of lifelong developmental disabilities caused by an abnormality of the brain. Most recent data

suggests that between 2 and 6 children per 1,000 have ASD or autism spectrum disorders. The impact on families of children diagnosed with ASD is tremendous. The Department of Health and Human Services is dedicated to finding the answer to what causes autism and how it can be prevented. While my focus today is on vaccine safety related issues, it should be noted that HHS has implemented an Interagency Autism Coordinating Committee. The activities of this committee highlight the large scale coordinated response that has been launched by HHS in order to understand, prevent and treat autism.

Some parents, researchers and others have expressed concerns about potential links between autism and vaccines currently being used in the United States, focusing primarily on thimerosal, a preservative in some vaccines and second, on measles, mumps and rubella vaccine.

In mid-1999, the U.S. Public Health Service agencies, including NIH, FDA, HRSA and CDC took action working collaboratively with the American Academy of Pediatrics, the American Academy of Family Physicians, and vaccine manufacturers to begin removing thimerosal from the vaccine supply. While the risk of harm was only theoretical, the decision was made as a precautionary measure in order to reduce overall mercury exposure of infants. As a result of this action, all manufacturers are now producing only vaccines that are free of thimerosal or have only trace amounts for routine infant immunization.

The suggestion that MMR vaccine, which has never contained thimerosal, triggers autism was initially based on some reports of cases of autism in which parents noted the onset of autistic behaviors shortly after MMR vaccination. Over the last few years, a number of studies have been performed in countries around the world to address this issue. Systematic scientific reviews by some of the most prestigious medical bodies around the world, including the Medical Research Council of the UK, the American Academy of Pediatrics and the Institute of Medicine of the National Academy of Sciences in the United States have unanimously concluded that evidence does not support a relationship between MMR and autism.

CDC is actively involved in detecting and investigating vaccine safety concerns and supporting a wide range of vaccine safety research to address safety questions. We talked earlier about the VSD. In order to enhance the understanding of rare, adverse effects of vaccines, CDC did develop the VSD in 1990. The project is a collaborative effort which utilizes the data bases of eight large HMOs. The data base contains comprehensive medical and immunization histories of approximately 7.5 million children and adults. The VSD enables vaccine safety research studies comparing evidence of health problems between unvaccinated and vaccinated people.

Another critical part of our vaccine safety effort is the objective scientific evaluation of safety concerns by independent experts. In this report regarding association between MMR vaccine and autism spectrum disorder in April 2001, the IOM made several recommendations regarding future research. CDC takes this issue very seriously and is currently funding five separate research stud-

ies that address the recommendations from the IOM. These are described in my written testimony.

In October 2001, the IOM Committee published a report on the possible association between thimerosal containing vaccines and neurodevelopmental disorders. In this report, the IOM concluded, "The evidence is inadequate to accept or reject a causal relationship between exposure to thimerosal from childhood vaccines and the neurodevelopmental disorders of autism, ADHD and speech or language delay." The IOM made several recommendations regarding future research on this topic and CDC takes this issue very seriously and has undertaken six separate studies that address the IOM recommendations. These are also described in my written testimony.

We remain vigilant to assure the safety of vaccines. We must also remember that vaccines benefit the public by protecting persons from the consequences of infectious diseases. Continued high U.S. vaccination rates are crucial to prevent the spread of diseases such as measles, pertussis and rubella among U.S. children. Vaccines are cited as one of the greatest achievements of biomedical science and public health in the 20th century. We can point to the remarkable success we have had in controlling numerous infectious diseases which used to be widely prevalent in the United States including polio, measles, pertussis and others. In fact, several of these vaccine preventable infectious diseases are known to cause developmental disabilities including hemophalous influenza Type B or Hib vaccine and congenital rubella syndrome, one of the few known causes of autism. Rubella vaccine, by preventing CRS, thus prevents some cases of autism. Prior to routine immunization with Hib vaccine, of young children who developed Hib meningitis, 5 percent died and another 15 to 30 percent were left with residual brain damage leading to language disorders and mental retardation.

In conclusion, CDC remains committed to collecting accurate data on the prevalence of autism and conducting studies on vaccine safety. Research is already underway and more is planned to look at the relationship between the MMR vaccine and autism, and also on thimerosal related questions. We want each child to be born healthy and to grow and develop normally so that they are able to lead productive lives. Vaccines are one of our most valuable weapons against disease and have afforded us one of our proudest achievements in public health.

Thank you, Mr. Chairman and members of the committee for the opportunity to testify before you today. I would be happy to answer any questions you might have.

[The prepared statement of Dr. Bernier follows:]

Testimony
Before the Committee on Government Reform
United States House of Representatives

CDC's Vaccine Safety Research Activities

Statement of
Roger Bernier, Ph.D., M.P.H.
Associate Director for Science,
National Immunization Program
Centers for Disease Control and Prevention,
U.S. Department of Health and Human Services

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For Release on Delivery
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Good afternoon Mr. Chairman, Congressman Waxman, and members of the Committee. I am Dr. Roger Bernier, of the National Immunization Program at the Centers for Disease Control and Prevention (CDC). Thank you for the opportunity to testify today on CDC's activities on vaccine safety research.

I am accompanied today by Dr. William Egan, Deputy Director, Office of Vaccines Research and Review, Center for Biologics Evaluation and Review, Food and Drug Administration, and Dr. Stephen Foote, Director, Division of Neuroscience and Basic Behavioral Science, National Institute of Mental Health, National Institutes of Health. At your request, Dr. Robert Chen of CDC's National Immunization Program and Dr. Frank DeStefano of CDC's National Center on Birth Defects and Developmental Disabilities are here to respond to questions.

AUTISM AND VACCINES

Autism spectrum disorders (ASD) are a group of life-long developmental disabilities caused by an abnormality of the brain. The most recent data suggests that between 2 and 6 children per 1,000 have ASD. The impact on families of children diagnosed with autism spectrum disorders is tremendous. We recognize that there is considerable public interest and concern on this issue and we are committed to addressing concerns of parents and families. The Department of Health and Human Services (HHS) is dedicated to finding the answer to what causes autism and how it can be prevented. There is a great deal of ongoing research throughout the various public health agencies. While my focus today is on vaccine safety related issues, it should be noted that HHS has implemented an Interagency Autism Coordinating Committee (IACC). The IACC is

composed of representatives from MIH (top which the Department has delegated a leadership role in organizing and supporting the committee), CDC, FDA, the Health Resources and Services Administration (HRSA), the Agency for Toxic Substances and Disease Registry (ATSDR), the Substance Abuse and Mental Health Services Administration (SAMHSA), the Department of Education, and four public members appointed by the Secretary of HHS. The IACC takes as its mandate enhanced coordination of the autism-related activities of these federal agencies, from biomedical research to services delivery. At the most recent IACC meeting, topics included the progress being made on implementation of autism research centers programs by NIH and CDC; efforts to comprehensively map the autism research field in order to analyze its strengths and weaknesses; information about each of the individual grants that collectively constitute the majority of the NIH autism research portfolio; strategies to improve the coordination of gene and tissue banking, data sharing, and federal interactions with voluntary organizations; and, strategic planning for the development of treatments and interventions for autism. The activities of this committee highlight the large-scale, coordinated response that has been launched by HHS in order to understand, prevent and treat autism.

Some parents, researchers and others have expressed concerns about a potential link between autism and vaccines currently being used in the United States, focusing primarily on thimerosal, a preservative in some vaccines, and secondly, on measles, mumps, and rubella (MMR) vaccine.

In mid-1999, the United States Public Health Service agencies, including NIH, FDA, HRSA, and CDC took action, working collaboratively with the American Academy of Pediatrics, the

American Academy of Family Physicians and the vaccine manufacturers, to begin removing thimerosal preservative from the vaccine supply. While the risk of harm was only theoretical, the decision was made as a precautionary measure in order to reduce overall mercury exposure of infants. As a result of this action, all manufacturers are now producing only vaccines that are free of thimerosal as a preservative for routine infant immunization.

The suggestion that MMR vaccine, which has never contained thimerosal, triggers autism was initially based on some reports of cases of autism in which parents noted the onset of autistic behaviors shortly after MMR vaccination. Over the last few years, a number of studies have been performed in countries around the world to address this issue. Systematic scientific reviews by some of the most prestigious medical bodies around the world including the Medical Research Council in the United Kingdom, the American Academy of Pediatrics, and the Institute of Medicine of the National Academy of Sciences have unanimously concluded that evidence does not support a relationship between MMR and autism. The most recent review was conducted in the United Kingdom and commissioned by the British Medical Association. British experts reviewed five decades of research on the MMR vaccine and concluded that there is no link to autism or bowel disease. However, despite these findings and because of continued public concerns, CDC is committed to further scientific research on this issue as detailed in this testimony.

CDC'S COMMITMENT TO VACCINE SAFETY

CDC is actively involved in detecting and investigating vaccine safety concerns and supporting a

wide range of vaccine safety research to address safety questions.

In order to enhance the understanding of rare adverse effects of vaccines, CDC developed the Vaccine Safety Datalink (VSD) project in 1990. This project is a collaborative effort, which utilizes the databases of eight large health maintenance organizations (HMOs). The database contains comprehensive medical and immunization histories of approximately 7.5 million children and adults. The VSD enables vaccine safety research studies comparing incidence of health problems between unvaccinated and vaccinated people. Over the past decade, the VSD has been used to answer many vaccine-related questions, and has been used to support policy changes that have reduced adverse effects from vaccines.

CDC recognizes the importance of data sharing when questions are raised regarding a particular study's design and methodology. Therefore, CDC has been actively engaged with the participating HMOs to determine how their clients' personal medical records can be maintained confidentially and the proprietary interests of the HMOs protected, while still allowing for external researchers to reanalyze the data from studies which have been conducted through the Vaccine Safety Datalink. As a result, CDC has developed a data sharing process designed to allow an independent researcher to replicate or conduct a modified analysis of a previous VSD study, while maintaining the confidential nature of the data.

Another critical part of our vaccine safety effort is the objective, scientific evaluation of safety concerns by independent experts. In collaboration with NIH and other U. S. Public Health

Service agencies, CDC requested the Institute of Medicine (IOM) to conduct independent reviews by independent scientific experts to determine: 1) whether the available scientific information favors, or does not favor, vaccines playing a role in causation, 2) the level of public health priority the concern should receive, and 3) recommendations for research. The IOM Immunization Safety Review Committee has released reports on MMR Vaccine and Autism, Thimerosal and Neurodevelopmental Disorders, Hepatitis B and Neurological Disorders and the Multiple Immunizations and Immune Dysfunction. The IOM was asked to review the available scientific information on these issues. CDC has initiated a broad range of studies to address recommendations made by the IOM Immunization Safety Review Committee.

MMR and Autism Studies

In its report regarding the association between the MMR vaccine and autism spectrum disorder (ASD) in April 2001, the IOM concluded "the evidence favors rejection of a causal relationship at the population level between MMR vaccine and autism spectrum disorder." The IOM made several recommendations regarding future research including the following epidemiological studies:

1. Explore whether exposure to MMR vaccine is a risk factor for ASD in a small number of children;

2. Develop targeted investigations of whether or not measles vaccine-strain virus is present in the intestines of some children with ASD;

3. Study the possible effects of different MMR immunization exposures; and

4. Conduct further clinical and epidemiological studies of sufficient rigor to identify risk factors and biological markers of ASD in order to better understand genetic or environmental causes.

CDC takes this issue very seriously and therefore, is currently funding five research studies that address the above four recommendations from the IOM:

The first study, the Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP) MMR/Autism Study, is a large case-control study. The autism cases for the study were identified through MADDSP. The control subjects were selected from the same or similar schools in the Atlanta area and matched to cases based on age and gender. The study is assessing the relationship between the timing of receipt of the first MMR vaccine and risk for developing autism. The analyses for this study and a manuscript should be completed by early fall 2002.

The second study, the MMR/Regression Autism Study funded by CDC and the National Institutes of Child Health and Human Development (NICHD) is also a large case-control study that is using a sample of autism cases identified as part of the NICHD and the National Institute on Deafness and other Communication Disorders (NIDCD) 10 Collaborative Programs of Excellence in Autism (CPEA). This study is specifically designed to examine the association between regression autism and the timing of first receipt of the MMR vaccine. The study is being

carried out over a three-year period and results from this study are expected in the spring of 2004.

The third study, the Denmark MMR/Autism Study, is a recent study that was carried out in Denmark in collaboration with CDC. The study was designed to follow-up on approximately 537,000 children born in Denmark during the period from January 1, 1991 to December 31, 1998. Of these, 82% received MMR vaccine. The cohort was generated based on data obtained from the Danish Civil Registration System and subsequently linked with other national registries. This manuscript has been submitted for publication this year.

The fourth study is a large epidemiological study to identify risk factors and biological markers of ASD to better understand genetic or environmental causes. The study is being planned in the four Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE), which are being supported by CDC.

Additionally, CDC is in the early stages of planning a study to investigate whether or not measles vaccine-strain virus is present in the intestines of some children with ASD.
There have been a limited number of laboratory reports of the finding of measles virus sequences in intestinal tissue and white blood cells of children with ASD; therefore, there has been speculation that MMR vaccine either precipitates or aggravates ASD. However, other epidemiologic and laboratory studies do not support this observation. To resolve differences in results from previous studies that may have occurred due to differences in study design, sampling

biases, and differences in laboratory asstesting procedures and their sensitivity, an independent, multicenter study is being designed. The study plan is to determine the prevalence of measles virus vaccine strain gene sequences in bowel biopsy tissue from children with gastrointestinal tract complaints with and without ASD. The study will be designed to ensure use of standardized clinical and laboratory protocols, appropriate enrollment of controls, blinding of specimens, use of standardized laboratory reagents and assays, and appropriate statistical evaluation.

Thimerosal and Neurodevelopmental Delay Studies

In October 2001, the IOM Immunization Safety Review Committee published a report on the possible association between thimerosal-containing vaccines and neurodevelopmental disorders. In this report, the IOM concluded "that the evidence is inadequate to accept or reject a causal relationship between exposure to thimerosal from childhood vaccines and the neurodevelopmental disorders of autism, ADHD (attention deficit hyperactivitity disorder), and speech or language delay." The IOM made several recommendations regarding future research studies including several epidemiological studies. They recommended:

A. Case-control studies examining the potential link between neurodevelopmental disorders and thimerosal-containing vaccines;

B. Further analysis of neurodevelopmental outcomes in several cohorts of children outside the U.S. who participated in a clinical trial of DTaP vaccine; and,

C. Conducting epidemiological studies that compare the incidence and prevalence of neurodevelopmental disorders before and after the removal of thimerosal from vaccines.

While there have been no vaccines being produced for routine childhood immunization for over a year that contain thimerosal as a preservative, CDC takes this issue very seriously and therefore, has undertaken several studies that address the above IOM recommendations:

The first study, the Thimerosal Screening Analysis in the Vaccine Safety Datalink (VSD) project, was started in the fall of 1999. The VSD, described earlier, was used to screen for possible associations between exposure to thimerosal-containing vaccines and a variety of renal, neurologic and developmental problems. In the first phase of this study, the CDC used data from the 2 VSD HMOs with automated outpatient data (where more subtle effects of mercury toxicity might be seen). The CDC and VSD researchers found statistically significant associations between thimerosal and neurodevelopmental disorders, such as language and speech delays, ADHD, stuttering, and tics. No association was shown with autism. However, the associations were weak and were not consistent between the two HMOs. In the second phase of the investigation, CDC investigators examined data from a third HMO with similar available automated vaccination and outpatient databases to see if these findings could be replicated. Analyses of these data using the same methods as the first study did not confirm results seen in the first phase. A statistically significant relationship between autism and thimerosal was not found in either the preliminary study or the later, larger analysis. Due to the methodological

limitations of the screening analysis using automated data and the difference between the preliminary study and the later analyses, the results required further examination.

CDC and VSD researchers are committed to clarifying the results encountered during the VSD Screening Analysis; therefore, a Thimerosal Follow-Up Study will be conducted. This second study will be designed to assess whether preliminary results from automated data used in the Thimerosal Screening Analysis can be confirmed using objective neuropsychological testing. The study will focus on the conditions found in the first screening analyses, including language and speech delays and ADHD. The design of the new study will address the main drawback of the Thimerosal Screening Analysis, which was that children were not objectively assessed on the neurodevelopmental disorders of interest. The various VSD HMOs categorize neurodevelopmental disabilities in different ways, provide different services for these disorders, and often refer children out of the health care network when they are identified with these particular disorders.

The Thimerosal Follow-Up Study is planned to examine approximately 1200 children between the ages of 7 and 9 years of age randomly selected from four VSD HMOs based on thimerosal exposure during the first 3 months of life. All 1200 children will be brought into their respective HMOs and will be assessed using a standardized set of neuropsychological test batteries. The preliminary proposal for this study was presented to a panel of external consultants including a consumer representative in March of 2001. In September of 2001, CDC awarded a contract to Abt Associates Inc. to carry out the planning phase of the study. The panel of external

consultants continues to provide individual input into the study design and the planning phase should be completed by June 2002. Data collection is expected to begin in the latter half of 2002. Abt Associates Inc. is expected to present the results of the study by the end of 2003.

Several additional studies are being planned to address additional issues raised by the IOM. These include:

The Thimerosal/Autism Study will be a case-control study to be conducted simultaneously with the Thimerosal Follow-up Study. Autism cases identified through review of automated medical records will be assessed objectively by using a standardized autism assessment tool. Controls will be selected from the Thimerosal Follow-up Study and matched to cases by age and sex.

CDC has developed a proposal for a pilot study to conduct further analyses of a group of Italian children who had participated in a prior DTaP trial in which thimerosal exposure was randomly allocated. CDC is pursuing this to determine the feasibility of recruiting these participates for a follow-up study of neurodevelopmental outcomes.

Two other studies being planned will examine changes over time in the diagnosis of neurodevelopmental delays including autism. These studies will use inpatient and outpatient discharge diagnoses to compare rates of these conditions over time with changes in levels of thimerosal in recommended childhood vaccines. Because recommendations for the removal of thimerosal from vaccines did not occur until 1999, several years of data following the removal of thimerosal will be necessary before these comparisons can be made. Thus, results will not be

available until 2005 or later.

BENEFITS OF VACCINES

We remain vigilant to assure the safety of vaccines. We must also remember that vaccines benefit the public by protecting persons from the consequences of infectious diseases. Continued high U.S. vaccination rates are crucial to prevent the spread of diseases such as measles, pertussis (whooping cough) and rubella among U.S. children. Current measles coverage is approximately 91% in children 19-35 months old and about 97% at school entry, and only about 100 cases of measles have been reported per year; many of the cases are imported; and ongoing indigenous transmission of measles no longer occurs. From 1989-91, a measles epidemic in the United States led to more than 55,000 cases of measles and more than 11,000 hospitalizations, with 123 deaths in three years. Before this epidemic, vaccination coverage was estimated at 61-66% nationally and at 51-79% in 15 major cities. These outbreaks stopped only when vaccination coverage increased. Thus, if pre-school coverage dropped by 25-30% below the current level, large measles outbreaks are likely to occur once again. Additionally, pertussis has continued to be a public health threat. For example, in 1999, there were 7297 cases of pertussis in the United States, with 15 reported deaths.

Vaccines are cited as one of the greatest achievements of biomedical science and public health in the 20th century. We can point to the remarkable success we have had in controlling numerous infectious diseases which used to be widely prevalent in the United States, including polio, measles, and pertussis. In fact, several of these vaccine-preventable infectious diseases are known to cause developmental disabilities, including Haemophilus influenzae type b (Hib) and

congenital rubella syndrome (CRS), one of the few known causes of autism. Rubella vaccine, by preventing CRS, thus prevents some cases of autism. Prior to routine immunization with Hib vaccine, of young children who developed Hib meningitis, 5 percent died and another 15 to 30 percent were left with residual brain damage leading to language disorders and mental retardation.

While we have made great progress to reduce the number of cases of vaccine-preventable diseases, the threats posed by vaccine-preventable diseases are known and real. The viruses and bacteria that cause vaccine-preventable diseases still circulate in the U.S. and around the world. Maintaining vaccination coverage and high levels of immunity are crucial to protect the U.S. population and to continue progress toward elimination of diseases that, at one time, caused millions of infections in the U.S. each year and that globally remain the leading causes of death and of preventable birth defects.

CONCLUSION

CDC remains committed to collecting accurate data on prevalence of autism and conducting studies on vaccine safety. Research is already underway, and more is planned, to look at the relationship between the MMR vaccine and autism. We want each child to be born healthy and to grow and develop normally, so that they are able to lead productive lives. Vaccines are one of our most valuable weapons against disease and have afforded us one of our proudest achievements in public health.

Thank you, Mr. Chairman and members of the Committee, for the opportunity to testify before you today. I would be happy to answer any questions that you may have.

Mr. BURTON. I will start the questioning.

How do you account for the epidemic of autism? It has gone from 1 in 10,000 and maybe it was because of reporting, maybe it was more than that, maybe it was 1 in 5,000 but now HHS says it is 1 in 250. How do you account for the epidemic, the growth in the epidemic?

Dr. BERNIER. I will let my colleague, Dr. DeStefano, answer that because he works in the Center for Birth Defects and Developmental Disabilities where the autism research is carried out.

Dr. DESTEFANO. I think this is a complex issue that we are studying as well as NIH to try to resolve what is going on. It is clear from current data that more children and other people do have autism than was felt to be the case in the past. Current estimates are that between 2 and 6 per 1,000 children have an autism spectrum disorder and that is probably tenfold higher than what was believed in earlier years.

The question is, is this an increase or is it due to better ascertainment, changes in diagnostic criteria, etc. We are trying to get a better estimate and are funding studies at CDC and several States to determine what the prevalence of autism is, if there is geographic variability, and to be able to monitor its occurrence in the future. Unfortunately data used different criteria and there was different knowledge of autism in the past. I don't believe we are ever going to be able to resolve definitively whether this has been an increase due to changes in diagnostic criteria and ascertainment versus a true increase in disease occurrence. We will get some leads on that as we better determine what the causes of autism are.

Mr. BURTON. That is a long way of saying you don't know why there is this tremendous increase?

Dr. DESTEFANO. That is right. That is why there is research going on to try to determine its causes.

Mr. BURTON. Have you replicated any of the studies of the doctors we had before the committee today, Dr. Wakefield or any of the others? Has CDC or HHS tried to replicate their studies?

Dr. BERNIER. I think in some of these 11 studies that I alluded to, 5 relating to MMR and autism and 6 that are thimerosal related. There is going to be an effort led by CDC to try to create a multi-centered laboratory study that will examine some of the same questions that Dr. Wakefield and others have looked at, so yes, that effort is underway and good progress has been made in trying to organize this kind of multi-centered study but we are trying to do this in such a way that we can overcome some of the shortcomings or limitations that may have existed on some of the earlier work.

Mr. BURTON. So what you are saying is you are in the process of doing it now but you have not yet done it?

Dr. BERNIER. Specifically relating to the work that Dr. Wakefield and his colleagues have done, that is correct, but there is a lot of other work that has been done and has been reviewed by the IOM and these other committees that I have talked about. I wouldn't want to leave the impression that there is a big void of information. I wouldn't want to leave the impression that we know everything

we should know and I certainly don't want to leave the impression that there is a void either.

Mr. BURTON. How long have we been talking about this? How many times have I had people from HHS and FDA up here? It has been a couple of years, hasn't it?

Dr. BERNIER. It has been often.

Mr. BURTON. Two or 3 years? Yes, it has been often. Now you are starting to look into it. I want to tell you we appreciate that and I am sorry it took so much prodding to get it started.

We were talking about the vaccine safety datalink. For 2 years now we have tried to get that information so that other doctors and scientists who are not connected to our health agencies, who have credentials, could start using that information to do studies on their own. We were told in January or February that was going to be made public. Before this hearing, we asked why it had not yet been made available to responsible people in the scientific community and we were told, it has been made available. I didn't know it. Did you make any kind of report to the public that you had announced this in a press release or anything?

Dr. CHEN. I think several members of the audience were present at the meeting and we discussed several issues. The VSD project is a very important and unusual project that contains the personal medical records of about 7.5 million persons in the United States. With all the public concern about data privacy, it is very important to work out a process in which we can balance the need to respect the privacy of these individual's medical records on the one hand, as well as the desire for us to have researchers be able to independently look at the data.

It has taken us 2 years to develop a process, when we first approached the HMOs, there were severe concerns by all of them that they would not agree to this and that they would withdraw from the project. So we have had to take the time to work out a compromise in which they would still be willing to participate in this partnership with the Government in terms of our ability to look at data safety issues as well as meet the needs of the HMOs in terms of protecting their privacy. I think that answers the question in terms of why it has taken time, so we have come from where each of the HMOs, not only the principal investigators, but also their governing bodies were opposed to this idea and we have worked with each of them to convince them to come around the other way, to accept the research data center. This convinving is what has taken a considerable amount of time.

Mr. BURTON. Let me pursue this. So in February, you had a meeting and other CDC employees were involved with committee staff and they discussed the release of the Vaccine Safety Datalink raw data to researchers. At that meeting, CDC provided a draft proposal. It is in your file there, exhibit No. 1 for researchers to access the VSD data. At that time, the staff was told the project was ready to go in February.

[Exhibit 1 follows:]

Data Sharing Principles and System

National Immunization Program (NIP)

Draft Proposal 2/21/02

Background: Science relies on the replication of study findings by independent researchers. The science of epidemiology likewise benefits when different researchers address the same question, examine it from different perspectives, and compare their results. Unlike the basic laboratory sciences, epidemiologic research relies on the complex analyses of large amounts of information obtained directly or indirectly from individuals. Historically, replication of epidemiologic findings has relied on repeating a study in another population. However, given the large number of individual patient records contained in NIP's Vaccine Safety Datalink (VSD), other researchers would need access to the original data set to verify or refute the original results.

The decision to allow access to database involves more than the original researchers' confidence in their results and their willingness to permit replication of the original analyses. Also involved are the confidentiality of individual patient records and the proprietary interest of the companies that collect the information as part of their business practice.

The American College of Epidemiology has proposed 10 principles as a guide to epidemiologists interested in data sharing. Relevant selections from these principles include:

> Under appropriate conditions, data sharing enhances the veracity of epidemiologic findings and enhances science.
> The rights and privacy of people who participate in epidemiologic research must be protected.
> Limited informed consent for future use of data beyond the original study should be obtained.
> Data should be made available for sharing as soon as possible after the completion of the original study, preferably at the time of publication.
>
> Archiving of unique data sets should be encouraged.
> Cost of making data available to secondary users should be borne by the secondary user.
> Data sharing is not always appropriate. The decision to release a data set should be made by an Institutional Review Board after the secondary user has explained precautions to be taken and made a pledge to protect the confidentiality of individually identifiable data.

It is preferable for secondary investigators to work with original investigators (sometimes on site) to understand the nuances involved in data collection, the reliability of variables, and the particularities of the data set.

Co-authorship of the original investigators should not be requirement for release of the data set to other researchers. The secondary analyses should be peer-reviewed by the original researchers.

Established CDC Model - NCHS Research Data Center: CDC's National Center for Health Statistics (NCHS) has established a system to permit access to potentially confidential data collected through their national surveys using their Research Data Center (RDC). The RDC is a physical space where researchers are allowed controlled access to restricted data files. Access depends on NCHS approval of a research proposal, as outlined below.

NCHS reviews projects based on their scientific and technical feasibility, availability of RDC resources, risk of disclosure of confidential or restrained information and whether each proposal meets NCHS's mission to provide statistical information that will guide policies to improve the health of the American people. The review board consists of the RDC director, the NCHS Confidentiality Officer, staff involved in the original survey, and a RDC staff person assigned to oversee the project. This board meets within 3-4 weeks of receipt of a proposal and if it is approved, the RDC prepares a data set containing the requested variables. On-site use of data sets at the RDC costs $1,000 per week. More than one researcher may work on the project at the RDC site.

NIP Proposed system: Based on the American College of Epidemiology's principles and the NCHS model, NIP proposes to make VSD data available for the independent re-evaluation of publically reported VSD research studies as described below.

Research proposals would be submitted to NIP and contain the following:

Cover letter
Project Title
Abstract
Full personal identification and institutional affiliation of researchers
Current resume or *Curriculum vitae* of the principal investigator
Proposed dates for conducting the analyses at the RDC (or equivalent)
Source of funding
Detailed summary of the

proposed research

Complete list of requested data including fields, variables, years etc. Details of any data that may be merged with the data provided by NIP. This includes documentation, file layout, and number of records

Software requirements

NIP will review the submitted proposal for its completeness and feasibility and to determine which HMOs' data will be necessary to complete the project. If these conditions are met, NIP will send the proposal to the IRBs of each involved HMO.

Each HMO's IRB must review and approve the proposal.
Once approval is obtained from each involved HMO's IRB, the principal investigator will make arrangements with NIP to conduct the analyses at NCHS RDC (or equivalent). NIP will prepare the necessary files.

Before using the files, each researcher must sign a 308(d) Assurance of Confidentiality Agreement.
Each researcher will conduct the approved analyses at the established RDC (or equivalent.
Researchers will be allowed to leave only with copies of their summary results after they have been reviewed for confidential information.

Researchers will be charged a fee, dependent upon the costs of the study.

Dr. CHEN. That is correct.

Mr. BURTON. We did not receive up to this meeting today a press release or an advertisement in any medical journal or on any CDC Web site regarding this new program. If you are going to make an announcement, how do you propose to let anybody know unless you tell us?

Dr. CHEN. As I mentioned at the meeting to the people that were present, this is the first time we have tried to develop this mechanism with the National Center for Health Statistics. It is a pilot project using their Research Data Center which historically has not made this type of personal medical records available for public use. This center has been used only for public access to results of national health interview surveys, generally conducted kind of over the telephone, where people are willing to answer questions about their health status. This is a pilot process, so until we work out all the potential concerns through the first couple of test projects, it is our sense that it would be premature to widely advertise it.

Mr. BURTON. With the quantum leaps that we have seen in technology, there is not any real risk if you don't want the researchers from the outside to know who the individuals are on the data. You can do that, you can protect the privacy of those individuals. You can make sure there is no public announcement about that.

Dr. CHEN. Unfortunately, that turns out not to be really feasible in this data base. If you could imagine that for any vaccine safety study, you need several parameters that are key to be able to conduct the analysis. You need to know the date of birth of that individual, the date of vaccination of that person and any medical visits and what diagnoses they had. You need those elements in order to be able to do your analysis. It turns out that with the key variable on date of birth, so this was one of the major concerns expressed by one of our HMOs in Colorado, the principal investigators, his daughter recently had a sprained ankle and therefore, he posed hypothetically to his analyst that if you attended a birthday party and knew my daughter's date of birth and you also happened to find out the child had a sprained ankle the previous week, could you find this child? In fact, he very easily was able to find the medical record of the PI's daughter.

Mr. BURTON. I see where you are going. We are talking about how many people, 6 million?

Dr. CHEN. 7.5 million.

Mr. BURTON. And you are concerned because there is a sprained ankle, somebody goes to a party, they might be able to tell by using the birthdate who this person was.

Dr. BERNIER. Mr. Chairman, may I interject, if I may? I want to put on the record very clearly that CDC does support sharing information and trying to work transparently which I think is where you have been trying to get us to go.

Mr. BURTON. What I am trying to find out right now is why when we were told in February they were going to release this, every day is important to people who are going through these problems, my grandson, my granddaughter, all these people out here who have kids who are autistic, the people whose kids are becoming autistic, every day is important to them. When we were told in February we were going to get information and here we are at

the end of June and haven't received it, and we have been told, it was made public a long time ago but nobody knew it, that is important. That is what I am trying to get at here. If you made a decision, why didn't you tell us? Why didn't we know about it? Why didn't all these people and the scientific community that wanted to get started on this, why weren't they told about it?

Dr. BERNIER. First of all, we have been trying to strike the right balance between the interests of all the concerned parties. That is part of the reason. The other thing is this is new for us. We are not interested in highly publicizing something where it is a pilot type of project. When we can iron out the wrinkles, we potentially will be in a position to make this more available. Part of this is this is a new pilot project and there have been efforts to try, as Dr. Chen alluded to, to protect the cooperation of the HMOs. We have the proprietary interests of the HMOs and the privacy rights of the patients, so we are trying to strike a balance and we are trying to make this work as smoothly as possible. We don't know all of the issues we will confront when we do bring in these researchers to reanalyze some of the studies we have done. So we are trying to move cautiously so that we can do so, but we will get to where you are going for people who want to reanalyze studies that CDC has done and the VSD.

Mr. BURTON. I have more questions but I will yield to my colleagues. As I said before as I yield to Dr. Weldon, we all want you to be cautious, we don't want to make mistakes. We all support vaccinations done in a responsible way because it has protected the health of this country, but you have people every day starting to suffer. There are huge quantities of people who have children now suffering under these diseases. The quicker we move, the better and the more people that get involved in the research, the better. Having outside responsible scientists having this data so they can get started on it quickly is very, very important.

Dr. Weldon.

Dr. WELDON. Let me start by saying to you, Dr. Bernier, we all support the vaccine program. I am a physician and I vaccinate hundreds and hundreds of people every year in my practice. We all recognize the tremendous accomplishment of the vaccine program in preventing death and morbidity in the United States and world over.

We have had a lot of hearings on this issue over the years. A lot of people from the vaccine community come forward and point out all of that over and over again. We don't really question any of that. Our concern is that there has been clinical evidence that there are some very serious problems with our vaccine program and that officials in the United States and officials in Great Britain have been trying to avoid addressing them straight up.

To cite as one example, Dr. Bradstreet did a chelation on his kid and chelated out a mountain of mercury from his kid. In other panels, we had physicians with autistic kids who did hair analysis on their kids and discovered they had toxic mercury levels.

I am very glad you are getting around to the studies now and I am very, very pleased you said you have six studies going on but I want to underscore that we all support the vaccine program, we all know it saves millions of lives, we all want to see it continue.

Credibility is also one of the other issues at stake here. It is not just the science of the matter, it is the credibility of our vaccine program.

The last thing I personally want to see is that public confidence gets undermined like it has been in Great Britain and you have thousands of families refusing the vaccine now. As I understand, you have outbreaks of measles going on over there. I would like to see us handle it better. Let me say, and you can take this back to your bosses, one of the things I continue to be very, very disappointed about is the amount of money that is being thrown at this issue. We have about a million people with HIV AIDS, the CDC budget for HIV AIDS is $932 million, almost $1 billion for HIV AIDS for a million people. We have about half a million people, kids, with autism and the CDC budget is about $10 or $11 million. We have to start putting the resources to this problem to address this issue.

The access to the data, you guys have to work through that problem and you have to allow skeptical people to look at the data because the impression is being generated that there is a cover up going on. I want to say that this study lends credence to the concern of there being a cover up. Dr. Chen, I would love for you to respond to my question. You have a claim in here in your conclusions, "Vaccination with MMR and other measles containing viruses or the timing of the vaccination early in life does not increase the risk of inflammatory bowel disease." You aren't the principal author, it was Robert Davis and there are 10 different authors here, so maybe you didn't write that conclusion.

The statisticians are telling us you don't have the power in this study to make that sort of claim. What is really disturbing to me is now in clinical evidence, sort of the Bible in medicine, this study is being quoted in clinical evidence that there is no relationship but the statisticians I have talked with tell me the data doesn't support the claim at all. This suggests again that you are circling the wagons and not really addressing the issues straight up, honestly.

Dr. CHEN. Dr. Weldon, let me address some of your points. If you take a look at my record over the years, I have done everything I can to build the infrastructure that is needed for us to address some of these issues. I started the Vaccine Adverse Event Reporting System [VAERS], I started the Vaccine Safety Datalink Project and I think in retrospect, part of our challenge in the field of vaccinology is that there was one additional missing piece of the infrastructure which in part has created an unnecessary gulf between the clinicians and the population scientists.

If you think about it, adverse events obviously occur rarely so that any particular doctor reporting to VAERS would be pretty much doing so for the very first time. Our difficulty has been finding a way in which these types of cases can be assessed in a standardized way. The analogy would be that we do not expect the average primary care physician to be able to diagnose and treat a rare type of leukemia on their own. We create a subspecialty of hematology oncology which over time, as a sub specialty, is able to make progress on these rare outcomes. The analogous situations with vaccine safety is that by and large these events are rare. What we need is a tertiary infra-structure to be able to study them. We have

just started the Clinical Immunization Safety Assessment Centers in this current fiscal year. So I think we will have a mechanism to conduct the type of research needed to bridge between the population and the individual level.

Dr. WELDON. Let us talk technical stuff here. The issue is power and the problem with the power in this study, the power calculation renders the study invalid because you do not have enough people in your control group who were not vaccinated and the only way we can get a statistically valid study because the penetration of this vaccine is so extremely high is that we would literally have to have a multinational effort to try to address the question you attempted to answer in this study which you really didn't answer.

Dr. CHEN. I agree that this was one study and it provides evidence; that the more studies are conducted, the better the evidence is, they are replicated.

Dr. DESTEFANO. I am a co-author of this paper. The low power that was alluded to earlier kind of missed the main point of this paper. It combined all measles vaccine into one group and therefore, we found that 94 percent were vaccinated. By time of this study, the hypothesis with IBD and measles vaccine had shifted, to it is MMR vaccine that is the culprit. Before that there had been studies done looking at single antigen measles vaccine, one done by Montgomery, which Dr. Wakefield is co-author, a cohort study of a 1970 British birth cohort. They did not find any association with single antigen measles vaccine. Similarly a case control study by Feeney did not find an association with single antigen measles vaccine.

Subsequently the study by Montgomery was the one in which there were two cases in which the individuals, again with long term follow up to about age 26, about two cases where the individuals had wild type measles disease and mumps disease in the same year. Those two cases had a high relative risk. I think it was from that finding that the theory or hypothesis that having the two antigens exposure at the same time may be more detrimental. From there, I think that is part of the evidence that it is combined measles/mumps/rubella vaccine that is really the more dangerous combination and calls for single antigen vaccine.

At the time of this study, the main new information issued or addressed was MMR vaccine. If you will look in this study, the proportion vaccinated with MMR was 66 percent. I think the relevant table is Table II where we are looking at ever vaccinating with MMR vaccine and you will see that the upper end of the 95 percent confidence interval for inflammatory bowel disease is 1.69. We can be over 95 percent confident that the relative risk for inflammatory bowel disease in this population associated with MMR is well below 2.

Dr. WELDON. We have a range of 0.21 to 1.69.

Dr. DESTEFANO. This is not a flat range. You have to look at the odds ratio of 0.59 because that is our best estimate. If you would repeat this study, it would be statistically like a bell shaped curve, most of the results would be around 0.59. You may have a few out there around 1.6 or maybe a few down by 0.2 but they are mainly going to cluster, our best estimate is 0.6, and it is for MMR. I agree we were much more limited in looking at Table III with the specific

ages of vaccination and that we are more limited in looking at Crohn's Disease or ulcerative colitis. I think our power was reasonable or at least as the confidence intervals would suggest to address the main issue that was extant at the time.

Dr. WELDON. Let me reclaim my time here. The issue is this is a relatively low probability event. The data suggests the vast majority of girls can take this vaccine and it is probably less than 1 percent. If this hypothesis is correct that MMR alone or MMR somehow interacting with mercury is causing regressive autism associated with inflammatory bowel disease or autistic enterocolitis, the data is that it may be 1 percent of boys and it is well below 1 percent of girls, maybe on the order of 0.2 percent or less of girls. So even an odds ratio that you are putting forward here in Table II, I will give you credit, of 1.69 doesn't answer the question. On the basis of the data you provided here, you cannot substantiate the conclusion.

Frankly, I have been reading the archives for years, not the archives of Pediatric and Adolescent Medicine, the archives of Internal Medicine, but it is published by the same publisher, the AMA, and I am surprised this would be accepted for publication and I am even more disturbed that data is being cited in other publications as further evidence that there is no relationship. Meanwhile, we have more and more clinical studies.

We heard from another researcher totally unaffiliated with Dr. Wakefield but basically substantiating Dr. Wakefield's findings and now we have more disturbing development of a researcher telling us he is finding measles in the cerebral spinal fluid in these kids. Maybe the CDC is the wrong agency to be addressing these questions. None of you are with NIH, correct? You are with NIH.

Dr. FOOTE. Yes.

Dr. WELDON. The NIH budget I think is even more disturbing. You have in 2003, $2.7 billion on HIV AIDS related research, which I don't quibble with, it is a terrible problem but $70 million, you have 500,000 people with autism and 1 million people with AIDS, why don't we just apply the dollars. I have heard you say you have to get quality research and you can't just throw money out, that you want quality, but I know enough about research that if you dangle the money in front of them, the quality research will start coming forward. There are a lot of researchers who will say I can do that, why don't we get answers to some of these questions?

Dr. FOOTE. As we discussed several weeks ago when I last testified before this committee, even in that time we have made strides toward funding our first large autism research centers and there will be a formal announcement about that in several weeks. In those centers, for example, is where the kind of training will occur that will allow young investigators to develop skills, to develop quality grant applications to design very rigorous experiments to undertake these issues.

Your message is well taken that there is a need for biomarkers for this disorder. There is a need for more clinical investigation and we have put the money on the table, we are working with investigators with a great deal of technical assistance to them about how to prepare grant applications and so on.

Dr. WELDON. I want to underscore a very, very important point in all this. I don't mean to keep picking on AIDS, but you are going to have another dramatic increase in your funding. The President wants it, the House and Senate all want it. You are going to get hundreds of millions of dollars more. Keeping this kind of a ratio, you have to start applying disproportionately more money to autism so we can get answers to some of these questions. One of the reasons I feel so strongly about this is unlike AIDS, where it is clearly a behavioral related disease, these kids may be getting this from a Government mandated vaccination and if we get answers to some of these questions, we may be able to prevent it whereas in the case of AIDS, we can't really prevent it because it is behaviorally related. It is not something mandated by the Government that has caused it. So a shift in priorities can have a dramatic impact.

I am going to yield. I just want an answer for the record. The issue brought up by the ranking member on using various coding regions in the RNA and in the proteins as biomarkers to determine whether or not there is a wild type versus vaccine strain, I want to introduce for the record a research article published by Dr. Christopher L. Parks entitled, "Analysis of Noncoding Regions of Measles Virus Strains in the Edmonston Vaccine Lineage."

I yield back.

Mr. BURTON. Without objection, we will submit that for the record. We also have another article. We will put those in the record.

[The information referred to follows:]

1: J Virol 2001 Jan;75(2):921-33

Analysis of the noncoding regions of measles virus strains in the Edmonston vaccine lineage.

Parks CL, Lerch RA, Walpita P, Wang HP, Sidhu MS, Udem SA.

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The noncoding sequence of five Edmonston vaccine viruses (AIK-C, Moraten, Rubeovax, Schwarz, and Zagreb) and those of a low-passage Edmonston wild-type (wt) measles virus have been determined and compared. Twenty-one nucleotide positions were identified at which Edmonston wt and one or more vaccine strains differed. The location of some of these nucleotide substitutions suggests that they may influence the efficiency of mRNA synthesis, processing, and translation, as well as genome replication and encapsidation. Five nucleotide substitutions were conserved in all of the vaccine strains. Two of these were in the genomic 3'-terminal transcriptional control region and could affect RNA synthesis or encapsidation. Three were found within the 5'-untranslated region of the F mRNA, potentially altering translation control sequences. The remaining vaccine virus base changes were found in one to four vaccine strains. Their genomic localization suggests that some may modify cis-acting regulatory domains, including the Kozak consensus element of the P and M genes, the F gene-end signal, and the F mRNA 5'-untranslated sequence.

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Analysis of the Noncoding Regions of Measles Virus Strains in the Edmonston Vaccine Lineage

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ABSTRACT

The noncoding sequence of five Edmonston vaccine viruses (AIK-C, Moraten, Rubeovax, Schwarz, and Zagreb) and those of a low-passage Edmonston wild-type (wt) measles virus have been determined and compared. Twenty-one nucleotide positions were identified at which Edmonston wt and one or more vaccine strains differed. The location of some of these nucleotide substitutions suggests that they may influence the efficiency of mRNA synthesis, processing, and translation, as well as genome replication and encapsidation. Five nucleotide substitutions were conserved in all of the vaccine strains. Two of these were in the genomic 3′-terminal transcriptional control region and could affect RNA synthesis or encapsidation. Three were found within the 5′-untranslated region of the F mRNA, potentially altering translation control sequences. The remaining vaccine virus base changes were found in one to four vaccine strains. Their genomic localization suggests that some may modify *cis*-acting regulatory domains, including the Kozak consensus element of the P and M genes, the F gene-end signal, and the F mRNA 5′-untranslated sequence.

INTRODUCTION

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Measles virus (MV) is a highly contagious human pathogen best known as the cause of one of the classical "rash" illnesses of children. Few escaped this acute infection and disease prior to the development of the currently used live attenuated virus vaccines. Severe, even fatal complications, particularly involving the respiratory and central nervous systems, were not uncommon even in industrialized countries. Unfortunately, in many parts of the less-well-developed world, measles continues to be the major cause of preventable childhood mortality (9, 15, 16).

MV is an enveloped RNA virus of the genus *Morbillivirus*, family *Paramyxoviridae* (32). Like other members of this family, its genome is nonsegmented and of negative sense. The 16-kb linear RNA contains six nonoverlapping cistrons (3′-N-P-M-F-H-L-5′) that encode eight known polypeptides (16, 27). In addition to the protein coding regions, nearly 11% of the 16-kb MV genome is composed of noncoding RNA. Presumably, this relatively small viral genome has maintained a significant noncoding nucleotide sequence content for its functionally important *cis*-acting elements.

cis-acting regulatory sequences found in all viral genomes are essential for the orderly progression of the viral life cycle. These elements serve to specify, organize, and control gene expression and genome replication, often exerting these effects through interaction with virus-encoded proteins or host cell factors. The important role of *cis*-acting sequence elements is well illustrated by the complex transcriptional regulatory schemes employed by large DNA viruses such as herpes simplex virus or adenovirus (38, 42). It is equally clear that *cis*-acting regulatory elements are exploited by the smaller genomes of negative-strand RNA viruses to control their replicative strategy (27). In MV, like other paramyxoviruses, *cis*-acting sequences have been identified that have roles in genome replication, genome packaging, translation, and mRNA synthesis, processing, and editing (2, 16, 19, 27, 41).

The known or proposed *cis*-acting signals in the MV genome are summarized in Fig. 1 (2, 16, 19, 27, 41). The noncoding 107 nucleotides at the 3′ end of the negative-strand genome (called the leader transcriptional control region [TCR]) include promoter sequences that initiate two distinct RNA synthesis pathways: (i) production of an end-to-end copy of the genome to generate the positive-strand replication intermediate and (ii) an elongation-termination-reinitiation transcription pathway that produces mRNAs corresponding to the six cistrons. Transcription termination and reinitiation during mRNA synthesis is mediated by conserved sequence elements located in each intergenic region: a gene-end (GE) plus a gene-start (GS) signal separated by the characteristic GAA nucleotide triplet forms the GE/GS signal. The highly conserved GAA triplet is found between all intergenic GE and GS signals except between the H and L genes, where a GCA triplet is found. In addition to guiding transcription termination and reinitiation, the GE/GS signal also directs mRNA polyadenylation.

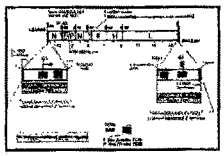

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FIG. 1. MV genome map. The location of protein coding regions (white boxes: N, P, V, C, M, F, H, and L) and noncoding regions including the leader and trailer (black terminal boxes) and intergenic regions (shaded blue) are shown, along with specialized sequence motifs (2, 16, 19, 27, 41, 52). The TCRs at the 3' end of the genomic RNA (leader TCR, nucleotides 1 to 107) and the 3' end of the antigenomic RNA (trailer TCR, nucleotides 15785 to 15894) are enlarged below the genome map. Genomic RNA synthesis initiation is shown as open arrowheads in the enlargement of the leader and trailer TCR regions. Sequence motifs shown in the expanded TCR maps include the leader, trailer, GE and GS signals, the 16-base conserved terminal sequence (shown 3' to 5'), the repeated B- and B'-box motif, the G(N)5 motif, the ATG codon for the N gene adjacent to the leader, and the L protein stop codon outside of the 5' end of the trailer. The positions of GE/GS signals are designated with a combination of solid arrowhead (GS) and a black box (GE). The leader TCR GE/GS symbol lacks a GE box, and the trailer TCR GE/GS lacks a GS arrowhead to signify that these sequences may not function identically to GE/GS elements in the intergenic regions. The mRNA editing site is indicated below the V protein coding region (6). Part of the F gene mRNA 5'-untranslated nucleotide sequence is shown to illustrate the three in-frame AUG initiator codons (5). At the bottom of the figure, several symbols found in the TCR maps are defined.

cis-acting sequences similar to those in the leader TCR are also located in the 3'-terminal 109 nucleotides of the positive-stranded antigenome (the trailer TCR; Fig. 1). The trailer TCR exclusively directs initiation of negative-strand genome synthesis. Important sequence motifs found in the leader and trailer TCRs (Fig. 1) include the terminal 16 nucleotides that are thought to be part of the primary site of RNA polymerase recognition (20, 28), the G(N)5 (52) and B-box motifs (2) that have been implicated as regulators of MV transcription and replication, and a potential GS signal in the leader TCR prior to the N gene and a GE signal in the trailer TCR that terminates L gene mRNA synthesis (16, 19, 27, 41).

Two additional functional *cis*-acting sequences have been identified in the MV genome. One is the RNA editing site in the P cistron that permits addition of a G residue in some P mRNAs, resulting in the translational frameshift that directs synthesis of V protein (6). The second *cis*-acting sequence is found within the rather long noncoding intergenic region between the M and F genes. Part of this region specifies the nontranslated leader sequence of the F gene mRNA which has been shown to be an important determinant of translational efficiency and AUG codon selection (5, 13). Deletion of this translational control element from recombinant viruses also appears to compromise replication in vivo (55). Identification of yet other *cis*-acting elements is likely to occur as more of the MV noncoding sequences are scrutinized with transient assay systems and recombinant viruses.

cis-acting elements can be an important determinant of virus attenuation. For example, mutations in the leader sequence of human parainfluenza virus type 3 (PIV3) vaccine candidates have been shown to specify

the temperature sensitivity, cold adaptation, and attenuation phenotypes (46). Some attenuated respiratory syncytial virus A2 (RSV A2) strains contain a nucleotide change in the GS signal of the M2 gene that contributes to their temperature-sensitive and attenuated phenotypes (56). Also, a GE signal mutation in the M gene of an attenuated RSV B strain has been found to compromise expression of the downstream SH gene (D. A. Buonagurio, personal communication). Similarly, a *cis*-acting sequence mutation has been noted within the GE signal of the mumps vaccine virus F gene that appears to also disrupt normal expression of the downstream SH gene (51). Taken together, these studies indicate that specific alterations of noncoding *cis*-acting sequence elements of negative-strand RNA viruses can modulate virus virulence and attenuation.

Genomic modifications that attenuate MV have only recently begun to be defined. For example, several studies have shown that viruses defective for V or C protein expression display attenuated growth characteristics in some model systems (12, 31, 34, 53, 55). Additionally, mutations in genes encoding C, V, P, and L proteins have been associated with reduced viral replication in the B95 lymphocyte cell line (50). Although these studies have started to define roles for various proteins in MV attenuation, the potential role of *cis*-acting sequences has so far received less attention. In one case, deletion of most of the F gene mRNA 5′-untranslated region from a recombinant MV strain did result in less-efficient replication in human thymus-liver implants engrafted into SCID mice (55), demonstrating that modification of this *cis*-acting sequence can modulate attenuation.

To learn more about the potential role of noncoding *cis*-acting sequences in MV attenuation, a comparative sequence analysis was performed on viruses in the Edmonston vaccine lineage. This study was based on posing two relatively simple questions. (i) Do the noncoding sequences from several optimally attenuated vaccine viruses differ from the Edmonston wt progenitor strain or an underattenuated Edmonston vaccine strain? (ii) If differences exist, do they affect noncoding sequences that may function as *cis*-acting sequences controlling gene expression or replication? The Edmonston virus lineage (39) is attractive for this type of comparative study for a variety of reasons. Six viruses from the vaccine lineage are available for comparison, including five independently generated vaccine strains and a low-passage laboratory isolate of Edmonston wt (10, 11, 16, 18, 21, 26, 30, 39). This provides a unique opportunity to examine the molecular consequences of similar but independent vaccine derivation schemes (39). Comparison of Edmonston wt and five different vaccine strains also provides an opportunity to examine the diversity of molecular mechanisms by which the attenuated phenotype is produced by different genotypes. Furthermore, the vaccine strains differ in the level of attenuation. Four of the five vaccines are adequately attenuated, while Rubeovax proved to be reactogenic (26), and this is an important point for comparison that should provide insight into what genome changes influence the degree of attenuation. Finally, transient expression systems and cDNA rescue technologies provide experimental systems to further analyze the genetic changes identified by sequence analysis (35).

To identify potential attenuation determinants within MV *cis*-acting regulatory elements we have sequenced the noncoding regions of a low-passage isolate of Edmonston wt and five vaccine derivatives. Base changes were identified at 21 noncoding positions when the vaccine genomes were compared to Edmonston wt. Five nucleotide substitutions were common to all vaccine strains, while the remaining substitutions were present in one to four vaccine viruses. The sequence comparison also revealed that

Moraten and Schwarz contained identical noncoding region sequences and differed at five nucleotide positions from closely related Rubeovax.

MATERIALS AND METHODS

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Cells, virus, and genome sequencing. Cell culture and MV propagation was performed as described in an accompanying article (33). The Edmonston wt isolate (11, 16) was a gift from Judy Beeler (Center for Biologics Evaluation and Research). Edmonston B (Rubeovax) (10, 26), AIK-C (30), Schwarz (Rimevax; SmithKline Beecham) (26, 40), and Zagreb (21) were generously provided by William Bellini and Paul Rota (Centers for Disease Control) (39). Moraten (Attenuvax; Merck & Co) (18) and a second preparation of Schwarz (Rimevax, SmithKline Beecham) (26, 40) were obtained from commercially available vaccine preparations. The two separate sources of Schwarz were analyzed independently.

Viral genome sequence was determined directly from DNA fragments generated by reverse transcription-PCR (RT-PCR) of RNA extracted from infected Vero cells (33). Cycle sequencing (17, 25) was performed using dye-labeled terminators and *Taq* DNA polymerase (Applied Biosystems), followed by analysis on an ABI Prism automated sequence apparatus. Primers used for PCR amplification and sequencing on both cDNA strands were designed based on published MV sequences (GenBank accession numbers K01711 and S58435). Data analysis was performed using the MacVector (Oxford Molecular Group) and Lasergene (DNAstar, Inc.) software packages. The MV sequences have been deposited in GenBank (Edmonston wt, AF266288; AIK-C, AF266286; Moraten AF266287; Rubeovax, AF266289; Schwarz, AF266291; Zagreb, AF266290).

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Comparative sequence analysis. Evidence that the base changes within the *cis*-acting elements of the MV genome may contribute to viral attenuation was sought through comparative analysis of the noncoding region nucleotide sequence of five Edmonston vaccine viruses and a low-passage Edmonston wt isolate. Potentially attenuating *cis*-acting nucleotide substitutions were indeed located, providing the framework for design of future genetic studies aimed at dissecting the molecular basis of attenuation using the MV minireplicon and recombinant MV systems.

Interpreting such comparative sequence analyses requires caution given the lack of the true Edmonston wt progenitor virus. Fortunately, a low-passage derivative of the Edmonston clinical isolate was available for these studies. This virus was passaged 13 times (39) prior to the analysis presented here, so it is possible that some degree of tissue culture adaptation may be reflected in the Edmonston wt sequence. Nevertheless, it is the best approximation of the original clinical isolate available, and the passage number has been kept to a minimum in hopes of obtaining a meaningful comparison with the vaccine viruses.

The issue of additional nucleotide changes arising during cell culture passage also applies to sequence analysis of vaccine virus genomes. Propagation of vaccine virus strains in cell culture to produce RNA for analysis can lead to genome changes that reflect adaptation to culture conditions and host cell type used for infection. This concern has been addressed in two ways. First, the number of cell culture passages was limited to three or less while generating viral stocks and RNA. Although this may result in some degree of cell culture adaptation, the additional minimal passage number is unlikely to affect greatly the majority of genomes in the infected cell population. Second, the sequence determination used RT-PCR products rather than cloned cDNA fragments. Sequence obtained from RT-PCR products should represent the majority sequence in a population of viral genomes and help alleviate the influence from minor viral populations that began to evolve during passage in Vero cells.

Leader and trailer transcriptional control regions. The 107 3′-terminal noncoding nucleotides include the MV genomic promoter (43, 44) and are referred to here as the leader TCR (Fig. 1). Within this TCR lie several discrete sequence elements that are thought to act in *cis* to modulate MV transcription, replication, and gene expression. Two of these are highly conserved, well-accepted *cis*-acting regulatory elements of the TCR. One is the terminal 16 bases of the leader (Fig. 1). The second is the GS signal that directs N gene mRNA synthesis (2, 16, 19, 23, 27, 41). Additional *cis*-acting elements in the leader TCR [B-box and G(N)5 sequences] have been proposed based on genomic sequence comparisons (2, 8) and analyses of defective interfering RNAs (44), and the existence of these proposed elements has been substantiated by studies with Sendai virus (52). Nucleotide substitution in any of these elements or yet-undefined *cis*-acting sequences could have a significant effect on virus-cell interaction through changes in replication or gene expression efficiency.

Comparison of leader TCR sequences of Edmonston wt and the five vaccine strains revealed nucleotide differences at three positions (Fig. 2A). Nucleotide transversions were detected in all vaccines at positions 26 and 42. The wt U residue in the negative-sense genome strand was changed to an A residue at position 26. The wt U residue at position 42 was substituted with a G in AIK-C, Moraten, Schwarz, and Rubeovax, and an A residue in Zagreb. The location of these base substitutions is shown in Fig. 2A relative to previously described sequence motifs (Fig. 1). The position 26 and 42 base substitutions were located between the terminal leader TCR domain and the GS sequence (Fig. 2A; see also Fig. 7A). The third leader TCR substitution was detected only in Zagreb at position 96. This C-to-U transition occurred within the B box sequence and at the 5′ boundary of the G(N)5 motif.

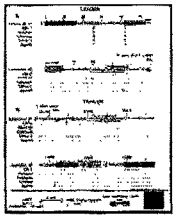

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FIG. 2. Sequence comparison of Edmonston wt and vaccine leader and trailer TCRs. Terminal 110 bases of genomic sequence (3' to 5') containing the leader TCR (nucleotides 1 to 107, part A) and trailer TCR (nucleotides 15785 to 15894, part B) of Edmonston wt are shown and labeled with genome nucleotide positions. Sequence motifs are illustrated on the sequence according to the key at the bottom of the figure. Relevant protein start or stop codons also are included. The sequence corresponding to the GE region in the leader TCR and the GS region of the trailer TCR are not shaded in gray to indicate that these sequence motifs may not function identically to their intergenic GE/GS counterparts. Illustrated below the wt sequence is the sequence comparison with vaccine strains. Nucleotide identity is given as a dot, and a typed nucleotide indicates disagreement with wt.

Little variability was detected in the trailer TCR and no base substitution was common to all of the vaccine viruses. Transitions were identified at position 15,789 (C to U) in AIK-C and at position 15,843 (U to C) in Zagreb. Neither mutation was located in a previously described sequence motif, although the Zagreb mutation was adjacent to the 3' boundary of the GE signal that terminates transcription following the L gene (Fig. 1 and 2B). Both mutations changed bases in the 3' noncoding region of the L mRNA.

Intergenic regions. Three variable nucleotide positions (Fig. 3A) were found in the intergenic region between the N and P genes (N/P). None of these nucleotide substitutions were common to all vaccines. Two were in the N cistron affecting the region that specifies the 3'-untranslated region of the N mRNA. These substitutions included a U-to-C substitution at position 1702 shared by all vaccine viruses except AIK-C. In the same region, Moraten and Schwarz contained a G-to-U transversion at position 1724. Within the P cistron, a C-to-U transition was identified at position 1806. This nucleotide substitution was found in Moraten, Schwarz, and Rubeovax, and it changed the base immediately upstream of the P protein translation start codon.

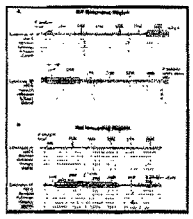

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FIG. 3. Comparison of N/P and P/M intergenic regions of Edmonston wt and vaccine viruses. Description of this figure is as described for Fig. 2.

Only one nucleotide change was identified in the P/M intergenic region (Fig. 3B). This occurred in the M cistron at nucleotide 3431, where a wt A nucleotide was changed to a C residue in Moraten and Schwarz. This nucleotide substitution alters the sequence of the 5' noncoding region of the M mRNA at nucleotide position −7 relative to the M gene translation initiation codon.

Nine different nucleotide positions differed from wt in the long M/F intergenic region (Fig. 4). None of these mutations were found within the GE/GS signal. Four of the base changes were detected in the 3'-untranslated region of the M gene mRNA. These were at genomic positions 4536 (C to A in AIK-C), 4574 (C to U in AIK-C), 4608 (A to G in Rubeovax), and 4611 (G to A in AIK-C and Zagreb). The five remaining M/F intergenic region changes occurred within sequences encoding the 5'-untranslated region of the F gene mRNA. Two of these base substitutions were found only in one vaccine strain, at genomic positions 5030 in AIK-C (G to A) and 5308 in Rubeovax (A to G). The other three were conserved in all vaccine strains. These changes were two A-to-G transitions at 4978 and 5349 and a G-to-C transversion at 5073.

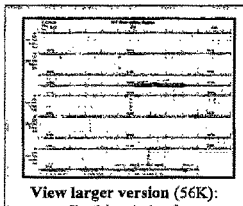

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FIG. 4. Comparison of M/F intergenic regions from Edmonston wt and vaccine viruses. The description of this figure is similar to that for Fig. 2. One line of dots indicating homology to all vaccines is shown under the wt sequence if there were no base changes to report. The sequence shown in this figure extends beyond the noncoding intergenic region to show the position of the three F gene AUG codons. The second AUG codon is the predominately used initiation codon (5). Vaccine virus names are abbreviated as follows: AIK-C (AIK), Moraten and Schwarz (Mor/Sch) Rubeovax (Rubeo) and Zagreb (Zag).

Few nucleotide changes were identified in the F/H and H/L intergenic regions (Fig. 5). One nucleotide

substitution was present in the F/H intergenic region at nucleotide position 7243 (Fig. 5A). This A-to-G transition was present within the boundaries of the F gene GE signal of Moraten and Schwarz (Fig. 5A). In the H/L intergenic region, two base substitutions were located in the 3'-untranslated region of the H gene mRNA (Fig. 5B). At position 9139 a G-to-A substitution was present in AIK-C, and a U-to-A transversion at position 9144 was detected in both Moraten and Schwarz.

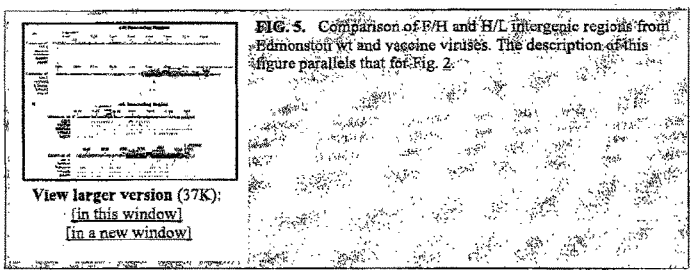

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FIG. 5. Comparison of F/H and H/L intergenic regions from Edmonston wt and vaccine viruses. The description of this figure parallels that for Fig. 2.

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These analyses, though limited by the considerations described earlier, revealed distinctive base substitutions within multiple noncoding region sequences that perform potential *cis*-acting functions (Fig. 2 to 5). Analyses of human PIV3 and RSV A and B vaccine candidates also have identified base substitutions in *cis*-acting regions (7, 14, 18; D. A. Buonagurio, personal communication), indicating that this characteristic is shared by negative-strand vaccine virus strains. None of the five Edmonston vaccine viruses accumulated base changes resulting in gross alteration of a noncoding region, suggesting that these sequences do contain important components of the viral regulatory apparatus and that alteration is not well tolerated. It may also suggest that only subtle adjustments to *cis*-acting sequences controlling gene expression and replication were required to facilitate growth in the semipermissive cells used for vaccine virus selection.

Why MV noncoding region mutations accumulate in potential *cis*-acting sequences is currently speculative, but it seems reasonable to suggest that at least some of these mutations confer a selective advantage for viral replication under conditions used for vaccine derivation. Whether any of these mutations contribute to the attenuated phenotype remains to be established. Answering this question will require further studies using reverse genetics and recombinant viruses in studies like those ongoing with RSV and PIV3 vaccine candidates (7, 45, 46, 56-58).

Nucleotide substitutions in MV noncoding *cis*-acting sequences may be a favored response to changes in viral polypeptides induced by passage in heterologous cell types. In one simple model describing the biological selection process (33), it has been proposed that selective pressure is initially driven by a

requirement for interaction between semipermissive host cell factors and viral proteins involved in the earliest stages of viral infection, particularly transcription and replication. It follows that the early stages of infection in semipermissive cells would be inefficient because viral proteins are not well equipped to deal with the semipermissive host cell environment. As the passage process progresses, mutations in viral protein coding regions are favored if they enhance the ability of viral proteins to functionally interact with proteins found in the semipermissive host cell. Although these protein modifications may enhance the level of interaction between viral and cellular proteins, they may be costly to other aspects of the virus life cycle. To help compensate for any adverse effects of amino acid substitutions, the virus evolves second-site compensatory mutations that subtly change gene expression and replication through base changes in *cis*-acting regulatory sequences and additional amino acid substitutions. As implied by this model, many of the noncoding region base changes identified in the Edmonston vaccines seem to have the potential to modify *cis*-acting regulatory components of the virus genome.

The noncoding region base substitutions can be grouped into three categories based on their potential to modify *cis*-acting regulatory functions: (i) base substitutions that may affect protein translation through changes in mRNA stability or modification of translational regulatory elements in message, (ii) base substitutions that could affect mRNA synthesis by altering promoter activity in the leader TCR or GE/GS signal function, and (iii) base substitutions that could affect the activity of replication promoters in the leader or trailer TCRs. Below, the identified MV vaccine noncoding base substitutions and their attenuation potential are discussed in the context of these categories. Figures 2 to 5 provide the sequence data for each gene region, while Fig. 6 summarizes these results schematically.

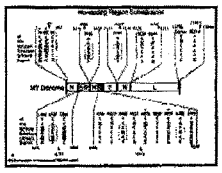

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FIG. 6. Summary of noncoding region nucleotide substitutions. A genome map similar to Fig. 1 is shown along with the nucleotide positions that varied in vaccine strains. The relative position of the GE/GS signals is shown by an arrowhead plus the nucleotide position corresponding to the central A residue in the conserved GAA motif. Boundaries of the noncoding regions are indicated at the ends of the brackets containing the nucleotide substitutions. Nucleotides highlighted in gray depict changes from the Edmonston wt sequence. An asterisk above a column of nucleotides indicates that a base change occurred in all vaccine strains. The dashed box outlining groups of three nucleotides shows positions where Rubeovax differs from Moraten and Schwarz.

Base substitutions and *cis*-acting regulation of translation. Mutations within the 5'- or 3'-untranslated region of mRNAs can alter protein expression by affecting mRNA stability or translation efficiency (22, 29). The combination of noncoding sequence and poly(A) tail at the 3' end of mRNAs is known to play an important role in determining mRNA stability (22). Destabilizing sequences are generally AU-rich and commonly contain the pentamer AUUUA. It is plausible that mutations in the 3'-untranslated region of MV mRNAs could affect a destabilizing sequence by interrupting an AU-rich motif or altering the secondary structure near a destabilizing motif. Base substitutions in 3' noncoding regions were found in multiple locations, including the N, M, H, and L genes. None of the mutations affecting the 3'-untranslated regions

of MV mRNAs, except possibly the base substitution at position 15843 in Zagreb (Fig. 2B), obviously affects an AU-rich element (Fig. 2 to 6), but the potential of any of these base changes to alter mRNA stability can only be determined experimentally.

The 5' end of several vaccine virus mRNA sequences included base substitutions located in positions that may affect translation initiation (Fig. 6 and 7C). In both the P (Fig. 3A and 6) and M (Fig. 3B and 6) genes, base substitutions were identified near the AUG translation initiation codon in the Kozak element (Fig. 7C). The Kozak consensus sequence influences AUG codon selection and efficiency of translation initiation (24). In the P gene of Moraten, Schwarz, and Rubeovax, a G-to-A transition (mRNA sense) was found at position −1 relative to the AUG codon for the P open reading frame (Fig. 7C). In the Moraten and Schwarz M gene, a U-to-G transversion (mRNA sense) occurred at position −7 relative to the AUG codon (Fig. 7C).

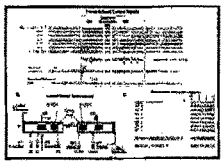

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FIG. 7. Vaccine nucleotide substitutions in *cis*-acting sequence motifs. (A) Alignment of MV TCRs containing the GE/GS signal. Similarity between the signals and a consensus sequence is outlined by the box (yellow). The leader TCR GE and trailer TCR GS regions are presented in lower case to indicate that these sequences may not function like the corresponding sequences of the intergenic GE/GS elements and that these sequences were not considered in evaluating the consensus. Below the consensus are the two GE/GS sequences that contained vaccine virus base substitutions. The nucleotide substitution is highlighted by a blue box. (B) Summary of the base changes found in the leader and trailer TCRs. The description of the leader and trailer TCRs can be found in Fig. 1. Nucleotide changes are illustrated below the leader and trailer TCRs. Base changes are highlighted in blue. (C) Comparison of the Kozak element (24) found in wt MV mRNAs. Variation in vaccine virus P and M gene Kozak sequences is shown below the wt sequences.

The initiator codon context of both the M and P mRNAs deviate from the Kozak sequence at positions considered most important for AUG strength (24). The M mRNA deviates at the highly conserved +4 position, resulting in a less-favorable context for translation initiation. This potentially increases the influence of other nucleotides in the vicinity of the AUG such as the U residue at position −7 that was changed in the Moraten and Schwarz vaccines. Similarly, the P mRNA lacks a purine at position −3, which is the most highly conserved base in the Kozak element (24). Absence of a purine at −3 will likely increase the importance of other bases in the P mRNA Kozak element, such as the base at position −1 that was changed in Moraten, Schwarz, and Rubeovax. If these changes in initiation codon context alter translation efficiency, the effect may be quite subtle since the codon context is changed only by a single base substitution. This does not mean that these base substitutions are not important since it is possible that attenuation is the result of the cumulative effect of numerous relatively small adjustments in the virus life cycle.

The poor agreement between the P gene AUG context and the Kozak element consensus may have evolved

to permit a certain percentage of ribosomes to scan through the P AUG codon and engage the C protein mRNA AUG codon located downstream. This also suggests that base changes in the P Kozak element may influence the ratios of P, V, and C protein synthesis in the infected cell. The possibility that the P AUG codon context may influence translation of C protein has been examined previously. Alkhatib et al. (1) placed the P gene into a recombinant adenovirus and analyzed the levels of P and C protein synthesis in infected cells. Deletion of the P AUG codon had little effect on the synthesis of C protein in this system. This implies that C protein mRNA AUG codon strength is independent of the presence of the upstream P gene AUG codon and further implies that altering the P mRNA Kozak element would have little if any effect on C protein synthesis. This conclusion, however, may be worth reexamining in an alternative system since the P gene cDNA was fused to the adenovirus major late transcription unit tripartite leader sequence. These adenovirus sequences function as a *cis*-acting translational control element in adenovirus-infected cells (42) and may negate some of the intrinsic *cis*-acting elements found in the measles virus P mRNA. Clarification of possible interplay between the P and C mRNA AUG codons may best emerge from study of appropriately designed recombinant MVs.

Further evidence linking translation and attenuation may be found by examining the F gene. MV has maintained the 1-kb intergenic region between the M and F genes that in part specifies a long untranslated 5' end for the F mRNA (Fig. 1 and 4). This untranslated sequence is dispensable for recombinant virus growth in a Vero cell culture (36). However, it has been found to modulate translation and play a role in the selection of a predominant initiation codon from several closely positioned AUG sequences that are in frame with the F coding region (Fig. 1 and 4 and reference 5). In comparing Edmonston strains, five base changes were detected in the vaccine virus F gene mRNA untranslated 5' end (Fig. 4). Given that the F mRNA 5'-untranslated sequence functions as a *cis*-acting element and that three base substitutions in this sequence were common to all vaccine strains, it seems likely that modification of this sequence may have been favored for MV growth in semipermissive cell types. Whether the F mRNA untranslated region plays a role in attenuation remains uncertain, but studies showing that recombinant virus lacking most of this sequence replicates less efficiently in human thymus-liver tissue transplanted in SCID mice (55) suggests that the untranslated region may play a role in pathogenicity.

Base substitutions and the control of mRNA synthesis and processing. The second category encompasses mutations with potential to influence viral mRNA synthesis, specifically mutations in GE/GS signals and the leader TCR. One such base substitution occurred within the F/H intergenic GE/GS signal (Fig. 7A). This mutation was found in Moraten and Schwarz, where an A-to-G transition occurred in the GE signal (nucleotide position 7243; Fig. 7A). The effect of this base substitution is not known as yet, but it may perturb normal transcription termination and reinitiation at the F-H gene boundary, leading to altered expression of the downstream H gene. This phenomenon has been observed in some strains of RSV, PIV, and simian virus 5, where less-efficient GE signal variants cause reduced transcription termination with overproduction of readthrough bicistronic transcripts at the expense of normal monocistronic mRNA synthesis of the downstream gene (3, 37, 47, 54) (D. A. Buonagurio, personal communication). Reduction in correctly initiated mRNA synthesis from the downstream gene, coupled with the likelihood that the fused bicistronic transcripts are inadequate templates for translation of the gene distal to the 5' mRNA cap (24, 60), will restrict protein synthesis encoded by the downstream gene. This effect could result in diminished H protein expression if Moraten and Schwarz produce elevated levels of a F/H bicistronic

message.

It also may be relevant to mention the mutation at position 42 in this context even though it is possible that the GE signal located in the leader TCR may not function analogously to GE signals found in intergenic regions. The position 42 mutation was present at the 3' boundary of the GE/GS signal consensus drawn in Fig. 7A, raising the possibility that it may modify GE/GS signal function. This could be significant if transcription initiating at the genomic 3' end must terminate and reinitiate to effectively transcribe an N mRNA and the position 42 mutation alters termination or reinitiation function. Whether a termination and reinitiation mechanism applies to mRNA synthesis initiated from the MV leader TCR is uncertain given the failure to detect abundant small leader RNA products in infected cells that would be indicative of termination prior to the N gene GS signal (4, 8). However, it is worth noting that attempts to detect the small leader RNA in infected cells have relied on infection with laboratory-adapted Edmonston strains that have vaccine leader mutations.

If the base 42 substitution negatively affects termination efficiency, greater accumulation of leader-N mRNA fusions will result. These readthrough transcripts introduce an AUG sequence upstream of the authentic N gene initiation codon, potentially reducing N protein expression. In addition, leader sequences attached to N mRNA should serve as substrates for interaction with N protein. Encapsidation of leader-N gene fusion mRNAs should render them unavailable for translation. Given these considerations, the position 42 base substitution could reduce the level of N protein synthesis in all vaccine viruses by altering GE function.

mRNA levels also may be influenced by promoter strength of the leader TCR. As noted above, three base changes were observed in this region of the vaccine viruses. One was a C-to-U transition that was unique to Zagreb at nucleotide position 96 (Fig. 2B). The other two mutations were at positions 26 and 42. The position 26 and 42 pyrimidine-to-purine transversions were conserved in all vaccine strains. Alignment of leader TCR mutations to previously described sequence motifs (Fig. 1, 2, and 7B) showed that the position 26 mutation was excluded from any currently described motifs while, as described earlier, the base change at 42 lay within the boundaries of the GE/GS consensus sequence (Fig. 7A). The unique Zagreb mutation at position 96 (Fig. 7B) was present within the boundaries of the B box (2, 8) and the overlapping G(N)5 motif (52).

The possibility that these leader TCR mutations affect mRNA synthesis is speculative but intriguing to consider further. It is noteworthy that the leader TCR changes at 26 and 42 were located within a region that is not highly homologous to the trailer TCR (Fig. 8). Considering the functional similarity between the leader and trailer TCRs, it seems reasonable to expect significant sequence homology in regions that perform largely identical functions. Alignment of both TCRs shows, as described before (2, 8), that they share two regions of strong homology. One includes the terminal 16 bases, and the second encompasses the B and B' boxes. The fact that only the Zagreb mutation (position 96; Fig. 2 and 6 to 8) fell within one of these homologous sequences (the B-box region) may indicate that these sequence elements are relatively intolerant of nucleotide substitutions. Alternatively, it may imply that virus passage in semipermissive cells favored changes in sequences that were unique to leader TCR. This may further imply that these leader TCR changes were favored because they modulated a leader TCR-specific function such as the initiation of mRNA synthesis.

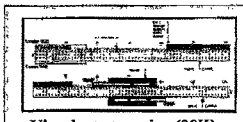

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FIG. 8. Alignment of the Edmonston wt leader (minus strand) and trailer (plus strand). The alignment illustrates the homology between the terminal 16 nucleotides at the 3' end of the leader and trailer, as well as the B-box regions. The motifs identified in the figure are described in the legend to Fig. 1. Vaccine virus leader TCR base changes are shown above the wt sequence, and vaccine trailer TCR changes are shown below.

That the position 26 and 42 base changes may primarily affect mRNA transcription function of the leader TCR is consistent with the base 42 mutation localization to the leader TCR GE consensus sequence boundary (Fig. 1A and 7). Moreover, it is possible that the region between nucleotides 17 and 42 performs a function unique to mRNA transcription initiation. Perhaps it acts as a polymerase pause site where the decision is made between genome synthesis and mRNA synthesis. It could also serve as a contact site that has specificity for a modified polymerase complex that is used for mRNA synthesis. Both of these possibilities imply that replacing two pyrimidine residues at 26 and 42 with purines may affect the efficiency of mRNA transcription initiation by interrupting important polymerase contacts in the leader. These contacts could be perturbed if the substitutions replace important contact nucleotides or induce a subtle change in phasing caused by substitution of pyrimidines with bulkier purines.

Leader and trailer TCR base substitutions and the control of genome replication. Base substitutions in the leader or trailer TCR could influence replication by altering the efficiency of genome-length RNA synthesis. As described above, three base substitutions were found in the leader TCR. While it was suggested that these mutations might act at the level of mRNA transcription, they may additionally or alternatively have an impact on the initiation of antigenome synthesis or modulate the pathway that controls the preferential selection of antigenome or mRNA synthesis. In that context, the unique Zagreb mutation at position 96 present in the B box is interesting because its location in a motif that is conserved in both the leader and trailer TCRs suggests that this homologous sequence domain regulates the replication pathway.

Only two base changes were found in the trailer TCR, and these were specific to individual vaccine strains. Neither the AIK-C mutation (position 15789) nor the Zagreb mutation (position 15843) lie within the 16-base conserved terminal promoter sequences or the overlapping B box-G(N)5 domains. Although localized to the trailer TCR, these base substitutions also fall into the category of mutations that modify untranslated regions of mRNAs. Both mutations reside in the 3' noncoding region of the L mRNA. Were they to affect the phenotype of these vaccine strains, it would likely be through the changes in the L mRNA stability. Additionally, the Zagreb trailer TCR mutation is positioned at the GE/GS consensus region (Fig. 8). Although it does not function as a GE/GS signal in the positive genome strand, this relative positioning could indicate that this region makes contact with the polymerase complex bound at the trailer. It remains to be determined if this Zagreb mutation affects the replicative function of the trailer.

Beyond their putative capacity to influence transcription and replication, the mutations in leader and trailer

TCRs can theoretically affect encapsidation efficiency. During genome synthesis, the first sequences that become accessible for encapsidation are the leader and trailer, suggesting that nucleation sites mediate encapsidation within these regions. Thus, base substitutions in the leader or trailer could affect the interaction of N protein with nascent genomes. This seems a less likely scenario given studies with vesicular stomatitis virus delimiting the encapsidation signal to the terminal 14 bases (41), a region that was unaffected by base substitutions amongst the Edmonston MV strains.

Contribution to attenuation. Not all of the vaccine virus noncoding region base changes are expected to have equivalent impact on replication or gene expression and the levels of attenuation. The base changes found in the P and M mRNAs, within the Kozak consensus sequence, might affect protein expression either positively or negatively. The alteration in the M mRNA AUG context could influence virion maturation and possibly gene expression (16, 49, 59) if the levels of M protein synthesis are altered. The case of the P initiation codon is particularly interesting because changes in the AUG codon strength could affect the translation of P (and V) as well as the translation of C protein from the downstream AUG. Regulation of P, V, and C mRNA translation as a means of achieving attenuation is particularly attractive because each of the P gene-encoded proteins, and their balance, likely play a central role in controlling genome replication and mRNA transcription (16, 19, 41). Given these multiple and vital functions, even small changes in the relative concentrations of P, V, and C proteins in the infected cells could significantly influence viral replication in the infected host (12, 31, 34, 53, 55).

Base changes in the untranslated leader of the F gene also may contribute to the attenuated phenotype. Expression of F protein is essential for cell fusion and effective cell-to-cell spread of MV (16, 59), and it has been demonstrated that the F gene 5'-untranslated region plays a role in determining translation efficiency and AUG codon selection (5). The fact that three mutations were common to all vaccine F gene mRNAs implies that passage in semipermissive cells selected for alteration in this *cis*-acting element. The most obvious advantage accrued by base substitutions in this region is their ability to alter the levels of F protein expression levels, perhaps through changes in the higher-order structure of the mRNA 5' end. Perturbation of this function may also be responsible for the reduced viral titers observed in the human thymus-liver tissue-SCID mouse model system (55) when the thymic implants are infected with a recombinant Edmonston B strains that lacks much of the sequence for the F mRNA 5'-untranslated region.

Base changes in the leader TCR also are likely attenuation candidates. It was proposed above that the position 26 and 42 pyrimidine-to-purine transversions may influence gene expression by changing the interaction between the promoter and the viral polymerase. In this scenario, base substitutions disturbing normal levels of mRNA transcription certainly might contribute to an attenuated phenotype. It is also noteworthy that amino acid coding changes were identified in vaccine virus genes for the polymerase complex proteins (P and L) and accessory proteins (C and V) (33). Possibly, the vaccine virus base changes in the leader TCR and the amino acid changes in protein components of the gene expression apparatus have evolved together to optimize expression in semipermissive cells such as chicken fibroblasts. A by-product of these changes is that upon infection of the human host this adapted form of the transcriptional apparatus is less efficient and leads to an attenuated phenotype.

Finally, these comparative analyses included comparison of highly related vaccine viruses that differ in attenuation level. Optimally attenuated Moraten and Schwarz were found to contain identical noncoding

region sequences, and these sequences differed from the underattenuated Rubeovax strain by only five nucleotides (Fig. 6, nucleotides highlighted with a dashed box). Two of these differences were substitutions unique to Rubeovax, and these were both T-to-C transitions (mRNA sense) in the M/F intergenic region. One of these base substitutions was present in the M gene mRNA 3'-untranslated sequence, and the other was present in the F gene mRNA 5'-untranslated region. These mutations could affect expression by changing mRNA stability or efficiency of translation. The third base that distinguished Rubeovax from Moraten and Schwarz was found in the 3'-untranslated region of the N mRNA. In this case, Rubeovax contained a wt nucleotide compared to the base change contained in the other two vaccines. Again, if this base contributes to a difference in attenuation levels it would probably be the result of altered mRNA stability. The final two bases that distinguish Rubeovax from Moraten and Schwarz have somewhat more compelling links to attenuation. These two substitutions in Moraten and Schwarz remained wt in Rubeovax. They altered a base in the M mRNA Kozak consensus sequence at position 3431 and a base in the F gene GE signal at position 7243. As mentioned earlier, the base change in the M gene could influence translation of M protein resulting in altered virion maturation (59) and possibly transcription regulation (49). The F GE signal mutation may similarly downregulate expression of the downstream H gene if it compromises transcription termination or subsequent reinitiation. One or more of these five features may be responsible for subtle differences between Moraten and Schwarz and the underattenuated Rubeovax strain that helps account for the difference in attenuation levels.

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FOOTNOTES

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Comparison of Predicted Amino Acid Sequences of Measles Virus Strains in the Edmonston Vaccine Lineage

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Protein-encoding nucleotide sequences of the N, P, M, F, H, and L genes were determined for a low-passage isolate of the Edmonston wild-type (wt) measles virus and five Edmonston-derived vaccine virus strains, including AIK-C, Moraten, Schwarz, Rubeovax, and Zagreb. Comparative analysis demonstrated a high degree of nucleotide sequence homology; vaccine viruses differed at most by 0.3% from the Edmonston wt strain. Deduced amino acid sequences predicted substitutions in all viral polypeptides. Eight amino acid coding changes were common to all vaccine viruses; an additional two were conserved in all vaccine strains except Zagreb. Comparisons made between vaccine strains indicated that commercial vaccine lots of Moraten and Schwarz had identical coding regions and were closely related to Rubeovax, while AIK-C and Zagreb diverged from the Edmonston wt along slightly different paths. These comparisons also revealed amino acid coding substitutions in Moraten and Schwarz that were absent from the closely related reactogenic Rubeovax strain. All of the vaccine viruses contained amino acid coding changes in the core components of the virus-encoded transcription and replication apparatus. This observation, combined with identification of noncoding region nucleotide changes in potential *cis*-acting sequences of the vaccine strains (C. L. Parks, R. A. Lerch, P. Walpita, H.-P. Wang, M. S. Sidhu, and S. A. Udem, J. Virol. 75:921–933, 2001), suggest that modulation of transcription and replication plays an important role in attenuation.

Measles is a highly contagious disease that most commonly strikes children. The causative agent, measles virus (MV), is generally transmitted by aerosolized secretions deposited on upper-respiratory-tract mucosal surfaces. Exposure leads to local respiratory tract replication; infection of regional lymphoid tissues then occurs followed by viremia and systemic dissemination as revealed by the characteristic skin rash. Most children recover uneventfully from the illness, but serious complications can occur, including pneumonia and involvement of the central nervous system (17, 27, 28). Despite the highly contagious nature of the disease, MV can be controlled effectively by immunization with live attenuated vaccines. The effectiveness of MV vaccines is well illustrated by the epidemiology of the disease in the United States. Prior to 1963, before use of the earliest vaccines, there were over 500,000 reported cases per year. Twenty years later, MV incidence was less than 2,000 cases per year (11, 28). The availability of these effective vaccines has not eliminated the threat from MV, and measles still causes significant levels of morbidity and mortality in developing countries largely because of inadequate and unsustained vaccination efforts (17).

Several effective MV vaccines were derived from a single clinical viral isolate called the Edmonston strain (28, 66). Enders et al. (20) developed the first MV vaccine by the classical approach (1) of propagating the pathogen in heterologous cells and tissues. Specifically, MV was serially propagated in semipermissive chicken embryos and chick fibroblast cells. Variations of the Enders approach have led to the development of a number of independently derived but effective Edmonston-based vaccines (28, 66).

MV is a member of the genus *Morbillivirus* in the *Paramyxoviridae* family and, like other members of this family, it is an enveloped RNA virus that contains a single-strand, negative-sense, nonsegmented genome (28, 47). The 16-kb MV genome encodes eight known proteins from six nonoverlapping cistrons arranged 3′-N-P-M-F-H-L-5′. The major structural polypeptide is encoded by the N (nucleocapsid) gene. The N protein is essential for packaging the genome into a ribonucleoprotein complex that serves as template for transcription, replication, and packaging into progeny virions. The P cistron specifies three polypeptides: P, C, and V. The P (phosphoprotein) polypeptide is a subunit of the viral RNA polymerase. P protein also acts as a chaperone that interacts with and regulates the cellular localization of N protein and probably assists in nucleocapsid assembly (28, 33, 70). The C and V polypeptides are nonstructural proteins that are translated from P mRNAs through the use of alternative reading frames; C protein is synthesized from a downstream translation start signal, whereas V protein is translated from an edited mRNA that contains an extra G residue (28, 33, 70). The M gene encodes the matrix protein that lines the inner surface of the viral envelope and participates in virion maturation (28, 83). The F (fusion) and H (hemagglutinin) genes encode envelope glycoproteins that mediate cell surface recognition, membrane fusion, and virus entry (28, 83). Finally, the L (large) gene encodes the multifunctional catalytic subunit of the RNA-dependent RNA polymerase (28, 33, 70).

How changes in individual MV proteins may influence vaccine virus attenuation is not well understood. Partial sequence data for MV vaccine virus genomes clearly indicates that multiple mutations have accumulated in more than one protein

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coding region, but these analyses have so far failed to point to an underlying mechanism of MV attenuation (28, 66). To facilitate further analysis of the molecular basis of MV attenuation, we have determined the nucleotide sequence of all protein coding regions from an early-passage laboratory isolate of the original Edmonston virus (see Fig. 1, Edmonston wild type and reference (66) and five Edmonston vaccine strains. Comparison of deduced amino acid sequences has revealed amino acid coding substitutions common to all of the vaccines, as well as changes found only in subsets of the vaccine viruses. The results of these comparisons identified a number of mutations that appear to be strong candidates for attenuation determinants. In addition, we also suggest a model that correlates modulation of gene expression with the attenuated phenotype.

MATERIALS AND METHODS

Cells and virus. Vero cells were maintained in Dulbecco modified Eagle medium (Life Technologies) supplemented with 5% fetal bovine serum. Stocks of MV were prepared by infection of Vero cell monolayers at a multiplicity of infection of approximately 0.1 PFU per cell. Infected cells were harvested by scraping the monolayer when the cytopathic effect was detectable in 70 to 80% of the cell monolayer. Harvested cells were collected by centrifugation and resuspended in serum-free OPTIMEM (Life Technologies) and lysed by one freeze-thaw cycle. The Edmonston wt isolate (21, 28) was kindly provided by Judy Beeler (Center for Biologics Evaluation and Research). Edmonston B (Rubeovax) (20, 28, 45), AIK-C (52), Schwarz (28, 45, 69), and Zagreb (28, 38) were generously provided by William Bellini and Paul Rota (Centers for Disease Control and Prevention) (66). Moraten (Attenuvax, Merck & Co.) (28, 31) and a second sample of Schwarz (Rimevax, SmithKline Beecham) (28, 45, 69) were obtained from commercially available vaccine preparations. The Schwarz virus strain from each source was analyzed independently.

Viral genome sequencing. Sequencing was performed on DNA fragments generated by reverse transcription and PCR amplification (RT-PCR). Total RNA was extracted from infected Vero cells by the guanidinium-phenol extraction procedure (12) using Trizol reagent (Gibco-BRL). RT-PCR required first NT of approximately 1 μg of total infected-cell RNA with avian myeloblastosis virus (AMV) reverse transcriptase (Pharmacia) and random hexamer primers (Pharmacia), followed by *Taq* DNA polymerase-mediated PCR amplification (Amplitaq; Perkin-Elmer) with sequence-specific primers. Some single-tube RT-PCR reactions were performed by RT in the presence of gene-specific primers and AMV reverse transcriptase, followed by amplification with the high-fidelity enzyme mixture in the Titan RT-PCR kit (Roche Molecular Biology). Terminal fragments were either amplified by RT-PCR performed across the junction formed after circularization of the RNA genome with RNA ligase (71) or amplified by using the RACE (rapid amplification of cDNA ends) procedure (24). Amplified DNA fragments were purified for sequencing by electrophoresis in low-melting-temperature agarose (FMC). DNA was recovered from gel slices with the Wizard DNA Clean-Up System (Promega) or by digestion of gel slices with β-agarase (New England Biolabs). Cycle sequencing (29, 44) was executed with dye-labeled terminators and *Taq* DNA polymerase (Applied Biosystems), followed by analysis on an ABI Prism 377 automated sequence apparatus (Applied Biosystems). Primers for PCR amplification and sequencing of both cDNA strands were designed based on published MV sequences (GenBank accession numbers K01711 and S58435). Sequence data were analyzed using the MacVector (Oxford Molecular Group) and Lasergene (DNAStar, Inc.) software packages. A rooted phylogram was prepared from a CLUSTAL W alignment by the neighbor-joining method and plotted by using NJplot (61, 79).

RESULTS AND DISCUSSION

Nucleotide sequence analysis. MV coding region sequences were analyzed to reveal genetic modifications in vaccine strains and thereby identify candidate vaccine-specific coding changes for future studies of MV attenuation. The virus strains sequenced are shown on the Edmonston vaccine lineage in Fig. 1 (28, 66). Figure 1 also includes the passage history as described by Rota et al. (66). The virus, referred to as Edmonston wt (Fig. 1), was the lowest-passage stock available of the original Edmonston clinical isolate. It had been passaged 13 times (66) prior to our analysis. At several points in the passage history of this isolate, the virus has been shown to retain pathogenicity (2, 3). The virus samples obtained for sequence analysis were passaged minimally (one to three times) in Vero cells to generate virus stocks, and these stocks were then used to infect cells for the isolation of infected-cell RNA. Purified RNA was used to generate RT-PCR products from all protein coding regions. These PCR fragments were sequenced on both strands (see Materials and Methods) to provide a "consensus" sequence representing the population of viruses replicating within the infected cells. Direct sequencing of these PCR products helped alleviate concerns associated with sequencing cloned RT-PCR products that could represent a selected subpopulation of viral genomes or include nucleotide substitutions introduced by PCR amplification. Minor virus populations accumulated during limited Vero cell passage should not notably affect consensus sequence determinations since the RT-PCR products should reflect the majority sequence in the viral RNA pool.

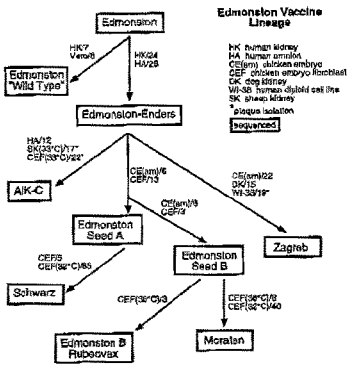
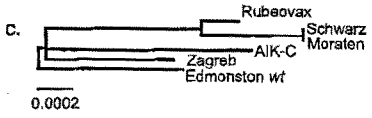


FIG. 1. Edmonston vaccine lineage. Passage history of the Edmonston vaccines as described by Rota et al. (66) and adapted with permission from Elsevier Science. The protein coding region nucleotide sequence was determined for each virus highlighted in the gray boxes.

The compiled sequence data, summarized in Fig. 2 and 3, demonstrated that the coding region nucleotide sequence of the vaccine viruses differed from Edmonston wt by at most 0.3% (Fig. 2A). Comparison of predicted amino acid sequences revealed substitutions in the five vaccine strains that differentiated these viruses from the low-passage Edmonston wt isolate (Fig. 2B). Eight amino acid coding substitutions were shared by all of the Edmonston vaccine strains, and two substitutions were found in all vaccine strains except Zagreb (Fig. 3). Less-well-conserved amino acid coding substitutions were

A.

Virus	Base Subs	Coding	Silent	Accession
Wild Type	—	—	—	AF266288
AIK-C	30	25	5	AF266288
Moraten	31	22	9	AF265287
Rubeovax	27	18	9	AF266289
Schwarz	31	22	9	AF266291
Zagreb	22	15	7	AF266290



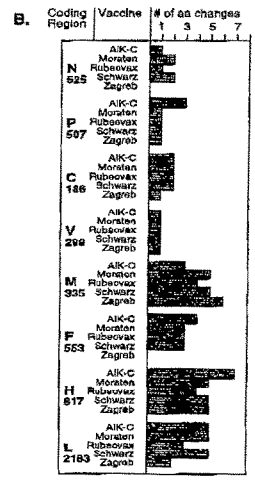


FIG. 2. Comparison of MV protein coding region sequences. (A) The total number of vaccine virus protein coding region nucleotide substitutions is shown, and values are categorized further into coding and silent substitutions. GenBank accession numbers are provided. (B) Number of predicted amino acid changes in vaccine virus protein coding regions. The size of each protein is given below the gene designation. (C) The phylogram was generated using Edmonston wt as the out group. The sequences were aligned using CLUSTAL W (79), and the phylogram was generated by the neighbor-joining method using NJplot (61). The scale represents the number of substitutions per nucleotide.

also found that affected one to three of the vaccine strains. Generation of a phylogram (Fig. 2C) indicated that the Moraten and Schwarz vaccine viruses contained identical coding sequences and were closely related to Rubeovax. Zagreb and AIK-C were obviously distinguishable from this group of vaccine viruses.

The most highly conserved vaccine virus amino acid coding changes shown in Fig. 3 (shaded in red) represent a "vaccine strain signature" that should prove useful for comparison with viruses isolated during MV outbreaks or isolated from suspected cases of vaccine-related illness. Although these coding changes are characteristic of the vaccine viruses, some of them may not be entirely unique to Edmonston vaccine strains. Several have been detected in circulating wt virus strains and in subacute sclerosing panencephalitis brain tissue RNA (amino acid positions 73 in C, 61 in M, 46 and 481 in H, and 1717 in L [data not shown and references 4, 16, 43, and 67]). It is possible that some degree of cell culture adaptation during viral propagation contributes to this observation.

The presence of amino acid substitutions shared by nearly all five vaccine strains also implies a strong correlation between at least some of these genome changes and the attenuated phenotype. These conserved nucleotide and amino acid changes represent important targets for future studies aimed at understanding the molecular basis of attenuation. Additionally, it will likely be important to consider some of the less-well-conserved amino acid substitutions in these studies. These changes could in fact play important roles in determining the attenuation level of individual strains.

How these genome modifications produce an attenuated phenotype is unknown, but their origin must reflect selection that favors growth in the cells of animals other than the natural host (Fig. 1). An indication that the particular tissue culture passage scheme determines the composition of genome modifications can be seen in the sequence data when it is examined in light of the details of the MV lineage (Fig. 1) (66). The phylogram (Fig. 2C) showed that Moraten, Schwarz, and Rubeovax were the most closely related vaccine viruses, while AIK-C and Zagreb have distinguishing genetic characteristics. In the lineage (Fig. 1) we can see that all of the vaccines were derived from the Edmonston-Enders strain; thereafter, however, their passage histories differ. The Moraten-Schwarz-Rubeovax group was propagated under very similar conditions, most notably the exclusive use of chicken cells. In contrast, AIK-C and Zagreb were both propagated in nonavian cell types that may account for their divergence from the Moraten-

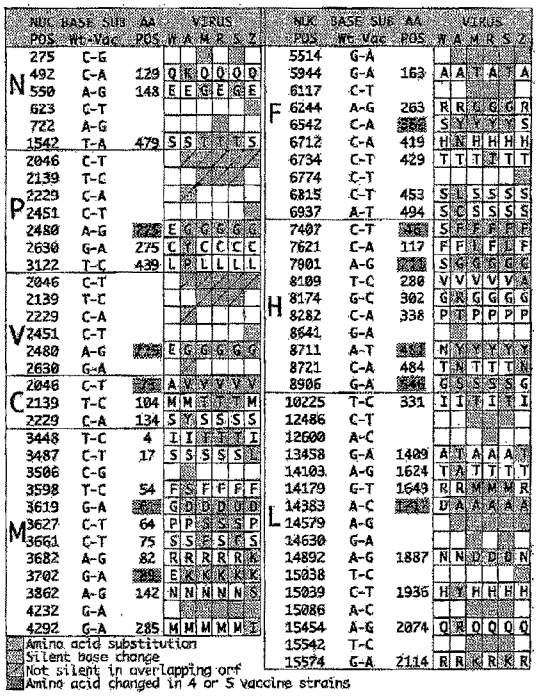


FIG. 3. Comparison of Edmonston wt and vaccine virus genomes. Nucleotide changes are shown for each coding region. Whether the nucleotide substitution results in an amino acid change or is silent is illustrated in the grid. Amino acid changes from wt are presented using one-letter amino acid symbols. Yellow shading in the grid highlights an amino acid substitution. Red shading of the amino acid position indicates a residue that is substituted in four or five of the vaccine strains. Blue shading in the grid without an amino acid symbol denotes strains that contain a silent base change; a line through a blue box indicates that the change is not silent in an overlapping reading frame. The F protein amino acid numbers are given relative to the predominant AUG codon at genomic nucleotide position 5458 (9). Abbreviations in the green header: NUC POS, MV genomic nucleotide position; BASE SUB, nucleotide substitution; Wt-Vac, wt and vaccine virus nucleotides; AA POS, amino acid position; W, Edmonston wt A, AIK-C; M, Moraten; R, Rubeovax; S, Schwarz; and Z, Zagreb.

Schwarz-Rubeovax group. These distinctions in the lineage correlate well with the phylogram displayed in Fig. 2C.

It was unexpected to find that Moraten and Schwarz contained identical coding region nucleotide sequences given the fact that they were passaged independently. It was a further surprise to find that the two viruses also contained identical noncoding sequences (59). It is possible that quasispecies subpopulation differences in the vaccines exist and were below the detection levels of consensus sequencing; but even if this was the case, the results still indicated that the two viruses were remarkably similar. Consensus sequence analysis of a second Schwarz vaccine specimen was performed, confirming the initial observation. The basis for the perplexing sequence identity of these two independently derived MV vaccine strains is un-

known. Possibly, the convergence of sequence in the Moraten and Schwarz viruses reflects a highly selective and delimited spectrum of nucleotide changes imposed by extensive passage in chicken embryo fibroblasts at reduced temperatures (Fig. 1).

The process of adapting MV to semipermissive cell types obviously generates strong selective pressure that favors the evolution of viral polypeptides that function more effectively in the new host cell environment. Although the following is speculative, it seems likely that early in the adaptation process the interaction between some viral proteins and proteins in the semipermissive cell are inefficient. This gives rise to slow viral growth and selective pressure that favors mutations leading to alterations in viral polypeptides that enhance functional interaction with host cell proteins. A prime target for some of the earliest mutations would be the genes encoding the transcription and replication apparatus since these proteins must adjust the initial stages of viral replication (mRNA synthesis and positive-strand synthesis) to the semipermissive cell environment. A potential disadvantage associated with these earliest mutations is that they may create viral proteins that enhance interaction with the host cell at the expense of other segments of the viral replication cycle. For example, a mutation that improves P protein interaction with a semipermissive host cell factor could have a negative effect on another function such as the P-N protein-protein interaction or recognition of template sequences by the P-L polymerase complex. This will generate additional selective pressure for "second-site repressor" mutations that help compensate for the effect of the primary mutations. We could imagine that these second-site repressor mutations would evolve in viral protein coding regions as well as *cis*-acting sequences as the virus attempts to fine-tune the replicative capacity to the semipermissive cell environment during the course of a prolonged passage scheme. In theory, these genetic adjustments give rise to the best-fit virus for growth in the semi permissive cells but ultimately render the virus less effective at interaction with the cellular proteins of the natural host. Thus, when this vaccine virus infects permissive human host cells, its accrued mutations lead to less-effective virus-host cell protein interaction and thereby reduce virus replication efficiency. Adequate time for the vaccine virus to revert some of the genetic change after vaccination is not available before an immunocompetent host clears the viral infection. We present below the data analysis for each gene region and describe how some of the genetic changes may relate to virus attenuation.

N gene. Analysis of the N gene identified three predicted amino acid substitutions (Fig. 2B and 3); none of these changes were conserved by all of the vaccine strains, and no single vaccine strain contained all three substitutions. Although the N protein substitutions were not conserved by all vaccine strains, they still represent attractive candidates for attenuating modifications. N protein plays a key role in the virus life cycle during genome packaging, genome replication, and gene expression (28). The role of the N protein in these diverse activities makes it seem probable that amino acid substitutions would have some impact on the virus. The nonconservative amino acid substitution found in the amino terminus of the Moraten and Schwarz N protein (position 148, glutamic acid to glycine) is a obvious candidate to alter N protein function. It occurred in a region of N protein that likely plays a role in several functions, including RNA binding (47), the formation of the nucleocapsid structure, and interaction with P protein (Fig. 4A). Computer predictions also indicate that this amino acid substitution would disturb an alpha-helical region of the protein. Interactions with P protein may also be influenced by the amino acid substitutions in N protein at position 479 in Moraten, Rubeovax, and Schwarz, as well as the position 129 substitution in AIK-C (Fig. 4A) (5, 50). No coding region changes were detected in the Zagreb N gene. This indicates that successful attenuation can occur without substitutions in N, but that the accumulated strain-specific changes in N may be important contributors to the degree of attenuation in viruses such as Moraten, Schwarz, and AIK-C.

P cistron. Amino acid substitutions detected in the P gene included a change shared by all of the vaccines at position 225 (Fig. 2B and 3). The amino-terminal portion of the P gene open reading frame (ORF) also encodes two-thirds of the V polypeptide; therefore, all of the vaccine virus V proteins contain the same amino acid substitution. The C protein coding region embedded within the P gene contained three substitutions (Fig. 2B and 3) which were silent with respect to the overlapping P and V ORFs.

P protein is a multifunctional polypeptide that is a component of the polymerase complex. It also plays a role in viral RNA encapsidation and regulates the cellular localization of N protein (28, 33, 37, 47, 70). Given its pleiotropic activities, substitutions in P protein are likely to significantly impact viral replication efficiency. The position 275 and 439 substitutions in AIK-C P (Fig. 3) protein may be significant in the context of this strain. They map within P domains (Fig. 4B) that mediate interaction with N protein as well as promote its own multimerization (30, 37, 80). The position 225 substitution (Fig. 3), found in all of the vaccines, replaced an Edmonston wt glutamic acid with a glycine. Substitution of this glutamic acid with a nonpolar residue occurred in a region of P protein that may be involved in a chaperone function of P protein that regulates the cellular localization of N protein (37, 80). The fact that the N-P protein-protein interaction is essential for several functional activities suggests that any mutations that alter P protein and influence the N-P interaction could affect gene expression, replication and ultimately the degree of attenuation.

The 225 substitution also affects V protein (Fig. 3 and 4B). As mentioned above, this substitution occurred within one of the P protein domains (Fig. 4B) that plays some role in the interaction with N protein (30, 37). This region appears to play a similar role in V protein (80). Thus, it is possible that the position 225 substitution could affect the interaction between the N and P proteins as well as between the N and V proteins. Perturbing these interactions could lead to changes in the relative ratios of N-P and N-V complexes and possibly alter the effective availability of N protein for encapsidation.

V protein is dispensable for growth in cultured cells (68), but several studies indicate that V protein may be a virulence factor. Sendai virus defective for V protein synthesis is less pathogenic in mice (18, 36, 40, 41). Furthermore, a recombinant lab strain of Edmonston B that is defective for V protein expression replicates less efficiently in some experimental model systems (56, 60, 80, 81). The connection between pathogenicity and V proteins suggests that mutations in the V ORF should be considered potential attenuation determinants.

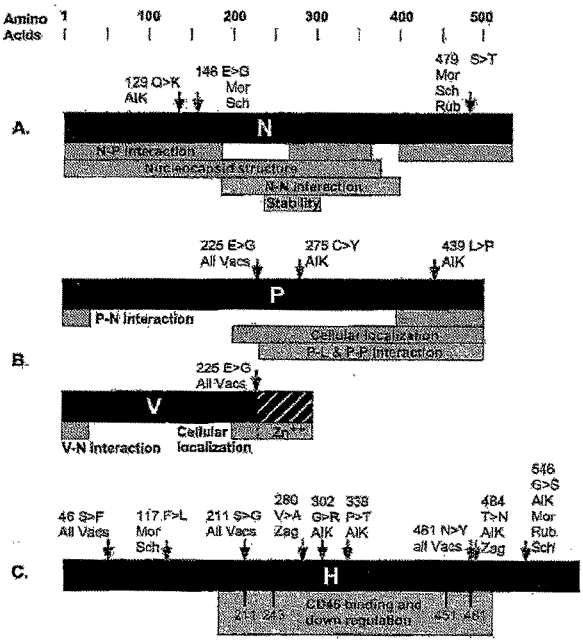


FIG. 4. Protein domains and vaccine virus amino acid substitutions. Domain maps for N, P, V, and H proteins are shown along with arrowheads marking the position of predicted amino acid substitutions. Vaccine virus names are abbreviated as follows: AIK-C (AIK), Moraten (Mor), Rubeovax (Rub), Schwarz (Sch), and Zagreb (Zag). (A) The domain boundaries illustrated below the linear map of N protein are derived from Bankamp et al. (5) and Liston et al. (30). These include domains involved in N-P complex formation and nucleocapsid formation and a region that affects protein stability. (B) The linear maps of P protein and V protein drawn in black illustrate sequences shared by these proteins. The unique sequence in the carboxy terminus of V is designated with a cross-hatched box. Domain boundaries include regions that promote interaction with N protein, a region that affects the cellular localization of N-P complexes, a region of P protein that promotes interaction with L protein and the formation of P-P multimers, and the carboxy-terminal domain of V that binds zinc (30, 34, 37, 51, 60). (C) Illustrated below the map of H protein are amino acids that have been implicated in mediating binding and downregulation of CD46 (7, 35, 49).

Finally, the variability in the P cistron also affected the C protein ORF (Fig. 3). Like V protein, alterations that affect C protein are intriguing because C protein is dispensable for MV growth in Vero cell culture (63) but may be an important factor influencing pathogenicity. In the SCID mouse model system, transplanted human thymic tissue supports less viral replication if infection is performed with a recombinant Edmonston B strain that cannot express C protein (81). In addition, the C protein defect appears to hinder replication in cultured human peripheral blood mononuclear cells (23). How C protein regulates growth in these model systems is not understood, but it can be inferred from studies with Sendai virus (8, 15, 32) that MV C protein may modulate viral RNA synthesis. Also, in Sendai virus, C protein seems to counter innate immune responses to infection induced by interferon (26), raising the possibility that MV C protein may perform a similar function. Care must be taken when drawing these comparisons between MV and Sendai virus C proteins given that Sendai virus en-

codes multiple C protein species (48), while MV encodes only one known C protein. Yet it is interesting to note that Sendai virus C protein is dispensable for growth in cell culture like MV C protein and that Sendai virus defective for C protein expression is less virulent in mice (25, 46, 57).

M gene. Ten coding changes were identified in the vaccine virus M genes (Fig. 2B and 3). Only two of these were common to all vaccine strains (positions 61 and 89); these were two nonconservative changes that replaced a wt nonpolar glycine for an aspartic acid at position 61 and a wt glutamic acid for lysine at position 89. The substitution at position 61 has been detected also in some circulating wt strains (data not shown and references 16 and 67).

Changes in M protein could influence the level of attenuation by perturbing M protein function during virion maturation (83) or transcriptional repression (77). In addition, the accumulation of M gene mutations is one characteristic of latent genomes indicating that changes in the M gene can contribute to an atypical virus life cycle (10).

F and H glycoproteins. Since the glycoproteins are important determinants of MV host range and cell tropism (39, 76) it was expected that some mutations would accumulate in these genes after serial passage in cells of nonprimate origin. In addition, the role played by the viral glycoproteins in cell entry, cell fusion, and virus maturation (28, 83) raises the possibility that some of the changes in F and H may influence the cell-to-cell spread of the virus and contribute to the attenuated phenotype. The F protein coding region contained a number of codon changes, but none of these were conserved in all vaccine strains (Fig. 3). The specificity of nine codons varied in the H ORF. Three H amino acid substitutions were conserved among all of the vaccine viruses, and a fourth differed in all vaccines strains except Zagreb (Fig. 2B and 3). None of the amino acid substitutions should affect the glycosylation pattern of H (28).

The H gene actually accumulated the highest number of substitutions that were shared by all vaccine viruses (Fig. 3). This may reflect the fact that H protein is the receptor component of the virus envelope and significant changes were required to adapt H protein for effective infection of the heterologous cell types used during vaccine passage (22). These changes in H protein may also contribute to attenuation if they render the virus less efficient at infecting human cells. In fact, several of the amino acid residues that were changed in the vaccine viruses have received considerable attention recently because studies indicate that they play an important role in binding to one of the cellular receptors for MV (Fig. 4C). The amino acids at positions 211 and 481 are both important for interaction with one of the cellular receptors (CD46) for MV (7, 35, 49). Virus isolates with a wt asparagine residue at position 481 do not readily infect monkey kidney cell lines but efficiently infect a transformed marmoset lymphoid cell line (derivatives of B95-8 cells) (42, 54). In contrast, tyrosine at position 481 enhances the ability to infect monkey kidney cell lines. Interaction between H protein and CD46 also promotes clearance of CD46 from the infected-cell surface. This phenomenon also depends on amino acids at positions 211 and 481. H proteins containing the vaccine virus amino acids at these positions displayed an enhanced ability to remove CD46 from the cell surface (7, 49). This has led to speculation that more potent clearance activity of vaccine H protein may contribute to attenuation. Recombinant MV used in primate studies probably will be necessary to definitively determine the role of H protein in attenuation.

L gene. Nine amino acid coding changes were detected in the L gene. The only one shared by all vaccines was at position 1717, where a wt glutamic acid was substituted with an alanine. The L gene had one of the lowest frequencies of amino acid substitution (Fig. 3), presumably reflecting the intolerance of functional domains of this enzyme to amino acid substitution.

To better assess the changes in L protein, they were displayed on a domain map (Fig. 5). Domains of homology exist among various RNA-dependent RNA polymerases, including the paramyxovirus L proteins (6, 53, 62, 72). It has been proposed that these homologous regions (RNA-dependent RNA polymerase domains I to VI) (6, 53, 62, 72) are functional domains. Further comparison of morbillivirus L proteins has led to a somewhat different model of three large domains (morbillivirus domains 1 to 3) and two hinge regions (53). Curiously, only one vaccine virus substitution was located within the RNA-dependent RNA polymerase domains I to VI. This relatively conservative isoleucine-to-threonine substitution at position 331 was found in Moraten and Schwarz. This region of L protein is within a domain that interacts with P protein (34), suggesting that this amino acid substitution may affect L-P protein-protein interaction. This suggestion needs to be examined experimentally since a recent report indicates that a valine substitution found at this site in some circulating virus strains does not seem to affect the interaction between the L and P proteins (4). The remaining amino acid coding changes affecting L protein occurred outside the boundaries of RNA-dependent RNA polymerase domains I to VI. This may indicate that domains I to VI indeed contain regions essential for enzymatic function and that these regions are less tolerant of amino acid substitutions. Furthermore, it is attractive to speculate that the vaccine virus L protein amino acid substitutions occurred in regions of the protein that may modulate enzymatic activity rather than directly affect a region that contains an active site.

Silent mutations. Silent nucleotide substitutions were identified at 17 positions (Fig. 3). Three of these base substitutions were common to all of the vaccine strains (one each in the M, F, and L coding regions). An additional silent substitution in P and V is conserved in all vaccines, but it is not truly silent; three of the four silent base changes in the P and V coding regions result in amino acid substitutions in the overlapping C ORF. Identification of several silent mutations that were conserved in multiple vaccine strains could support the idea that some of these base changes provide a *cis*-acting advantage such as increased mRNA stability or more favorable secondary structure for translation or may reflect selection due to codon bias. More likely it simply reveals that some silent base substitutions were incorporated early during vaccine virus passage. These are tolerated after incorporation and can be maintained in the genome if they do not affect the fitness of the virus.

It was somewhat surprising to find that so few silent changes have accumulated in light of the fact that the negative-strand RNA virus polymerases have a relatively high error rate (19) and the vaccine viruses had been passaged extensively (Fig. 1). Although this is difficult to explain, it is not unique to the Edmonston vaccines. Biologically derived respiratory syncytial

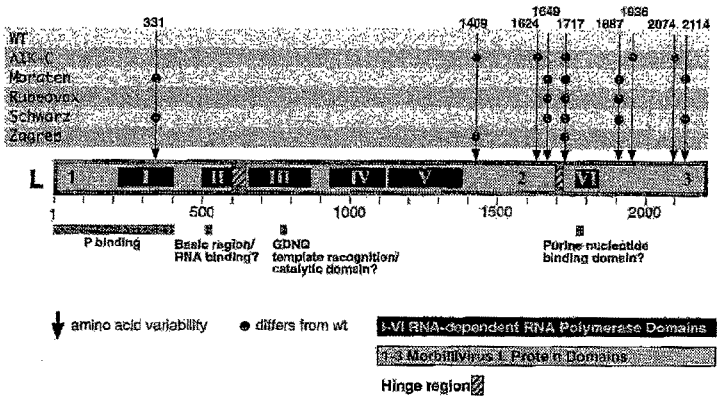


FIG. 5. Position of amino acid substitutions relative to the domain map of the L protein. The domain organization deduced from analysis of RNA-dependent RNA polymerase sequences is labeled with the roman numerals I to VI (6, 53, 62, 72), and the domain and hinge structures predicted for morbillivirus L proteins are labeled 1 to 3 (53). The location of amino acid substitutions is marked with an arrowhead, and circles identify changes from the Edmonston wt sequence.

virus vaccine candidates also have been noted to accumulate relatively few nucleotide substitutions after extensive passage in culture (13).

Comparison of AIK-C sequences. The complete genomic sequence of AIK-C was carefully analyzed previously in 1993 by Mori et al. (55). Comparison of the coding and noncoding (59) sequences generated by this laboratory (GenBank accession number AF266286) to the earlier AIK-C sequence (GenBank accession number S58435) revealed 21 nucleotide differences. Ten of these predict amino acid substitutions, six were silent, and five were located in noncoding regions. A likely explanation for many of these differences lies in the types of tools and methods used to analyze the virus genomes. Since 1993, sequencing technology, including the enzymatic steps and gel systems, has advanced dramatically and now allows for increased resolution of sequences containing secondary structure. Inspection of regions containing the nucleotide differences indicated that about 10 of the 21 discrepancies lie in areas of locally high G+C content or contain sequences that may form intramolecular duplexes. These regions would likely complicate sequence determination and explain some of the differences between the presented sequence and that of Mori et al. (55). A second source of variation may reflect the fact that Mori et al. analyzed cloned cDNA fragments, whereas we employed direct sequencing of RT-PCR fragments. Finally, a third difference lay in the passage history of the sequenced AIK-C viruses. Here, the virus was passaged a limited number of times in Vero cells, whereas Mori et al. used chicken embryo cells. Taken together, these technical variations probably account for the majority of nucleotide differences in the two sequence determinations.

Only two of the nucleotide differences between our sequence and that of Mori et al. (55) affected amino acids that distinguish between Edmonston wt and the currently proposed AIK-C sequence. Amino acid 362 in F protein was a serine in Edmonston wt and a tyrosine in AIK-C, while the sequence of Mori et al. predicted no amino acid change. Similarly, in F protein, we found that all of the viruses except AIK-C encoded an H residue at position 419, while AIK-C encoded an N. The sequence of Mori et al. again predicted no change from the wt.

Edmonston vaccine attenuation. Comparison of a low-passage isolate of the Edmonston wt strain with five vaccine virus derivatives revealed distinguishing genetic changes in all coding (Fig. 3) and noncoding regions (59). Finding genetic change in multiple genes and noncoding regions may indicate that viral replication in semipermissive cells requires modification of several components of the virus replication cycle, including cell entry, gene expression, genome replication, and virus maturation. Although a constellation of genomic changes may be essential for adaptation to semipermissive growth conditions, it remains to be determined whether all of these changes are indeed necessary for effective attenuation. Clues from other negative-strand RNA vaccine viruses and vaccine virus candidates suggest that only a subset of these genome changes may be essential for attenuation and that modification of the gene expression and replication apparatus is a particu-

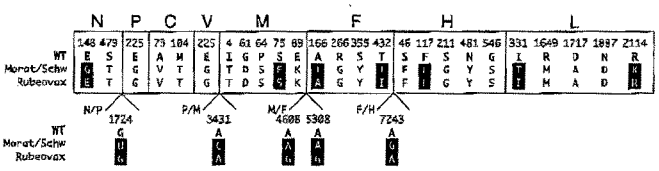


FIG. 6. Comparison between Moraten, Schwarz, and Rubeovax. Substitutions that distinguish between wt and this group of vaccine viruses are illustrated in the boxes representing each gene region. The amino acid positions are indicated above the columns of amino acids. Noncoding region changes (59) in the intergenic regions that distinguish Moraten and Schwarz from Rubeovax are shown along with the nucleotide position below the boxed gene designations. Black highlighting identifies substitutions that differentiate the identical genomes of Moraten and Schwarz from Rubeovax. Moraten/Schw, identical genomes of Moraten and Schwarz.

larly critical target. For example, mutations in the L polymerase gene of RSV have been found to effectively modulate the degree to which live virus vaccine strains are attenuated (82). Similarly, cold-adapted parainfluenza virus type 3 vaccine candidate strains contain polymerase gene mutations and base substitutions in the 3′ transcription promoter region that are attenuating (73, 74). Live influenza virus vaccines generated by replacing the genes for the hemagglutinin and neuraminidase glycoproteins retain an attenuated phenotype specified by mutations within the components of the replication apparatus (75). Taken together, these studies imply that polymerase mutations, as well as *cis*-acting signal mutations, are important contributors to the attenuated phenotype.

Consistent with this notion, all Edmonston vaccine viruses were found to contain mutations in the L and P genes (Fig. 3) as well as within the leader region (59). That polymerase gene mutations in combination with *cis*-acting signal mutations significantly contribute to attenuation by altering gene expression is a relatively simple and attractive hypothesis. Modulating the abundance of viral gene expression to achieve suitable immunogenicity while limiting virus replication, dissemination, and injury is an essential element of an optimally attenuated virus.

Modulation of MV gene expression as a mechanism of attenuation may involve more than the core polymerase complex and *cis*-acting signals in the leader. This concept also was proposed by Takeda et al. (78) after they found that the coding differences between a pathogenic MV strain and a Vero cell-adapted derivative resided in the core polymerase genes (L and P), as well as in the V and C coding regions. As described above, the vaccine viruses of the Edmonston lineage also have substitutions outside of the core polymerase genes that appear to have the potential to affect gene expression. These included substitutions within the N gene, the genes encoding accessory proteins (V, C, and M), and additionally in noncoding regions that may have important *cis*-acting functions (59).

The possibility that regulation of gene expression and replication plays a role in attenuation gains support from our analysis and can be illustrated by sequence comparison between the underattenuated Rubeovax strain and the identical genomes of the desirably attenuated Moraten and Schwarz vaccine viruses (Fig. 6). Presumably, some of the genetic differences between these viruses were responsible for the underattenuated phenotype of Rubeovax. Comparison of these virus genomes revealed differences in the L protein, the N protein (Fig. 3 and 6), and several putative *cis*-acting sequences. The noncoding region changes (Fig. 6) (59) included nucleotide substitutions in sequences corresponding to the long untranslated region of the F mRNA (nucleotides 4608 and 5308), the M gene translation start codon context (nucleotide 3431), and the gene end signal of the F gene (7234). It is also worth noting that most of the changes that distinguish Rubeovax from Moraten and Schwarz were due to substitutions in Moraten and Schwarz that did not occur in the Rubeovax genome. Thus, it is possible that the slightly more wt genotype in parts of the gene expression apparatus of Rubeovax is responsible for its underattenuated phenotype.

An attractive feature of the hypothesis that links gene expression to attenuation is the pathway it suggests for rational negative-strand RNA virus vaccine design—that downregulating viral RNA synthesis in human cells will effectively decrease replication and contribute to attenuation. Current molecular technology (14, 58, 64, 65) will facilitate the development of recombinant measles viruses with targeted mutations in different elements of the gene expression apparatus that can be used to test this model. If a recombinant MV can be developed that displays altered gene expression, reduced replicative ability, and safe levels of attenuation, it may be possible to apply these findings to a wider range of paramyxoviruses.

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Mr. BURTON. Mrs. Morella, do you have some questions?

Mrs. MORELLA. Thank you for this hearing and the continuation of a series.

Dr. Weldon makes exceedingly great points by virtue of his experience and knowledge. I agree with him that we should not be equating HIV AIDS with the money going into this research either. Let us just contribute the money to all of the research. I know he doesn't mean to say we take away from one with the other.

I am going to ask a series of questions of Dr. Chen. Dr. Chen, in the U.S. medical community, studies that have been done by CDC researchers are given a great deal of credence, aren't they?

Dr. CHEN. I hope so.

Mrs. MORELLA. Internationally, such studies tend to be viewed as the opinion of the Government, correct?

Dr. CHEN. You would have to ask those people. Again, we try to do the best science possible.

Mrs. MORELLA. Generally, medical authorities, particularly those in the international community tend not to distinguish between CDC employees publishing research and the CDC's official position, correct?

Dr. CHEN. Again, I have not done a survey to look at that.

Mrs. MORELLA. Isn't it true that HHS requires or perhaps should require that CDC ensure that its research regarding vaccines, for example, is of the highest caliber, is not misleading, and that a published study actually answers the question being asked?

Dr. CHEN. No, I think all studies have their strengths and weaknesses as seen by the discussion this morning. All we can do for any particular study is do our best to see what we can answer with the particular study design and address the strengths and weaknesses in the discussion.

Mrs. MORELLA. So if a given CDC study can't reach a conclusion, the CDC and the article needs to explicitly say so, correct?

Dr. CHEN. Again, in any particular discussion, hopefully we discuss both strengths and weaknesses. With rare exceptions, no single study on its own, is able to definitively arrive at a conclusion. You add to the weight of the evidence on a particular issue.

Mrs. MORELLA. It is our understanding that the Vaccine Safety Datalink Project was your idea, your concept. Is that true?

Dr. CHEN. I don't know if it is unique. I think there were several other predecessors who actually did smaller projects, versions of these large linked data bases. In fact, the drug safety folks actually came up with early versions of these linking up automated pharmacy files with automated outcome files. In science, we are always building on others ideas.

Mrs. MORELLA. You are being pretty modest about it. Was the project originally designed for a specific length of time or was it designed to go into perpetuity?

Dr. CHEN. I think the thought was that be we will continue to vaccinate and presumably there will continue to be vaccine safety issues. Our initial contract I think was for 5 years because that is how long government contracts could be, so I don't know if we actually thought in terms of how long it would run but definitely would run for 5 years.

Mrs. MORELLA. Five years I think was the original intent.

Why was the project extended past the original 5 year plan? Who made the decision?

Dr. CHEN. I think the main reason is there continued to be new vaccines added to the schedule and there continued to be new vaccine safety issues that arose. The main impetus in early 1990 when we got started was the Institute of Medicine review of the evidence available on the safety issues as part of the Vaccine Injury Compensation Act. About two-thirds of the issues they looked at, they had to take the agnostic position that there was inadequate evidence to accept or reject a causal relationship, so there was a large number of research issues that were backlogged from before.

Mrs. MORELLA. But who made the decision? Who at CDC determines what studies will be conducted?

Dr. CHEN. It is a decision like any multicenter research project. It is done collaboratively through the principal investigators, so we have a monthly conference call among the PIs to look at potential new study ideas. We take into account a variety of potential study ideas, be it from the Institure of Medicine, be it from VAERS, be it from case reports and the literature, and then, in an annual face to face meeting, we try to further prioritize among our ongoing studies.

Mrs. MORELLA. So it is collaborative?

Dr. CHEN. It is very much an unusual partnership. It is the largest collaborative project between CDC and managed care organizations. We have the public health interest to do the vaccine safety monitoring. This is perhaps one aspect that is different for us compared to Canada and Saskatchewan where there is national health insurance. The HMOs have their own internal administrative data bases as part of their regular internal private insurance organization. So we piggy-backed the VSD project onto data that is collected for routine medical care in the HMO's.

Mrs. MORELLA. In February of this year, I understand you and other CDC employees met with committee staff to discuss the release of the Vaccine Safety Datalink raw data to researchers?

Dr. CHEN. It was not the raw data. I think there is some confusion. We had talked about access in terms of the completed VSD studies. If individuals wished to do independent validation of our findings, we would make that available through the Research Data Center.

Mrs. MORELLA. At this meeting, CDC provided a draft proposal for researchers to access the VSD data. I understand the staff was told the project was ready to go. Is this project now up and running?

Dr. CHEN. I think someone contacted me yesterday in terms of the proposal process and we are in discussions with them.

Mrs. MORELLA. I understand no one has seen a press release? Have you done a press release or an advertisement in any of the medical journals or on the CDC Web site?

Dr. CHEN. Generally we do not publicize or issue a press release in matters like this. That is handled by the Department. We pursued this issue with the urging of the committee and made your staff aware of the availability of this new policy so that, if other researchers wish to replicate the findings, we would make it available.

Mrs. MORELLA. You can see what I am getting at, the idea that I think it is important that you make the announcement. Otherwise, how do you propose that people are going to know the program exists.

The committee was sent an email message last week saying applicants could send their applications to you? Do you have the procedures and the timeline for people to respond?

Dr. CHEN. As I mentioned earlier in response to a question, this is a pilot process we are working out and we want to accept those requests and just work it through and see how it goes. I think this is very much an experiment in terms of seeing whether, in fact, we are able to maintain this very valuable infrastructure for vaccine safety monitoring to the extent that the HMOs are still willing to continue to participate. We cannot mandate them to participate. It is really their patients, their data base and their institutional review boards who have oversight over the access to these data.

Mrs. MORELLA. Can outside researchers contact the HMOs who participate in the VSD directly with specific research proposals?

Dr. CHEN. If they wish, sure. Currently, the infrastructure the VSD has built has permitted a number of other folks interested in research, folks interested in doing vaccine related research, to work directly with the HMOs, yes.

Mrs. MORELLA. My name has expired. I would yield back. Thank you for your response. You can see we are looking at what that streamlined procedure will be, the openness timeline.

Mr. BURTON. We certainly want to see this opened as quickly as possible so that other researchers can check on all these things we are talking about.

Dr. Egan, one thing has bothered me for a long, long time. Do you know when thimerosal was checked for its safety initially?

Dr. EGAN. The first study that I am aware of I guess was in the late 1920's when some researchers from Eli Lilly first evaluated.

Mr. BURTON. Do you know of any safety studies after that one or is that the only one?

Dr. EGAN. That is probably the only direct.

Mr. BURTON. Do you know anything about the study? Have you ever looked at that study?

Dr. EGAN. Yes, the original publication of it. Yes.

Mr. BURTON. Do you know that everybody, from what I have been told, everybody in that study was suffering from some kind of meningitis and it was a fatal disease, and that every one of them died, so there was no way to know if the thimerosal was safe or not because every one of the people injected with it died. They died from the Meningitis. Did you know that?

Dr. EGAN. No I have to go back and look at that.

Mr. BURTON. You mean to tell me that since 1929, we have been using thimerosal and the only test you know of is the one done in 1929 and everyone of those people had meningitis and they all died?

Dr. EGAN. There are other reports about the use of thimerosal in various products.

Mr. BURTON. Yes and they took methiolate off the market.

Dr. EGAN. Yes, as a topical.

Mr. BURTON. But you don't know of any other study, thorough study, that showed the safety of thimerosal?

Dr. EGAN. No, other than those studies that were done using it in end products and at whatever doses they had where they did see some safety related issues.

Mr. BURTON. The point is before you put a product on the market, before you start using it and injecting it in children or putting it in the products that people can put on their skin that might be toxic, shouldn't there be a very thorough test to make sure it is safe?

Dr. EGAN. The product itself, the final formulation of the vaccine, is studied and these studies were done. The limitation of those studies is that they would only find the more acute, the more rapid adverse events that might occur.

Mr. BURTON. But you are not familiar with any study that specifically deals with thimerosal?

Dr. EGAN. There were animal based studies but not in humans other than those studies where it was in products where either people received too much by accident or what else and they could get ideas of what the toxic doses were and then the other studies that are environmental trying to get estimates of the toxicity of mercury.

Mr. BURTON. So the way you found if there was too much thimerosal given was from the person who got the shot? So they were guinea pigs because you really didn't know how much thimerosal was going to be tolerable in a human being?

Dr. EGAN. These weren't studies that were done directly like that.

Mr. BURTON. How did you know how much thimerosal could be put into a vaccine or a product?

Dr. EGAN. They started off with the amounts of thimerosal that were needed as preservatives. There were animal-based tests. The amounts were certainly much, much less than the amounts that gave out of those Lilly studies and then during the investigational drug phase, adverse events were monitored and none were seen.

Mr. BURTON. You testified before this committee on July 18, 2000 that the FDA's major concern regarding thimerosal in vaccines started around May 1999. That is on page 282 of the mercury hearing transcript. We would like you to see this FDA email sent by Dr. Peter Patriarca, a CBER employee, to Roger Bernier and Jose Cordero regarding an FDA plan in place for many years to remove thimerosal from vaccines. It is exhibit No. 15. Do you have that before you, sir? Can you take a look at exhibit No. 15? Dr. Chen, can you give him exhibit No. 15, please?

Let me read directly from exhibit No. 15. It says, in the email I just referred to, "The fact of the matter is that an interim plan for potential removal of thimerosal has already been in place for many years. We just need to speed up the existing plan, not create a new interim plan. We are proactive, not reactive. Thanks, Peter, P." Why wasn't thimerosal taken out of all these vaccinations, if the plan had been in place for many years according to this email, and why didn't this committee get a copy of the interim plan?

[Exhibit 15 follows:]

Brockner Ryan, Beth

From: Patriarca, Peter
Sent: Tuesday, June 29, 1999 12:39 PM
To: 'rhb2@cdc.gov'; 'jfc1@cdc.gov'
Subject: FW: "vaccine preservative WG"

Roger/Jose: have not yet received Roger's "position paper" by e-mail, but wanted to get some comments to you quickly. Draft we heard on the call is really excellent. However, (1) would add some of the elements of my "pros and cons" listing below (especially related to the BENEFITS of having thimerosal in the first place); and (2) try to avoid suggesting that the "interim plan" would be effective "immediately". The fact of the matter is that an "interim plan" (for potential removal of thimerosal) has ALREADY been in place for MANY YEARS ... we just need to "speed up" the EXISTING plan ... not create a "new" interim plan". We are proactive ... not reactive. Thanks. Peter P.

---Original Message---
From: Patriarca, Peter
Sent: Tuesday, June 29, 1999 9:42 AM
To: 'Myers, Martin G.'; 'sja2@cdc.gov'; 'ezg0@cdc.gov'
Subject: RE: "vaccine preservative WG"

PLEASE GIVE TO MARTY MYERS ASAP.

Marty: I have developed a "quick-and-dirty" pros and cons analysis for the AAP policy statement:

The AAP should release its policy statement in more-or-less current form:

PROS

Will demonstrate that the AAP reacted urgently to recently uncovered information, and to disclose this information to practitioners and consumers.

Will demonstrate that the AAP adopts the most conservative position possible when it comes to protecting American children.

Will force manufacturers to develop "crash" programs for removal of all thimerosal from all vaccines.

CONS

Will raise questions about FDA being "asleep at the switch" for decades, by allowing a potentially hazardous compound to remain in many childhood vaccines, and not forcing manufacturers to exclude it from new products. Will also raise questions about various advisory bodies about aggressive recommendations for use. [We must keep in mind that the dose of ethyl mercury was not generated by "rocket science": conversion of the % thimerosal to actual ug of mercury involves 9th grade algebra. What took the FDA so long to do the calculations? Why didn't CDC and the advisory bodies do these ciacutations while rapidly expanding the childhood immunization schedule?]

Will precipitate a vaccine shortage, leaving many children unimmunized. Removal of thimerosal could delay the availability of sufficient supplies of vaccines for at least 2 years, pending proper studies.

Thimerosal has benefits: it is there for a reason. Precipitous removal may generate problems in vaccine stability (affecting efficacy), and component inactivation (affecting safety). Proper studies must be done before it can be removed from products without a thimerosal-free presentation.

Will precipitate a worldwide crisis in confidence in vaccines. This is especially true for whole-cell DTP vaccines, which are still being used throughout much of the world. Thimerosal is used in these vaccines as an inactivating agent for pertussis cells.

ALTERNATE APPROACH: LOW KEY, SYSTEMATIC, DELIBERATE PRIVATE-PUBLIC APPROACH

PROS

Already going on for quite some time.

Shows careful consideration to all benefits and risks (as enumerated above) with rational and deliberate plan of action.

Consistent with European position.

CONS

Dr. EGAN. I am not aware of any interim plan.

Mr. BURTON. What is he talking about?

Dr. EGAN. I am not sure what he is talking about. There was probably some discussion.

Mr. BURTON. Have you read that? It says again, "The fact of the matter is that an interim plan for potential plan for removal of thimerosal has already been in place for many years." They already had an interim plan and you are not aware of that?

Dr. EGAN. No.

Mr. BURTON. Then it goes on to say, "We just need to speed up the existing plan." So there was a plan to get this mercury product out of vaccines for many years but you don't know about it?

Dr. EGAN. No. I know there had been some discussions with some of the manufacturers as they were developing vaccines to caution them not to add additional thimerosal.

Mr. BURTON. Why wouldn't you want to add additional thimerosal?

Dr. EGAN. Not to add additional thimerosal or to add thimerosal as a preservative if it could be avoided.

Mr. BURTON. I think anyone paying attention to this discussion probably gets the strong impression that the scientific community and our health agencies knew that the mercury was a dangerous thing to have in those vaccines and yet for some reason, even though it had been discussed time and again to remove it from these vaccines, they kept putting it in there. The only conclusion that I can come to is it was money, there was some kind of money involved. This a product produced by big pharmaceutical companies and used by pharmaceutical companies and to expeditiously take it off the market was going to cost them a lot of money and that brings us to the possible conclusion that there is undue influence being exerted on our health agencies by the pharmaceutical industry. What do you think about that?

Dr. EGAN. From my own experience, I would say no, that wasn't the case.

Mr. BURTON. Then why is thimerosal still in there? If this was an interim plan that had been discussed years before, why wasn't it taken out?

Dr. EGAN. As I said, I am not aware of this interim plan that was existing that Dr. Patriarca is referring to. I can only speak to my own personal involvement in this. In the late 1990's, I guess in 1999 around the summer when the issue arose, and did work with the vaccine manufacturers to remove and reduce thimerosal from their products.

Mr. BURTON. I know, because we have been raising so much cane about it and there is a lot of heat being generated. This email was to you, Dr. Bernier, wasn't it?

Dr. BERNIER. I don't specifically recall the email but if I can look at the exhibit?

Mr. BURTON. Sure, go ahead.

It is to RHB2. Is that your email address?

Dr. BERNIER. Yes, Mr. Chairman.

Mr. BURTON. You don't recall getting that?

Dr. BERNIER. I think looking at the date, this is late June 1999, in the early days when we were pulling together the first joint

statement on thimerosal. It looks like we were exchanging views about the pros and cons of moving forward with that joint policy statement. It looks like Dr. Patriarca was commenting on some of the pros and cons of moving forward in the direction we were moving. So, yes, I did get this email.

Mr. BURTON. On July 2, 1999, Dr. Robert Plesse sent Dr. Ben Schwartz, then of the NIP Office, an email regarding thimerosal and the drafting of answers to possible questions that would arise from the release of a statement. In this message it states, "You mean the FDA does not already know? How could they approve a product without knowing how much mercury it contains? What else is lurking that nobody knows about? That is exhibit No. 13. Are you familiar with that email? This is from Dr. Plesse of the FDA and it is to Ben Schwartz, the Acting Commissioner. Are you familiar with that?

[Exhibit 13 follows:]

Rob.

-----Original Message-----
From: Pless, Robert
Sent: Friday, July 02, 1999 9:33 AM
To: Schwartz, Ben (NIP); Allen, Curtis; Nowak, Glen; Broom, William L.
Cc: 'chenr@who.int'
Subject: RE: thimerosal Q&A's

Ben,

Beyond the basic questions, there will be others we can think of in response to the wording of any statement that comes out, unless they can be anticipated and written into the statement.
For example, the current draft Talking Points mentions the Dec 98 request by FDA for manufacturers to provide info on the thimerosal (ethylmercury) content of vaccines... YOU MEAN FDA DOES NOT ALREADY KNOW! HOW COULD THEY APPROVE A PRODUCT WITHOUT KNOWING HOW MUCH MERCURY IT CONTAINS? WHAT ELSE IS LURKING THAT NOBODY KNOWS ABOUT?

I think history leads us well here: there has been no vaccine safety issue to date that I can recall that was "well received" and generated a rational public response. There is also a recent history of rebuttals to every statement made by the authorities. When Bob and Frank wrote their editorial criticizing Wakefield's paper, CDC was attacked for trying to discredit independent research. When the epi study of SV40 was released suggesting no increase in cancer incidence, the same people felt free to attack it as biased since it was written by "government scientists". Can't win!

If we think along those lines, is it wise to even try to maintain the status quo with the vaccine schedule? I don't think we can say on the one hand, we are moving towards mercury free products, while on the other hand suggesting that any mercury is at safe levels so don't worry about your child. It is also no longer going to wash that "there is no data to suggest a risk". Opponents of vaccination don't need data to support allegations of a risk, and this frustrates us. Continuing to vaccinate until the new products arrive may be difficult...

If we consider that vaccination programs around the world may take a hit, perhaps we need to rethink the communications strategy. I cannot think beyond a "lose lose" situation. Is there a role to get some expert risk communicators together to problem-solve through the various scenarios - and come up with strategies without starting out with the premise that we must maintain the current immunization schedule and mandatory immunization laws. Even going so far as to "allow" for differals? In situations where it is not viable to defer or use single doses, such as WHO's concerns, we have to point out the risk of contamination (with specific examples?) that thimerosal is meant to mitigate, and for which there is no replacement at the moment.

As I figure, and have mumbled earlier, this is similar to BSE/CJD/nvCJD and blood and beef. It's "easy" to ban beef from the UK on theoretical grounds, and ignore the plight of the beef industry. Easy to recall blood products - and ignore the next trauma victim who arrives just as the last batches of blood or plasma are being wheeled out by regulators... At the level of the individual, theoretical population outbreaks of disease if coverage drops may not generate any concerns, but an outbreak in progress might lead to acceptance of

vaccination with a thimerosal-containing product. Just like if there was nothing else to eat but beef, and you are starving.

The public even then is not totally rational: David Salisbury once pointed out that at the height of the beef scare, nobody was buying British beef - until it went on sale!

Just some musings.

Rob

-----Original Message-----
From: Schwartz, Ben (NIP)
Sent: Thursday, July 01, 1999 6:37 PM
To: Pless, Robert
Subject: FW: thimerosal Q&A's

Ben Schwartz
404-639-8953 (tel)
404-639-8616 (fax)
bxs1@cdc.gov

-----Original Message-----
From: Nowak, Glen
Sent: Thursday, July 01, 1999 6:31 PM
To: Reynolds, Barbara S.
Cc: Thompson, Charlis J.; Allen, Curtis; Schwartz, Ben (NIP)
Subject: RE: thimerosal Q&A's

Thanks for the update. Could you forward the draft Q and A's for thimerosal? We're also developing additional Q and A's. In addition, here's the Q and A's developed by AAP's media office:

1. When was it determined that high levels of thimerosal content in vaccines is a potential problem? Why wasn't it detected earlier? Who's at fault? What made FDA begin to study the issue?

2. How do physicians review the contents of vaccines?

3. What should parents do (vaccinate or not vaccinate with thimerosal-containing vaccines)?

4. What proof do parents have that vaccinating their children is safe? What scientific information do you have to backup your recommendation to vaccinate?

5. What should pediatricians tell worried parents?

6. Can all vaccines be made thimerosal-free, or within accepted guidelines? If so, how quickly?

7. Are children who've been given vaccines with thimerosal at risk for adverse side effects? How can we know for sure? What are the possible side effects? What kind of treatment can a child receive?

8. How many children in the U.S. have been given more than the recommended amount of thimerosal through vaccines?

9. In light of this information, would you vaccinate your own children right now with thimerosal-containing vaccines?

From: Pless, Robert
Sent: Friday, July 02, 1999 9:33 AM
To: Schwartz, Ben (NIP); Allen, Curtis; Nowak, Glen; Broom, William L.
Cc: 'chenr@who.int'
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If we consider that vaccination programs around the world may take a hit, perhaps we need to rethink the communications strategy. I cannot think beyond a "lose lose" situation. Is there a role to get some expert risk communicators together to problem-solve through the various scenarios - and come up with strategies without starting out with the premise that we must maintain the current immunization schedule and mandatory immunization laws. Even going so far as to "allow" for differals? In situations where it is not viable to defer or use single doses, such as WHO's concerns, we have to point out the risk of contamination (with specific examples?) that thimerosal is meant to mitigate, and for which there is no replacement at the moment.

As I figure, and have mumbled earlier, this is similar to BSE/CJD/nvCJD and blood and beef. It's "easy" to ban beef from the UK on theoretical grounds, and ignore the plight of the beef industry. Easy to recall blood products - and ignore the next trauma victim who arrives just as the last batches of blood or plasma are being wheeled out by regulators... At the level of the individual,

Dr. EGAN. I haven't seen this but we certainly did know the amount of thimerosal that was in each vaccine, so I don't know what this means. FDA did already know and the amount of mercury that is in every product is published in the package insert.

Mr. BURTON. Who is Dr. Plesse? Do you know who Dr. Plesse is?

Dr. EGAN. He worked for the Bureau of Biologics in Canada and he currently works for the Centers for Disease Control.

Mr. BURTON. And he is the one that sent this. "You mean the FDA does not already know" and you say they did know?

Dr. EGAN. But we do know.

Mr. BURTON. Did you know then?

Dr. EGAN. Yes. The amount of mercury that is in each product is in the accompanying package insert. So we know it, and it is publicly available.

Mr. BURTON. Dr. Plesse also made the statement, "It is also no longer going to wash that there is no data to suggest a risk." Did anybody see that memo? Any of you? This was in 1999 and it says, this is also no longer going to wash that "there is no data to suggest a risk." That is 3 years ago. Three years ago a memo was sent saying it is not going to wash. It ain't going to wash that you don't know that there is a risk there and you continue to have thimerosal in the vaccines. When I asked at previous hearing like this one, I said why don't you just recall everything with thimerosal in it right now and put out there single doses of measles vaccine or whatever which doesn't contain this possible toxic substance and get it over with. Nobody had an answer.

The only answer I could figure out was that there was money involved. The pharmaceutical companies were going to lose some money if you pulled this stuff off the market. Is that assumption incorrect?

Dr. EGAN. I would disagree with it.

Mr. BURTON. What do you think about what this doctor said?

Dr. EGAN. I am not sure exactly what he is referring to. This was around the time that people were saying, yes, there is no data that suggests there is a risk. In other words, there is no positive data showing any risk, whether or not it is sufficient to just say that or whether one has to go out and generate data to show there is no risk or one is going to have to do something else.

Mr. BURTON. Here is the crux of the problem. If there is a risk when you are injecting something into a child, shouldn't we err on the side of caution and if you get a memo, an email that says, it is not going to wash, that there is no risk. If I were in an agency and I knew there was going to be a risk to human beings, I would say, we have to get on with this right away. We have to get this stuff taken care of.

Dr. EGAN. Again, I am not sure what he meant by that statement. I haven't had a chance to discuss it with him. This wasn't sent to me.

Mr. BURTON. Let us read it again. "It is also no longer going to wash that there is no data to suggest a risk." It doesn't take a rocket scientist to understand that.

Dr. EGAN. I don't know whether he meant that what we have to do is go out and do studies to positively demonstrate that there is no risk or that there is a risk rather than just simply say that

there is no evidence saying there is no risk. That may not be good enough.

Mr. BURTON. Do you think injecting mercury into a human being poses any kind of risk whatsoever?

Dr. EGAN. At the doses that were used, that have been used in the vaccines, no, there was no evidence that was posing a risk.

Mr. BURTON. Does mercury being injected into a human being have a cumulative effective? In other words, if you get eight or nine shots of mercury, would it have a cumulative effect in your brain?

Dr. EGAN. There may be some effect. That has to be looked at, finding out the rates of excretion versus the rates of deposition into various tissues and what those rates of clearance are. One thing I would like to stress is that as this issue came to the fore, the Public Health Service and the FDA did state that they wanted to reduce levels of mercury from all sources whenever possible and we did very, very actively work with manufacturers to eliminate and reduce mercury from all the routinely recommended pediatric vaccines. It was not a very simple and straightforward process doing that.

Mr. BURTON. Let me just say that according to "experts" my grandson got nine shots in 1 day that contained about 40 or 45 times the amount of mercury tolerable in an adult in 1 day and within just a few days, he became autistic. I imagine a lot of people in the audience and people around the country dealing with this sort of problem right now feel the same way. To have our health agencies continue with this on what appears to be the back burner really bothers me.

Let me ask a couple more questions of Dr. Chen. Have you received any requests to date for the data?

Dr. CHEN. On Monday, when I came back from some travel, there was a voice mail from one of the consumer groups on autism who asked us to work with them to make the data available.

Mr. BURTON. So you have only had one so far. Do you recall the name of the organization?

Dr. CHEN. I think it was Elizabeth Birt but I don't remember the agency she represents.

Mr. BURTON. At this time, no one outside the CDC or HMOs has had access to the VSD data so far, right?

Dr. CHEN. In terms of this new research data center, that is correct.

Mr. BURTON. You attended a staff briefing in late February with the committee which we have established. At the end of the meeting, the Secretary's representative informed the committee staff that prior to the committee request, about 18 months ago, no one had ever suggested to the CDC that the VSD data should be made available. Is that true?

Dr. CHEN. I don't know if that is true or not. Obviously people out there can say things without me being knowledgeable.

Mr. BURTON. You don't know of any at all?

Dr. CHEN. I don't know at this point, no. I don't recall, at least.

Mr. BURTON. The Office of the Secretary not having been a part of this program since its inception had to rely on you and your staff for their briefing, didn't they?

Dr. CHEN. I presume so.

Mr. BURTON. Do you agree with the statement that prior to our committee's request to make the VSD data available, that no one had made such a suggestion?

Dr. CHEN. Being a human being, to my best recall, that is the case.

Mr. BURTON. Can you give me a yes or no answer? Did anybody or any organization or scientist request this data from you prior to that?

Dr. CHEN. To the best of recall, I don't remember anyone making that request.

Mr. BURTON. When I was having my investigation in the previous administration, we had what we called an epidemic of memory loss and the reason that epidemic of memory loss occurred was because people were afraid they would be nailed for perjury. That is not the case with you, I hope.

Dr. CHEN. I hope not.

Mr. BURTON. Isn't it true that as early as 1993, the CDC was getting requests to make the VSD available to other researchers? Take a look at exhibit No. 3, the bottom of page 6, top of page 7. You are the guy in charge of this and this is 1993. You just said you didn't recall whether there had been any request. Here we are going back to 1993. Would you take a look at that, at the bottom of page 6, top of page 7. I will read the quote to you. In the meeting minutes from a CDC-sponsored meeting that took place on January 12, 1993, the large linked data managers meeting, a part of the VSD annual meetings, here is the reference, "Guidelines to using the LLDB files, data managers indicated that a growing number of people are expressing interest in using LLDB files for specific vaccine safety and other types of studies. Because the files are so complex, it is important to develop written guidelines, write model programs and provide SAS and/or consultation for other uses in order to insure the files are used correctly. This may become very resource intensive, especially as the datasets grow and LLDB results are presented."

Doesn't this mean then that almost from the beginning, the CDC was being prompted to allow access to the data base?

[Exhibit 3 follows:]

LLDB Study of Vaccine Safety
Data Managers' Meeting
January 12, 1993
UCLA Center for Vaccine Research

Present: Emmett Swint, Centers for Disease Control/National Immunization Program (NIP); Virginia Immanuel, Group Health Cooperative (GHC), Seattle; Loie Drew, Northwest Kaiser-Permanente (NWK), Portland; Ned Lewis, Northern California Kaiser-Permanente (NCK), Oakland; Pat Osbourne, Southern California Kaiser-Permantente (SCK), Pasadena; Connie Vadheim, Ph.D., UCLA Center for Vaccine Research (SCK), Los Angeles; Eilleen ;

Review of 1993 LLDB data management activities
Emmett distributed the agenda materials. The group reviewed the major data management components that were addressed during the year, including tape 1 edits, creation of an analysis file, adjustments for child-days, definition of acute events, and creation of a file to calculate acute outcome rates and vaccine rates. Preliminary work has been done for conducting geocoding and birth certificate matches when tape 2 files are submitted and local data management has been involved in quality control study activities. A major goal in the tape 1 edits and analysis was to become more familiar with the similarities and differences among HMOs for each of the files.

Status of tape 2
Tape 2 files were initially targeted for December, 1993 submission. The status among sites is as follows:

- GHC All files have been submitted.
- NWK All files but the PHARMACY and ADDRESS files have been submitted.
- NCK The target date for submission is April, 1994 due to the difficulties in identifying the study population.
- SCK The target date for submission is April, 1994.

Both NCK and SCK indicated they may be able to submit some files earlier. The following priorities was established:

(1) CONSTANT, ENROLL, OUTCOME, and VACCINE files -- these files would provide information for identifying the study population and calculating enrollment days, vaccine and outcome rates, and performing the cohort analyses relating vaccine exposures to adverse outcome events.

(2) GEOCODING and ADDRESS file -- The GEOCODING file contains the specific street addresses and zip codes that are used for a contracted geocoding facility to add census tape identifiers. These identifiers are used to merge with census tapes for abstraction of socio-economic status (SES) variables. The ADDRESS file contains other child demographic data.

(3) BIRTHMAT file and state birth certificate files -- These files enable NIP to perform birth certificate

matching for the abstraction of additional demographic data and for identifying antecedent conditions.

(4) Ancillary files (LAB, PHARMACY, PROCED as available) -- These files allow for verification of outcome events and new case findings. Until these files arrive, NIP will use the GHC outcome and ancillary files to explore how these files can best be utilized.

LLDB data management goals and activities for 1994

The group discussed the major activities that will be addressed at NIP and/or local HMOs in the following year:

(1) Edit tape 2 files;
(2) Compare tape 1 and tape 2 contents, including additional descriptions of local HMO methods in collecting data;
(3) Assess the need to adjust enrollment intervals;
(4) Update files used to calculate new vaccine and outcome rates;
(5) Create file for updated power calculations;
(6) Assess the method for computing acute outcome events;
(7) Create new analysis files for updating the cohort analysis;
(8) Work with the quality review committee to:
    (a) Finalize the SAMPLE file and submit files to NIP;
    (b) Standardize data collection procedures and automated quality review files that are used in any future quality review studies;
    (c) Determine how SAMPLE data can be integrated with existing automated data.
(9) Define, create and submit DEATH files resulting from linking study participants with state death files or other sources of deaths not occurring within the HMO.
(10) Work with the neurologists and statisticians to:
    (a) Review the methods proposed to verify neurology outcomes and insure they are consistent with current data flow at the HMO;
    (b) Define the data structure for the REVIEW file;
    (c) Determine how REVIEW data can be integrated with existing automated data.
(11) Incorporate ancillary data into analysis files:
    (a) Review the relationships of ancillary data with outcomes identified in various settings using GHC data;
    (b) Define the data structure for reporting new cases identified in ancillary data files;
    (c) Determine how new case data can be integrated with existing automated data.
(12) Identify SES identifiers from the geocoding process
    (a) Obtain census file indicators from geocoder.
    (b) Identify variables from census files that are to be used in the LLDB study for SES indicators;
    (c) Define the data structure for the SES file;
    (d) Incorporate SES variables into the cohort analysis files.

(13) Perform birth matching activities;
  (a) Match child identifiers with state birth files;
  (b) Refine the demographic, antecedent and underlying condition variables and data structure of items that are to be obtained from the birth certificates;
  (c) Incorporate birth certificate variables into the cohort analysis files.

(14) Expand and/or improve local collection procedures:
  (a) Enhance the software that defines of ICD-9 codes in the emergency room and urgent care and make available to all HMOs (NCK);
  (b) Implement outpatient outcome system in all clinics that reports ICD-9 codes for all visits (NCK);
  (c) Implement optical scanning outpatient coding sheet in clinics to identify reasons for visits (SCK);
  (d) Develop new automated files from local automated data systems:
    NWK -- LAB, PHARMACY (inpatient)
    NCK -- LAB, PHARMACY (inpatient and outpatient)
    SCK -- LAB, PHARMACY (inpatient and outpatient)

(15) Improve documentation of LLDB data management activities
  (a) Document data collection differences at different HMOs (supplemental to quality control booklets);
  (b) Document structure and characteristics of original automated files for NIP and HMO staff who wish to utilize LLDB data;
  (c) Document any adjustments made to the original automated files and the data structure of new analysis, rate and special study files;
  (d) Document and standardize naming of LLDB files on the mainframe and LAN;

(16) Provide technical support to NIP and HMO users who wish to use LLDB data for special vaccine safety studies:
  (a) Develop generic programs that can be used for study of specific vaccine-adverse event relationships;
  (b) Develop documentation for users not familiar with LLDB activities;
  (c) Provide consultation on LLDB file data structures and methods for SAS programming;

(17) Identify and implement hardware personnel and equipment resources to perform LLDB activities in a more efficient manner:
  (a) Acquire equipment to transfer from mainframe to local data processing;
  (b) Explore the ability to transfer large files between HMO sites and NIP via Internet NTP;
  (c) Hire contract personnel to help perform geocoding, birth certificate matching and other LLDB functions.

Issues surfacing during the past year
Emmett presented several data management issues that resulted in adjustments or special explanations. Data managers shared similar experiences at their HMO.

(1) Adjustment of enrollment dates
Three adjustments were used: (a) first start date was extended to the date of birth at NCK if the child was born in the HMO and had continuous HMO coverage; (b) enrollment dates were extended to a vaccine date that occurred outside the start and stop dates; and (c) enrollment dates were extended to an outcome date that occurred outside the start and stop dates;

Ned indicated that children within NCK are free to go to any outpatient clinic they choose and the first adjustment is no guarantee that the child received care at a LLDB study clinic. He hoped that tape 2 would be improved because children will be receiving HEP-B vaccine at a very early age. Eventually, as all clinic facilities implement the immunization and outpatient clinic outcome modules, defining the study population will be similar to other HMOs.

There was a caution about extending enrollment dates because of vaccine and outcome dates that are out-of-range. There was one suggestion that the amount of adjustment should be limited to a relatively small value (e.g., 30 days) equivalent to the number of days of error that might be introduced by the membership and other administrative files used to define the start and stop dates.

The problem of creating a zero-day target window in the cohort analysis file when a stop date to an out-of-range vaccine date was discussed. This adjustment probably should not be done unless there are also outcomes that fall after the stop date.

(2) Methods of combining vaccines into vaccine groups
Emmett explained that vaccines may be grouped differently in several types of LLDB analyses that were conducted. For example, vaccine rates for DTP components would combine all vaccines that have a vaccine component offering protection against diptheria, pertussis and tetanus while the cohort analysis would limited the DTP group to vaccines that only contained the same type of vaccine (i.e, DTP and DTPHIB but not DT(a)P or DT(a)PH). Documentation should identify how vaccine groups are formed.

(3) Impact of missing outpatient clinic outcomes
The group reviewed a table showing health care setting characteristics of the 34 outcomes of interest. Caution was made about using HMOs that do not report outpatient clinic visits to study outcomes of interest whose predominant setting is "CLINIC". Ancillary files would be used to help identify some of the children who have outcome events that could be not identified in the OUTCOME files.

(4) Overlap of ICD-9 code in outcomes of interest table

ICD-9 codes that appear in more that outcome of interest category, subcategory and item were reviewed and data managers indicated that there is probably not a way to define the categories so no overlap occurs. The overlap occurred in part because PIs are interested in viewing a specific subsets of a particular outcome (e.g., allergic purpura <287.0>, primary thrombocytopenia (287.3) and secondary thrombocytopenia <287.4> and unspecified thrombocytopenia <287.5> as subsets of purpura and other hemorrhagic conditions <287.*>) and partly because PIs were interested in viewing data from different classifications (e.g., mumps meningitis <072.1> as an Aseptic Meningitis outcome and mumps <072.*> as an Other Vaccine-Preventable outcome and epidemic or infectious parotitis <072.*> as an Parotitis outcome). Data managers felt the classification scheme was useful because it helps capture general as well as specific outcomes of interest, but one has to be aware where duplications occur when analyses are conducted and results are presented. A table was distributed identifying one method of removing duplicated ICD-9 codes at different classification levels.

(5) Definition of acute episodes.

Problems encountered with defining acute episodes were discussed. In general, data managers felt that any definition used should minimize separation of follow-up visits associated with an acute event. This could probably be accomplished more by adding the acute interval (or some number of days smaller than the acute interval) to the most recent event when defining the end of the episode rather than just the first one. Specific interval distribution analysis would be needed to refine acute interval values since many of those were best estimates based on clinical experience of the PIs.

(6) Same-day outcome and exposure records.

Data managers were to check the time stamp of records having ICD-9 codes occurring on the same day in the same setting to be sure they were from separate health care encounters. It was more difficult to determine the order of events when a child has a vaccine and outcome on the same day unless they occur in different settings. In some cases the time-stamp in the immunization module is the time of data entry, not time of shot.

(7) Clinic facilities are not known for vaccines and outcomes.

In tapes 1 and 2, NCK has only three clinics reporting outpatient visits and new clinics were added to the study once immunization modules were implemented at the clinic. About ten percent of the children with outpatient visits in the OUTCOME file were not from the clinics with automated outpatient records. This occurred because children are able to attend multiple clinics. Ned said facility codes were available for both vaccine and outcomes and will be added to the VACCINE and OUTCOME file to help determine give a better account of child-days for children with outpatient records in the OUTCOME file and help identify the amount of inter-clinic usage within the HMO.

Clarification of tape 2 data structure

(1) Enrollment of children who die near birth.

Connie (SCK) inquired whether other data managers enroll children in the LLDB study if they die at or near birth prior to any vaccine being given. NWK considers the child as being covered under the parent's membership for the first month of life and they would be excluded from the study because they would never appear in the membership file. GHC has an inactive membership file that would pick up new births who die or are terminated. NCK would include anyone receiving a vaccine on that date and probably would include others. This problem should be minimized in the future because children are being HEP-B vaccine within hours of birth and there is an interest in capturing all deaths, even if a vaccine is not given.

(2) New medications for the PHARMACY file.

Loie (NWK), Virginia (GHC) and Emmett (NIP) met after the meeting to discuss how to categorize medications that were not on the medication list.

New developments at local HMOs and CDC

Hardware (NCK). Ned reported that NCK purchased a new SUN-SPARK computer that allows up eight users, connects directly into the LAN, has 6.5 gigobytes of hard disk storage, 64 MB of memory, and a tape drive to read 1/2 inch cartridge tapes; has SAS BASIC and STAT programs running in the UNIX environment; and has an Internet connection to transfer large files rapidly. The processing time benchmarks are impressive when compared to mainframe, PC SAS and SAS for WINDOWS. Ned indicated that its main strength is analysis of large files very quickly while its drawbacks are printing to LAN printers, which requires special set-ups or copying the output back to the LAN system. An outside service contracts is essential. Ned will share specs to those that are interested.

Linking death and birth files (NCK). Ned indicated that NCK has purchased FORTRAN software to link death and birth files. The State of Washington performs this linkage on request at a small amount. NWK has several references and algorithms for matching birth certificate records.

Software for assigning ICD-9 codes to ER visits. Ned is developing a software package at NCK that assigns ICD-9 codes from text-strings and is supplemental to the existing autocoder. Other HMOs with Internet FTP capability will be able to transfer their text files and have ICD-9 codes assigned on a short time-frame.

Automated outpatient system (NCK). NCK is planning to implement an automated outpatient records system that will capture and assign ICD-9 outcomes to outpatient visits at all HMO clinics.

Guidelines to using LLDB files. Data managers indicated

that a growing number of people are expressing interest in using LLDB files for specific vaccine safety and other types of studies. Because the files are so complex, it is important to develop written guidelines, write model programs, and provide SAS and/or consultation for other users in order to insure the files are being used correctly. This may become very resource intensive, especially as the datasets grow and LLDB results are presented.

Identifying deaths outside of the HMO

(1) Methods of timely capture of non-hospital deaths.
Non-hospital deaths are missing from the OUTCOME files and often unknown at the HMO. The State Death Certificate can have a lag time of up to 18 months in some states. HMOs have explored ways to capture these deaths in a timely fashion from non-HMO data systems, such as the state death registry and SIDS databases.

GHC Monthly provisional tapes from State death certificate, SIDs database
NWK Monthly provisional tapes from State death certificate SIDS database
NCK Monthly provisional tapes from counties within HMO catchment area
Maternal and Health Care record file
SCK Monthly provisional tapes from seven counties within HMO catchment area
Maternal and Health Care record file

These sources identify children but may not contain all the underlying causes of death that is on the finalized Death Certificate. The SIDS registry or Maternal and Health Care record files are probably not good sources for identifying additional names since its source is the same as that used for death certificates but it may have some provisional causes of death that are not known until the death certificate is finalized.

Ned indicated that NCK has other automated data sources that he uses to identify some deaths. The date of death is not available and often these names do not appear in the State death files. These children are kept in the study until some more official record of the death becomes available.

(2) State Death Certificate Data Structures.
Data managers provided copies of the California, Oregon and Washington death certificates and data dictionaries. NIP will compare them to determine what information is common and the format their format. This will enable interested LLDB personnel to know data available for special studies.

(3) LLDB Death file.
Deaths will be reported in the OUTCOME file and not as a

separate file. There will be a different record for each ICD-9 code reported on the death certificate. Preliminary sources of death may have a single record with no DXCODE that is later replaced when ICD-9 codes become available.

Deaths occurring in other outcome settings (hospital, ER, clinic) should be completed as normal with the value of DEATH set to "Y". Additional ICD-9 codes from the death certificate are added, even if they duplicate the records of the other settings.

The variables and the values for death records are as follows:

CDCSITE	HMO code (C, O, S, or W)
STUDYID	Child's assigned study ID
CAREDATE	Date of death.
DURATION	0 (zero)
DXCODE	ICD-9 reported on death certificate. Provisional death records may not have any ICD-9 codes.
RULEOUT	" " (blank) unless an autocoder is used to interpret text strings.
FLAGOCOI	" " (blank) -- code is assigned at CDC.
FLAGACUT	" " (blank) -- code is assigned at CDC.
DXTYPE	Type of ICD-9 code on death certificate: "MC" = Cause of Death "MU" = Underlying cause of death "MO" = Other cause of death
LOCATION	Source of the death record "P" = Preliminary record from State or County death certicate files "F" = Final record from State death certificate "S" = SIDS registry (if used) "M" = Maternal and Health Care records "X" = Other local sources
DEATH	"Y" if death occurred

If the child died during a hospitalization, ER and clinic visit, the child may have two set of records: the first set is coded like all other outcomes in those settings (DXTYPE="BP", "BS", "HP", "HS", "EP", "ES", "CP", "CS" and LOCATION="I" or "O", DURATION=0 or hospital LOS, etc.) with DEATH set to "Y". The second set will be generated, using the variables codes above, when the death record is found in either the preliminary or final death certificate files.

All deaths are identified by subsetting on DEATH="Y". A given STUDYID may have more than one record with the same DXCODE (e.g., one from hospitalization and one from death certificate). All unique DXCODES associated with the death are found by sorting on STUDYID then DXCODE and selecting the first unique DXCODE. Unique children are found by sorting on STUDYID and selecting the first unique STUDYID record.

Automated versus non-automated data

Emmett provided an overview of how several LLDB components interact with each other. Basic to this model is the concept of automated data versus non-automated data. The LLDB files (CONSTANT, ENROLL, VACCINE, OUTCOME, etc.) represent data from automated sources. They are used initially for the cohort analyses, vaccine and outcome rates, etc. Information abstracted from birth certificates and from census tapes during the geocoding process are also part of the automated data.

The quality review process is the examination of 1%-2% of the records to estimate the accuracy of the automated data. It identifies the quality of specific automated systems at each of the HMOs and gives an indication whether the automated data can be used alone or whether case-cohort or case-control studies are needed. Associated with the quality review process is the SAMPLE file. It contains variables in the same format as the automated data but the values are those from the medical record or other document to which the automated data is compared. This file is submitted to CDC and may be used to replace the automated data in special analyses involving the 1%-2% sample. In addition other data not in the automated data, but collected during the quality control review audits, may be submitted and used to supplement the automated data in special studies.

The neurology review process is for verification of ICD-9 codes in the automated OUTCOME file. The results of the medical chart review are entered into the REVIEW file (e.g., reviewed/not reviewed, verified/not verified, period of review, new ICD-9 codes, etc.). This information is compared to the OUTCOME record to determine if the outcome is kept, deleted or modified. At that point the neurology outcome is considered verified automated data. Any additional information not in the automated files but collected during the neurology review process can be submitted to CDC to supplement the automated files when special studies are performed. This information may be general information applicable to all neurology outcomes, or specific information applicable to the ICD-9 code(s) being reviewed. At the same time, if the child were not already in the 1-2% sample, the quality control review could be done to provide additional verified automated data. NOTE: Collection of additional data and quality control reviews would depend on recommendations by the neurologist and statisticians group.

The automated ancillary files contain information that either

helps verify outcomes already in the automated OUTCOME file or indicate that a child has had an outcome of interest that was not reported in the OUTCOME file. These ancillary indicators may identify specific outcomes (e.g., insulin med and diabetes outcome) or general outcomes that would need medical chart review (e.g., EEGs, MRI, neurology referrals without any ICD-9 code in the OUTCOME file). These reviews would generate an outcome record that is in the same format as the OUTCOME file. When added to the OUTCOME file, they become outcome events that may be associated with vaccine exposures in cohort analyses. During the chart reviews, additional information and quality control review data may be collected and submitted in the same manner as in the REVIEW process.

Quality review process and the SAMPLE file
Data managers reviewed the status of the different components of the quality review process.

(1) Quality review analysis. Ned indicated he had tables for John Mullooly to help complete the analysis.

(2) SAMPLE file. Emmett requested data dictionaries from all HMOs describing the automated files they have developed during the first quality control review. The data should fall into several categories: (a) data that is equivalent to the automated files (e.g., vaccine and outcome codes and dates); (b) data that describes the confidence, source and review ranges of the data; (c) data that does not correspond to our current automated data but useful to have available for special studies with the 1%-2% sample; and (d) data that has local use but not submitted to CDC. Emmett will refine the spreadsheets begun in November of 1993 and develop the first format for the SAMPLE process.

(3) Future quality review studies. Data managers will assist the Quality Review committee in developing the procedures for conducting any future quality review studies. This includes (a) standardizing the procedure across sites; (b) identifying variables about the process (e.g., confidence and source of data) that need to be collected; and (c) standardizing the databases that are used to store the quality review findings. Some of this work has already been reported in the quality review committee minutes.

Neurology reviews and the REVIEW file.
The general process was discussed but the specifics could not be determined until the recommendations of the neurology meeting are known.

The REVIEW file would use the information from the OUTCOME file to identify the neurology outcome records that need to be verified. Emmett indicated that it is possible to other automated LLDB information could be printed with this if desired (e.g., other outcomes, ancillary information, demographics, etc.).

Variables in the file would fall into several types:
(1) Variables identifying the outcome record being reviewed
e.g., CDCSITE, STUDYID, CAREDATE, DXCODE and DXTYPE.
(2) Variables identifying the review status, e.g.,

NEEDREVW	Record needs review
REVIEWED	Flag indicating review is complete
DATERVWD	Date reviewed decision was made
RESULTS	Code describing if verification is positive or not supported.
DONEBY	Code describing who/how decision was made
TRIGGER	="N" to indicate neurology review

(3) Variables refining the outcome record

NEWICD9	New ICD9 (DXCODE) if RESULTS indicate the ICD9 code was incorrect in the automated data
ONSET	Probable onset date of the case, if different from the CAREDATE.

If other general data not in the automated file is collected during neurology review, it can be included as variables in this file. If data specific to the neurology outcome is collected in can be reported in separate files.

Ancillary reviews and the NEWCASE (?REVIEW) file.

(1) Uses of the ancillary files.
Loie described some of their work done at NWK to identify children with seizures and asthma from medications in the ancillary file. Virginia (GHC) reviewed the process they used to estimate the number of cases that would be identified at each HMO based on the outcome and ancillary sources available at that HMO. Emmett indicated that GHC's tape 2 data contains outcomes from all settings and has all ancillary components. CDC will compare the cases identified as outcomes with those cases in the ancillary file to determine how the ancillary files can best be used.

(2) Process to review cases from the ancillary files.
The general process was discussed but the specifics could not be determined until the recommendations of the neurology meeting are known.
The NEWCASE (?REVIEW) file would use the information from the different ancillary files to identify a specific outcome to be verified or no outcome, in which case, the medical chart would have to be reviewed to specify the ICD-9 code. Emmett indicated that it is possible to other automated LLDB information could be printed with this if desired (e.g., other outcomes, ancillary information, demographics, etc.).

Variables in the file would fall into several types:
(1) Variables identifying the outcome record being reviewed
e.g., CDCSITE, STUDYID, date, ancillary type, ancillary file. The last two variables would depend on the ancillary file used.
(2) Variables identifying the review status, e.g.,

	NEEDREVW	Record needs review
	REVIEWED	Flag indicating review is complete
	DATERVWD	Date reviewed decision was made
	RESULTS	Code describing if ICD-9 outcome was found or not supported.
	DONEBY	Code describing who/how decision was made
	TRIGGER	="A", to indicate Ancillary file
(3)	Variables	corresponding to variables in the outcome record:
	NEWICD9	New ICD9 (DXCODE) if ICD-9 code was found in the medical record.
	ONSET	Probable onset date of the case. It is equivalent to the CAREDATE.
	OSETTING	Setting where ICD9 was found in medical chart.
	OLOCATION	Location where ICD9 was found in medical chart.

If other general data not in the automated file are collected during ancillary review, it can be included as variables in this file. (?) If the child is not already in the 1%-2% sample, the quality review could be done in order to provide verified data of additional data.

Emmett indicated that Jessica Tuttle, M.D., at CDC has cross-referenced the different ancillary files to non-neurological reviews. PIs will need to specify the specific type of records are to have medical record chart reviews.

Dr. CHEN. This is a meeting back from January 12, 1993 among data managers and I was not present at that data managers meeting.

Mr. BURTON. So you weren't aware of any of this?

Dr. CHEN. I was not aware of this discussion, no, because I was not present.

Mr. BURTON. Would you not have received these minutes of this meeting?

Dr. CHEN. I may have received it but as most of us know, we don't always read every single word of the meetings we were not at, so I don't recall reading this.

Mr. BURTON. This is pretty important stuff. We are talking about release of some of this data so that other research scientists can go out and look into this stuff. You got this memo and didn't even read it?

Dr. CHEN. It looks like it is about 10–15 pages of very detailed discussion about different aspects of data management and I don't recall having read this one.

Mr. BURTON. Why do they even have these meetings and give you the minutes if you are in charge of this if nobody is going to do anything with it? Here it says, "Data managers indicated that a growing number of people are expressing interest in using LLDB files for specific vaccine safety and other types of studies." That is pretty important. Outside groups wanted to start doing this 9 years ago and you didn't know about it?

Dr. CHEN. As I mentioned, in all the discussions with the HMOs, their major concern was the protection of the privacy of their patients.

Mr. BURTON. That is not the point. You said you didn't know there was a request. Did you know there was a request for this or not?

Dr. CHEN. Again, I was unaware of this discussion.

Mr. BURTON. How about anytime since then in the last 9 years, were you aware that outside groups wanted this information?

Dr. CHEN. Until the recent discussion from a couple of years ago, no one has really approached us.

Mr. BURTON. In the last 2 years, are you aware of anybody asking for this information?

Dr. CHEN. There has been some Freedom of Information Act requests.

Mr. BURTON. So you did get some requests from outside groups in the last couple of years?

Dr. CHEN. Yes, that is correct.

Mr. BURTON. So you remember that.

Did you have something you wanted to say, Dr. Bernier?

Dr. BERNIER. I just wanted to suggest to Dr. Chen that he might want to talk a little bit about some of the collaborations that have occurred over the years. I don't want to leave the impression that this was a totally closed system. There are others who have made use of the system. Dr. Chen is in a much better position than I am to say that. There may not have been requests coming in under the Freedom of Information Act but again, I think the question was asked earlier this morning, can people collaborate with the HMOs and yes, it is my understanding, and again, let Dr. Chen comment,

but the HMOs are open to collaboration if people want to approach them.

Mr. BURTON. One of the things Dr. Weldon stressed was that credibility is extremely important. People have to trust their government. If they don't, you have a real mess on your hands. We currently have problems with some people who don't trust the FBI, they don't trust the CIA, they don't trust other agencies. One of the agencies they really should have to trust and be able to trust is the people who are prescribing needles being stuck into their kids' arms for vaccinations.

You talk about you having closed study just inside the CDC or HHS and doing a collaborative study with somebody else you might be able to control. What we are talking about is giving the information to scientists on the outside who can verify and make absolutely sure that the information is correct, that the vaccines are safe, that there is no problem with things like thimerosal. That is why these independent studies are important.

It appears as though there has been a circling of the wagons as Dr. Weldon said to keep everybody else out. That has to change if there is going to be a belief that our health agencies are shooting straight with the American people.

Dr. Chen, isn't it true that Dr. Harold Guess, an employee of Merck, who has been invited repeatedly into the VSD planning meetings, also suggested to you in 1995 that CDC needed to make the data available to outside researchers such as industry researchers? Did Guess, an employee of Merck, say that to you in 1995?

Dr. CHEN. He is also a professor at the University of North Carolina in terms of his status. I think in terms of discussion, that is a sensitive issue that the HMOs had. We have worked with them and I think we now have a research data center process to work that out.

Mr. BURTON. That isn't the question. You said, first, you don't remember anybody asking for this data. First you said you didn't remember. Then you said, yeah, there was a couple of years ago some people talked to me, so you got that far. Now we are going back to 1995. Dr. Harold Guess, an employee of Merck who has been invited repeatedly into VSD meetings, also suggested to you in 1995, 7 years ago, that CDC needed to make this data available. Do you recall that?

Dr. CHEN. I must admit I don't recall that.

Mr. BURTON. You don't recall that.

Dr. Chen, please go to exhibit No. 10, January 1995. It is the annual VSD meetings. I would like you to turn to page 4 of the section titled "Priorities." Do you see that?

[Exhibit 10 follows:]

Minutes of the Annual Vaccine Safety Datalink (VSD) Meeting
Oakland, California
January 25-27, 1995

Present: In addition to participants from four research sites and three Federal Agencies were three external advisors and one special guest.

Group Health Cooperative (GHC): William Barlow, Virginia Immanuel, Thomas Knauss, Robert Thompson, Bob Davis

Harbor-UCLA with Southern California Kaiser (SCK): Marlene Lugg, S. Michael Marcy, Constance Vadheim, Patricia Osborne, Joel Ward, Diane Petitti, Mike Wulfsohn

Northern California Kaiser (NCK): Steven Black, Henry Shinefield, Bruce Fireman, Jean Hayward, Ned Lewis, Paula Ray

Northwest Kaiser (NWK): John Mullooly, Lois Drew, John Pearson, William Shields

CDC: Robert Chen, Stephen Hadler, John Glasser, Steve Rosenthal, Janet Hardy, Jessica Tuttle, Emmett Swint, Phil Rhodes

FDA: Suresh Rastogi, Robert Wise, Peter Patriarca, Peter Lachenbruch

HRSA (Vaccine Injury Compensation Program): Vito Caserta

External Advisors: Marie Griffin, Alexander Walker, Harold Guess

Special Guest: Ed Marcuse (National Vaccine Advisory Committee)

PRELIMINARIES, JAN 25, AM:

Steve Black welcomed us to NCK's new research facility and described logistics and social events planned for the evenings.

Bob Chen reviewed portentous events in vaccine safety and development since we last met, among them integration of these issues on reorganization of the NIP. Notable elsewhere were the 10-year follow-up of children with chronic encephalopathy in the UK's NCES. The risk within 7 days of DTP was 5.5 times background (95% CI 1.6-23.7), and such children have poor long-term prognoses. The ACIP's recommendation, Vaccine Injury Table and Package Inserts are being revised to match the conclusion of

the 1991 and 1994 IOM Reports on Vaccine Adverse Events.

Three IOM workshops are planned to follow "Research Strategies for Assessing Vaccine Adverse Events," with topics under current discussion. FDA's VRBPAC, the NVP's NVAC, VICP's ACCV and CDC's ACIP all endorsed the active surveillance of which large-linked databases (LLDB) are now and vaccine registries eventually will be capable. The VAERS contract was renewed for another 5 years with such improvements as better follow-up of deaths and other serious reports, ability to report by telephone and facsimile, and request vaccine safety literature searches.

The government was conspicuous at the 1994 meeting of the ISPE with 10 abstracts and separate oral and poster sessions. Other countries emphasizing vaccine safety include Sweden and the UK, with UNICEF also concerned about ways to ameliorate problems largely caused by inadequate sterilization of needles.

Steve Hadler reviewed considerations that affect priorities and our ability to address them via LLDBs. He reviewed our current procedures. These include routine validation of neurological outcomes via chart review and ad hoc verification of outcomes plausibly associated with vaccination on screening. This permits a second level of screening using only validated cases and actual onset versus visit dates. Vaccine-associated outcomes that withstand such scrutiny may then be scheduled for nested, chart-based studies.

Steve reviewed plans for the remainder of this FY. This includes submission of another tape (including files not yet submitted as well as more enrollments), exposures and outcomes (see data manager's report), digestion of second screening results, completion of the nested seizure study, and chart reviews of other neurological and selected non-neurological outcomes. With regard to the seizure study, he expressed interest in distinguishing febrile and afebrile seizures, if not the finer categories discussed (e.g., simple and complex febrile), and considering new onset seizure disorders as well as exacerbation of chronic conditions. With regard to exposures, he indicated interest in old and new vaccines per se and in the combinations in which they typically are administered.

Power to detect associations with other neurological conditions likely is low, but effort required to review these charts is minimal, provided that protocols have been developed. Similarly for deaths, power likely is low, but once protocols have been developed for linking enrollment files to death certificates, minimal effort is required to identify and review records.

Other possible priorities arising from IOM reviews and recent literature include thrombocytopenia and MMR, GBS and both T-containing vaccines and OPV, seizure disorders and M-containing

vaccines, age-at-vaccination dependent risk of, or protection against, diabetes mellitus, Crohn's disease and M-containing vaccines, neither of which may be testable, and alopecia and hepatitis B vaccine, which may not be captured in automatic codes. Parent consumer groups are concerned about the risk of serious events following simultaneous vaccination, new vaccines and combinations.

Then Steve enquired about means of including our most recent screening results; should we consider any statistical association, only serious outcomes, and if so, how should seriousness be judged (e.g., via absolute or relative numbers hospitalized)? Finally, he proposed a straw man based on outdated power calculations that included studies not related to particular exposure-outcome associations, discussed resource needs and proposed a plan of action for later discussion.

Emmett Swint summarized the contents of files included in each HMO's second tape. He diagrammed general edits that were conducted prior to performing the screening analyses and computing exposure and outcome rates. Tape collection periods at each HMO indicate that between 12 and 31 months were reported. Birth cohort data indicate that GHC and NWK enroll approximately 6,000 children per year; NCK, approximately 33,000 and SCK, 40,000 children.

Emmett enumerated children with vaccination records and vaccination dates, and doses administered overall and within enrollment intervals by vaccine. Availability of manufacturer and lot number were indicated too. He also enumerated children with diagnoses, medical care dates, and diagnoses assigned, outcomes within enrollment intervals and LLDB outcomes of interest by setting. Finally, Emmett illustrated how he had created the exposure and outcome rate files, neurology review samples and screening analysis files via flow diagrams.

RESULTS, JAN 25, AM AND PM

John Glasser described the denominators for Emmett's rate calculations, antigen-specific vaccination rates, average numbers of doses administered and vaccine coverage. Then he illustrated the rates at which children presented with seizures by site and setting and argued that separate models of the age-specific rates within these strata provided most of the information needed about each outcome; conditional likelihood ratios complete the picture. He also tabulated the outcome rates and provided a graph whereby our ability to reject false null hypotheses could be guesstimated given real risks while he completed the exposure and outcome rates, projected the numbers of exposed and unexposed cases and estimated power more precisely.

Phil Rhodes described his second tome, which is similar to the first in containing outcome-specific results, but also includes a summary section. Various permutations of events and visits by site, setting, age, gender, item, exposure status and narrative summaries constitute his descriptions of each outcome. He provided site- and setting-specific analyses of possible associations with common childhood vaccines for common outcomes, three individual vaccine effects on seizures also were estimated by controlling for simultaneous exposure to the others, with rarer outcomes being represented only by site-specific analyses. His summary section enumerates common vaccine combinations by site, as did the first volume, but also compares the numbers of events and visits by site, setting and tape, and the timing of common exposures among children with each outcome by site. This masterful presentation of screening results should once again provide ample grist for review during the coming months.

Steve Black and Steve Rosenthal presented results of several ongoing ad hoc studies. Steve Black described studies of arthropathy among adult females following rubella vaccination, which had been presented at ICAAC, and comparison of events for which children presented at ERs or were hospitalized within 30 days of TD vaccination in two age groups, one corresponding to the currently-recommended age, 14-16 years, and one to the age that the ACIP is considering, 10-12 years. No significant difference was found. Then Steve Rosenthal described studies of seizures following DTP doses during the first and second years of life, which had been presented at an EIS conference, and following receipt of DTP and DTaP, which was being prepared for the next ACIP meeting.

MINUTES FUTURES (OR FUTURE ACTIVITIES), JAN 26, AM

Priorities

Discussions on priorities were held on day 1 (general overview), day 2 (discussion) and day 3 (specific assignments). There was consensus that "nothing focuses the mind like writing a paper" and the highest priority for the project was in publishing the results of the studies - thereby garnering visibility and hopefully continued support and funding. A six month target date was set for several paper topics and the primary sites responsible (see separate attachment).

Written status updates will be requested of each site prior to subsequent conference calls. A similar list of priorities will be developed by the statisticians and the data managers to track their progress.

Role of External Advisory Committees

The three external advisors attending this meeting, Drs. Griffin, Guess (representing PHARMA), and Walker, fortuitously were the same advisors that CDC sought advice from prior to the initiation of the LLDB project in 1990. At that time, they had offered a "yellow light" for this endeavor, i.e. proceed with caution, making sure to harmonize protocols among sites as much as possible. The advisors were intimate participants throughout the meeting, asking many questions and offering much valuable advice. There was consensus that similar advisors will be invaluable in future LLDB meetings. Joel Ward offered a comprehensive overview of the potential roles of such an advisory committee - one of which is to assure "buy-in" by interested parties. Drs. Griffin, Guess, and Marcuse have provided insightful suggestions and recommendations in writing subsequently (see separate attachments).

Vaccine Development and the LLDB (Handout)

Bob Chen outlined the new developments in biotechnology which as revolutionalized the new vaccines potentially available in the future. Due to the additional benefits of reduced number of visits needed to complete immunization, combination vaccines have been the focus of much recent work. For such combination vaccines, questions of safety (?sum>parts) are more difficult to answer than questions of immunogenicity (?sum<parts) as they require larger sample sizes. If vaccine development can be divided into Phases I, II, IIIa (clinical efficacy), IIIb (field effectiveness), IV (immediate post-licensure), and V (general post-licensure), LLDBs due to their large sample size, may potentially have important roles to play in phases III-V. Analogous to the prioritization process worked out for testing of acellular pertussis vaccine in Sweden, a similar process may be useful for the limited resource represented by LLDB's. Discussion focused on multiple topics, including 1) feasibility of LLDB charging "user fees" to vaccine manufacturers to minimize CDC resource needs to sustain the project, 2) feasibility of the HMO's organizing themselves into an independent consortium.

Vaccine Safety Bibliography (Handout)

Bob Chen discussed the need for an easily accessible repository of information on vaccine safety - somewhat analogous to what has been developed for hotlines on toxic substances. He noted that a variety of information are currently available (e.g. adverse event sections for respective vaccines in ACIP/AAP recs and textbooks), but these refs have not collated. The recent Institute of Medicine reviews of VAEs provide the most complete recent compilation of vaccine safety literature. The new VAERS contract calls for the contractor to maintain and update the IOM bibliography in an electronic format. In addition to the MESH

headings, the articles will be coded in both COSTART and ICD-9. Ultimately, electronic imaged articles may also be available. When VAERS shifts to the Windows NT architecture, this bibliography will become accessible to outside researchers on vaccine safety.

DEATH CAPTURE STUDIES UPDATE, JAN 26, AM

Bob Wise led a discussion on the progress made in capturing deaths that do not occur in medical facilities, or occur at facilities whose records are not automated.

The discussions were relatively brief as work is not fully underway on these studies. Status reports were given by each of the sites followed by Dr. Wise's comments and suggested questions the mortality data may help to answer in the future. Please refer to Dr. Wise's handout material for further details.

Status of the sites:

1) Similar to all sites, NCK and SCK are currently working on methodology and feasibility issues for collecting death record information for California. NCK has indicated that only 5 counties will contribute death record data (* NCK - please verify this statement). As noted in a later document, SCK has summarized their preliminary efforts and has provided a short protocol and timeline for completing the study over the next few months.

2) NWK has compared Oregon state information to death rates from their ER and hospital databases. The results of the comparison were somewhat poor and highlighted the need to directly access the death records. NWK also recognized the need to modify the LLDB method for subject capture so that information on infants who died before 1 month of age could be retrieved. They anticipate less than 50 deaths per year in the age range being studied.

3) R. Thompson summarized GHC's current status and discussed some expected difficulties in starting the death capture study. As with NWK, GHC anticipates capturing relatively few deaths per year. Please refer to their handout material for more detail.

Several programming options exist for matching death records to children registered in the study. Options being considered include the algorithm that J. Mullooly and his colleagues have developed at NWK as well M. Griffin's linkage program developed at Vanderbilt University.

IMPLEMENTATION, JAN 26, PM

OUTCOME DEFINITIONS:
In an all-afternoon session with J. Hardy, investigators from each of the sites discussed the outcome definitions in detail. Contributions were also made by Drs. Walker and Guess, consultants on the project. The document relevant to this review was J. Hardy's spreadsheet entitled: "Vaccine Safety Datalink: Automated Outcome Ascertainment" and indirectly to J. Glasser's document entitled "Vaccine Safety Datalink Tape II: Screening & Other Analytical Issues." The key decisions made were:

1) To rename the 3 columns pertaining to the need for chart review:
"Review not required" was changed to "Automated Data Sufficient for Screening Analyses"
"Review" was changed to "Chart Review Required"
"Review not warranted" was changed to "Do not include in Analyses"

2) To subdivide the outcome Encephalitis/opathy was into the following analytic groups:
Idiopathic disease
Disease due to vaccine preventable disease or vaccination
Other

3) To move some of the ICD9 codes in the outcome Ataxia to the "do not include in analyses" category. One of the codes in particular, ICD9 781.3 (lack of coordination), accounts for 80% of the cases of ataxia as presented in the tape 2 screening analyses.

4) The outcome Guillain-Barre Syndrome should now routinely contain all of the codes from the outcome Transverse Myelitis.

5) The outcome Polio and Acute Paralytic Syndromes should now routinely contain all of the codes from the outcomes GBS and Transverse Myelitis.

6) The outcome Allergic Reactions was subdivided into the following analytic groups:
Systemic Allergic Reactions, including anaphylaxis
Dermatologic Reactions, including all else but ICD9 code 999.5 (Other serum reaction)

7) Create a new subcategory entitled "Unspec. Adverse Events" which will contain all cases encoded 999.5 (other serum reaction). This code was previously analyzed under the outcome subcategory Allergic Reactions.

8) The outcome Thrombocytopenia was subdivided into the following analytic groups:
Thrombocytopenia
Purpura condition
Transient neonatal thrombocytopenia (* need to view counts of children sorted according to < or = 1 mth of age, versus > 1 mth of age prior to further decisions)

9) With the exception of a few ICD9 codes from each outcome, all of the codes in the outcome Arthropathy/Arthritis will be included in the outcome Autoimmune/Immune Complex Diseases and vice versa.

10) The outcome Non-bacterial Pneumonia has been renamed"Bacterial and Non-bacterial Pneumonia"

11) ICD9 code 775.6 (neonatal hypoglycemia) should be analyzed apart from the rest of the codes in the Hypoglycemia outcome.

12) The counts of children for the outcomes Breath Holding and Apnea need to be sorted according to < or = 1 mth of age, versus > 1 mth of age prior to further decisions.

13) The outcome SIDS should be restricted to children < or = to 1 year of age.

Other changes were made to each outcome at the item level & are documented in the enclosed updated spreadsheet.

NEUROLOGISTS SESSION - PROTOCOL UPDATE, JAN 26, PM

Participants: John Pearson, Tom Knauss, Jean Hayward, Paula Ray, Bob Davis, Vito Caserta, Connie Vadheim, Steve Rosenthal

There was general agreement among the group that good progress has been made in the development of the neurological outcome forms. The neurologists felt that the forms were developing nicely. A few of the lessons learned from the seizure abstraction experience were discussed. Much of the clinical and laboratory data questions presently on the forms was not particularly useful; it was decided that the other outcome forms could omit these questions. The case definition of encephalopathy was discussed and compared with the newly published definition by DVIC, and a final version will be distributed among the group.

Abstraction forms and instructions for the other neurologic outcomes will be finished within the next 2 months by the assigned centers. These will be distributed to the other sites and piloted.

DATA MANAGERS SESSION, JAN 26, PM AND JAN 27, AM

Participants: Emmett Swint, CDC; Virginia Immanuel, GHC; Ned Lewis, NCK; Loie Drew, NWK; and Patricia Osborne, SCK.

Data managers met the afternoon of 1/26/1995 and morning of 1/27/1995 to discuss LLDB data management activities.

LLDB Automated Tapes

Data managers reviewed automated files that are currently being submitted to CDC and projected when data may be available for other systems.

GHC Current: CONSTANT, ENROLL, VACCINE, OUTCOME (all components), HOSPDXHX, LAB, PHARMACY, PROCED, ADDRESS and GEOCODE
Future: None (all components currently are submitted)
Not Avail: None (all components currently are submitted)

NCK Current: CONSTANT, ENROLL, VACCINE, OUTCOME (hospital, ER and 3 clinics), HOSPDXHX, PROCED (excluding neurology referrals), ADDRESS and GEOCODE
Future: (1) Some LAB data from their old lab files will be submitted in mid-June for tape 3. Results from a new lab system will be submitted for tape 4. (2) Outpatient data for all clinics may be available for tape 4 from a new outpatient clinic system that was implemented in January, 1995.
Not avail: (1) Pharmacy file; (2) neurology referrals in the procedure file.

NWK Current: CONSTANT, ENROLL, VACCINE, OUTCOME (hospital and ER visits), HOSPDXHX, PROCED, ADDRESS, and GEOCODE files.
Future: (1) LAB file will be available in next six months
Not avail: (1) Clinic visits in the OUTCOME file. A system is under long-term development.

SCK Current: CONSTANT, ENROLL, VACCINE, OUTCOME (hospitalizations), ADDRESS and GEOCODE
Future: (1) OUTCOME (ER visits); (2) HOSPDXHX in summer, 1995; (3) LAB in June, 1995; (4) PHARMACY in fall, 1995; and (5) PROCED in Summer, 1995;
Not avail: (1) OUTCOME (clinic visits)

Files Involving Chart Reviews

SAMPLE file. Emmett indicated that Phil Rhodes would like to begin reviewing the first SAMPLE file results. SCK has submitted

their SAMPLE file to CDC. NCK and NWK indicated their files are available. GHC's file would not be available until after the third tape.

Neurology review files. CDC has received the seizure review file from NWK. In order for Bill Barlow to do additional analyses at GHC, he will send Emmett a list of studyid numbers. Emmett will return the file with enrollment, vaccine and any other automated variables.

Loie Drew indicated that NWK used ancillary information to identify additional children with seizures. Children appearing in the PHARMACY and PROCEDURE files were identified as prospects for any neurology outcome. Their medical charts were reviewed and all ICD-9 codes within a given time period of each ancillary reference date were identified. Children having any seizure ICD-9 code in this list were added to the seizure sample. The chart review was performed and all children were classified as either a seizure case or non-seizure case.

There was general discussion about the neurology review protocols. Data managers preferred that the formats have a common uniform component followed by questions that might be specific to a given disorder.

Files Involving Matching

The geocode and birthref files are used to match with census files and state birth certificate files. Emmett indicated that CDC will not perform these functions until additional contract FTEE can be obtained. The death file will be a new file that will require HMOs to match children with the state death certificate files and other local sources for deaths.

Data managers discussed the structure needed to report deaths. It was agreed that a separate DEATH file should be created but it should be consistent with existing LLDB files. It was agreed that the same death matching file could not easily be used at all HMOs. Emmett agreed to review previous documents that were written and to describe the methods that each HMO are using to identify deaths. Ned indicated that NCK deaths occurring outside the HMO were reported in the CONSTANT file. The target date for death files would after the tape 3 submission date.

LLDB Edits

Data managers reviewed some of the edits that were used with LLDB tape 2. It was requested that data managers apply these edits locally and resolve records that do not pass edits prior to submitting tape 3.

Corrections were identified and the following edits are to be added to the list:

(1) Vaccine file -- vaccines reported in tape 2 should appear in tape 3 unless the child has been dropped for ineligibility reasons or the vaccine record was corrected after tape 2.

(2) Outcome file -- diagnoses reported in tape 2 should appear in tape 3 unless the child has been dropped for ineligibility reasons or the vaccine record was corrected after tape 2.

Data Dictionary Modifications

The data structure of all LLDB automated files was reviewed to determine if changes were needed. Emmett will incorporate the corrections and republish the data dictionary. HMOs should proceed with tape 3 based on these changes.

Emmett indicated that the enrollment start and stop dates provided by the HMOs in the ENROLL file would be the ones used without additional adjustments. Ned agreed to describe the adjustments that each HMO uses, e.g., collapsing enrollments that are within 90 days of each other. There was discussion about whether shots and vaccines outside the enrollment intervals should be submitted as part of the VACCINE and OUTCOME files since analyses excluded these shots. Data managers preferred not to submit exposures and events outside these intervals.

NCK will be submitting adolescent data. Ned wanted to know how much historical hospital data should be included in the HOSPDXHX file. The files could become very large and local hospital discharge files may not be as accurate and complete for adolescents ready to age-out.

Transport Files

Emmett indicated that some form of SAS transport file would be needed for HMOs with non-UNIX operating systems to submit files to CDC. A routine was distributed describing how to prepare and read transport files. Ned Lewis indicated that some systems could not handle block sizes of 32000 or higher and recommended that "blksize=31920" be used when creating the transport dataset.

ANALYTICAL ISSUES, JAN 26, PM, AND JAN 27, AM

The statisticians met twice to discuss analytical issues, beginning with technical questions (i.e., why Phil had screened exactly as he had), some of which had been discussed before Michael joined SCK, but were worth reconsidering (e.g., matching more finely on calendar time than age accounts for different

probabilities of recent exposure on weekends and week days). Other issues concerned refinements of subsequent analyses.

Causing conditions is more interesting substantively than exacerbating them, which however might be more challenging statistically. With regard to the nested seizure study, someone suggested that first events and ones following febrile and afebrile first events be analyzed separately. Given that their records are complete, though not necessarily automated, children born into these HMOs and continuously enrolled might be analyzed separately to overcome the arbitrary nature of first events among those born before or elsewhere. This led to discussion of chronic conditions, which screening of first events, all events and ones remaining after application of our rule for distinguishing acute and follow-up care is meant to address crudely. Ideally, one would condition on prior occurrences such that comparison groups differ only in most recent exposure. The high risks associated with Flu and DT vaccines probably would disappear if otherwise similar children were being compared.

On another topic, the external advisors recommended reviewing the charts of exposed cases and sampling the others whenever associations were found; one could target children whose automated records indicated were behind, which likely are incomplete, as is being done routinely at NWK; the nested seizure study is being done differently, but it might be possible to remedy this at the larger sites where substantial fractions of charts remain to be reviewed. One goal of any such reviews might be discovering which associated codes (and ancillary information) are most predictive of validated cases; Janet Hardy is formulating just such a study.

Suggested analytical priorities were: (a) first event analyses of recurrent outcomes, (b) children born into study and continuously enrolled, (c) stratification to elucidate effect modification by age, (d) simultaneous administration (individual or synergistic effects?), (e) stratification for effect modification by gender. Further analyses were recommended only of exposure-outcome pairs that seem to be associated in screening. Advisors recommended that we not be paralyzed by multiple comparisons because outcomes are different, and that the VAERS be used for hypothesis generation and the VSD for evaluation.

Phil promised to make his programs more friendly and provide them to other statisticians as a means whereby they might become more comfortable with what he had done and possibly assume some of the responsibility. Which analyses others might perform were not specified, but some are interested to general issues (e.g., Michael in confounding, Bruce in Poisson regression, John in misclassification) and others in specific outcomes (e.g., Bill in seizures). This discussion should continue during analytical conference calls, whose participants also might consider a

proposed new rule for distinguishing acute and follow-up care, based on recent revision of the original periods beyond which follow-up didn't usually extend and provision of usual durations of acute care, and its empirical evaluation, the strange age-distributions of NCK and SCK, summary document entitled "Screening and Other Issues," particularly the questions and their analytical implications (e.g., windows of risk post-vaccination)

Dr. CHEN. OK.

Mr. BURTON. Would you read to the committee the two sentences beginning with "There was consensus?" "There was consensus that nothing 'focuses the mind like writing a paper' "and the highest priority for the project was in publishing the results of the studies, thereby garnering visibility and hopefully continued support and funding. Is this taxpayer funded project simply to keep a bunch of scientists employed and to pad your curriculum vitae with publications or is it to actively look for adverse events related to vaccines and to protect our children?"

Dr. CHEN. Well, it is both. You hope to be able to do vaccine safety monitoring but that those results need to be shared with the public in peer review research and as part of the scientific process. Hopefully, by demonstrating that productivity, you are also able to continue to get additional resources.

Mr. BURTON. Let me ask one or two more questions and we will call it a day. It has been a long day.

Dr. Bernier, as you know, there has been a great deal of concern about the changing of the definition of encephalopathy in the vaccine injury compensation program. This change resulted in many cases being ruled "off table" and thus harder to be compensated. We have repeatedly been told that the Department adopted an existing scientific definition. I am going to read to you verbatim from January 12, 1994 a VSD annual meeting summary written and approved by CDC employees.

"Encephalopathy, the definition developed by Jerry Finecel for revision of the Vaccine Injury Table and published in the Federal Register should be adapted." Dr. Bernier, it appears that Congress and the public have been misled about this definition. I am going to ask that you take back to the Secretary a request to revert to Congress' definition immediately. Do you have exhibit No. 5, page 2, paragraph 6.

[Exhibit 5 follows:]

Vaccine Safety Datalink (VSD) Meeting
Center for Vaccine Research; Harbor-UCLA Medical Center
Torrance, CA; January 12-13, 1994

Present: Group Health Cooperative (GHC) -- William Barlow, Virginia Immanuel, Thomas Knauss, Angela Salazar, Robert Thompson; Harbor-UCLA Medical Center and Southern California Kaiser (SCK) -- Nancy Goff, Jennie Jing, Marlene Lugg, Michael Marcy, Patricia Osborne, Constance Vadheim, Joel Ward, William Shields; Northern California Kaiser (NCK) -- Steven Black, Bruce Fireman, Jean Hayward, Ned Lewis, Henry Shinefield; Northwest Kaiser (NWK) -- Lois Drew, John Mullooly, John Pearson; Centers for Disease Control and Prevention (CDC) -- Robert Chen, Elias Durry, John Glasser, Stephen Hadler, Steven Rosenthal, Emmett Swint; Food and Drug Administration (FDA) -- Henry Hsu, Suresh Rastogi, Robert Wise; National Institutes of Health (NIH) -- Steven Wassilak.

Joint Session, January 12th, a.m.

John Glasser began the meeting with administrative remarks followed by welcome from Joel Ward. Attending staff members from each group were introduced by Robert Thompson, John Mullooly, Steve Black, Joel Ward, Suresh Rastogi, and Bob Chen.

Bob Chen described some developments relevant to the VSD study, including creation of the National Immunization Program (NIP), which reports to the Director of the CDC, and institution of the Childhood Immunization Initiative (CII). The CII sets goals of 90% vaccine coverage by two years of age for MMR, 3 OPV, 3+ DTP, and 3+ Hib; and 70% coverage of 3 HBV by 1996. It also sets morbidity goals of zero indigenous cases of measles, rubella, wild polio, diphtheria and tetanus among children less than 15 years old, and Haemophilus influenzae type b infection among less than 5-year olds by 1996. Currently the NIP is reorganizing to accomplish these goals, but the VSD probably will be minimally affected. Since July of 1993, two medical epidemiologists and an EIS officer have joined the Vaccine Safety Activity.

Bob also mentioned that the IOM has recently published its study of adverse events following receipt of childhood vaccinations against diseases other than pertussis and rubella (which J. Glasser had sent to the investigators). He highlighted their inability to reach conclusions about vaccine associations with 33 of the 54 studied adverse events due to insufficient evidence. He mentioned three workshops recently conducted on vaccine safety (by the FDA on simultaneous vaccination and harmonizing vaccine adverse event terms, and by the IOM on research strategies) and papers presented at the ISPE and ICAAC meetings.

Among the issues discussed during the IOM workshop was an advisory committee for the VSD and means of sharing with other

investigators this study's methodologies and findings. In regard to creating an external advisory group, Joel asked whether the CDC had decided to form such a committee. John Glasser replied that no such decision, including the necessity for a committee, had been made and that this issue would be discussed thoroughly with all investigators.

Following Bob's presentation, participants dispersed into three concurrent sessions for discussions of neurological outcomes or data management or analysis that lasted throughout the day.

Separate Sessions, January 12th

Neurological Group -- Tom Knauss, Robert Thompson (GHC); John Pearson (NWK); Jean Hayward, Steve Black, Henry Shinefield (NCK); Don Shields, Mike Marcy, Joel Ward (SCK); Steve Rosenthal, Elias Durry, Bob Chen, Steve Hadler (CDC); Steve Wassilak (NIH)

We began by clarifying the purpose of assembling the group. Unlike the other outcomes, the specificity of neurologic ones was deemed insufficient for reliance on automated data in screening for potential vaccine associations. Therefore, it was decided that, with the exception of aseptic meningitis, neurologic outcomes of interest required chart review to ensure that cases met definitions. Based on our results (and others in the literature), we may decide to perform more extensive nested case-control studies with more thorough chart abstraction and case definitions. But this was not the main charge for the day. The group then prioritized its discussion from the most to least difficult neurologic outcomes.

Acute/Persistent Seizures: It was decided that both issues are of interest in this study, but require different case finding methods. For acute seizures, the current method is workable, but for persistent seizure disorders, as much time as possible should be allowed to lapse before these charts are reviewed (e.g., at exit from the study, age 7 or departure from HMO).

Encephalopathy: The definition developed by Jerry Fenichel for revision of the Vaccine Injury Table and published in the Federal Register should be adapted without his distinction by age. Similar to seizures, the acute cases would need follow-up $\geq$1 year later to learn the status of their recovery. Acute episodes require hospitalization, with coma or stupor not attributed to medication or post-ictal state.

Sensorineural Hearing Loss: It was the consensus of the group that onset dates could not be assigned with any degree of accuracy. The diagnosis would be made in many children only when they start performing poorly in school, many years after initial onset. It was decided therefore to exclude this outcome from screening chart validations. Crude screening analysis using other dates (e.g., of diagnosis) may still be possible, but

results will always be questionable.

Ataxia: This outcome should be narrowed to Acute Cerebellar Ataxia.

Polio: Case definition should match that used by the CDC for vaccine-associated polio as closely as possible.

Cranial Nerve Disorders: The only cranial nerve disorder likely to be diagnosed is facial nerve (e.g., Bell's Palsy). There was consensus that the accuracy of this diagnosis is quite good by the average physician, so screening chart abstraction was unnecessary for this outcome.

Increased Intracranial Pressure: This outcome should be renamed Pseudomotor cerebri.

Other Aspects of Neurologic Outcomes: Relatively straightforward discussions were held that improved case definitions, chart abstraction forms, and search methodology.

Steve Rosenthal and Robert Thompson were assigned the responsibility to revise the case definitions and chart abstraction forms taking into account the day's discussion. Drafts are to be circulated in approximately 2 weeks, in time for a conference call among the neurologists in about a month's time.

R. Chen

Analytical Group -- Bill Barlow (GHC); John Mullooly (NWK); Bruce Fireman, Paula Ray (NCK); Peter Christenson, Marlene Lugg (SCK); Suresh Rastogi, Henry Hsu (FDA); Phil Rhodes, John Glasser (CDC)

We spent the morning conversing with Phil in Atlanta via telephone about solutions to problems that he had encountered in screening our 34 outcomes of interest for association with the common childhood vaccines, and most of the afternoon discussing packaging these results for various audiences, dealing with automated data of variable quality (e.g., whether to plan on case-cohort analyses or not, and if so, whether or not everyone should extract additional information the next time that they reviewed their 1-2% samples) and complementary analyses that other statisticians could perform (e.g., Poisson regression at NCK with misclassification corrections from NWK).

Phil employed a Cox model stratified on HMO, whether or not outpatient visits were captured and date of birth (within 3 days, but indicated that this could be modified as data accumulated or varied among sites to maintain comparable strata), with calendar time as the temporal dimension and allowing for multiple entries, exits and events. Whenever events occurred, times since most recent exposure to common childhood vaccines were calculated for every member of the risk set (same values of the stratifying

variables), and whether or not each was in various intervals and windows of particular vaccinations was determined.

Our original plan, formulated before Phil joined this project, was to perform cohort analyses if the automated data sufficed for this purpose and case-cohort ones, using augmented records of cases and members of the 1-2% samples, otherwise. Phil's choice was based on computational ease without much loss of efficiency, but won't be as easy to communicate to our primary audience, pediatricians and parents. We decided that Bruce would pursue a modification of the original course, namely use information about misclassification from John Mullooly's assessments of the automated data quality to correct his analytical results.

Phil advocated reviewing more records of children who appear to have experienced outcomes of interest, particularly those exposed on the same day (to ensure that exposures preceded these outcomes), but generally because our 1-2% samples contain far less information about rare outcomes than common exposures. In particular, he suggested over sampling such children in the age ranges where recent exposures are most likely. The value of learning more about outcome data quality notwithstanding, it wasn't clear how this would inform Cox analyses. Should we stratify on whether records were reviewed or sample what appear to be informative strata (i.e., cases and discordant risk sets) by virtue of the automated data alone, ...? The neurological case ascertainment provides an opportunity to review the records of children with one-third of our outcomes of interest; should we subject them to the 1-2% sample protocols?

J. Glasser

Joint Session, January 13th, a.m.

The meeting resumed with John Glasser highlighting the second day's agenda and announcing that PIs and POs would meet in executive session during lunch. He and Bob Chen summarized the concurrent neurological and analytical sessions on 1/12 (above; minutes of data management session were distributed separately).

ANALYTICAL RESULTS:

Descriptive Epidemiology (John Glasser)

John stated that his purposes in describing the exposures and outcomes were to (a) ensure that the data were sensible, (b) identify differences among sites that might implicate data management versus medical practice, and (c) inform subsequent multivariate modeling. Then he illustrated age-specific vaccination and cumulative vaccination rates (interpretable as average numbers of doses), and suggested that we perceive differences among sites as natural experiments. Defining

coverage as the quotient of these observed and the expected numbers of doses, he illustrated DTP coverage.

With regard to our study population, he illustrated the age distributions of all children and those whose clinic visits were captured, which indicate different population dynamics in the three HMOs. We capture outpatient encounters only at GHC and a similar-sized portion of NCK, but because we don't know which children's outpatient visits will be captured until they seek care at one of three large clinics, recruitment to this portion of NCK's population occurs during the first few months of life.

John also illustrated age-specific rates of selected outcomes among sub-populations whose clinic encounters we do and don't capture by site and setting where different. He assigned visits separated by outcome-specific intervals to sites hierarchically (i.e., children hospitalized following urgent care or clinic encounters were counted only as having been hospitalized) and modeled them using Poisson regression. Because our ability to detect differences among sites and settings varies with the number of observations, only substantive experts (e.g., local clinicians and data processors) can determine whether or not statistical differences are meaningful.

Taking seizures and persistent seizure disorders as an example, he indicated that models ignoring site and setting were superimposed on aggregate rates in the first of three figures; the other two illustrate only modeling results. The less well these models fit those data, the greater the differences among sites or settings. The second figure illustrates age-specific rates in the two sites at which only hospitalizations and urgent care encounters are captured, which pertains to roughly two-thirds of NCK and all of NWK, and the third illustrates them in the two sites at which clinic encounters also are captured, the remainder of NCK and all of GHC.

These rates or age-distributions differ with setting, but the nature of such differences varies among sites, most strikingly between GHC and the others: Children having seizures either present for urgent care or are hospitalized at NCK and NWK, whereas they most commonly seek care at GHC's clinics. The ages of children presenting at NCK's and NWK's facilities suggest that those with febrile seizures present at urgent care facilities while children with afebrile seizures are hospitalized, possibly after presenting elsewhere first, but their age distributions don't differ among settings at GHC.

John suggested that whether or not such differences affect our ability to detect vaccine associations was a matter that Phil Rhodes might discuss. Meanwhile, he asked investigators to study the descriptive results illustrated in his handout and share any insights about the apparent differences in exposure or outcome rates by site and setting.

Automated Data Quality (John Mullooly)

To assess the quality of automated data, John compared automated and conventional records using 1-2% samples of the study cohorts.

When he compared automated vaccination dates with those abstracted, accuracy differed among sites. These differences probably are attributable to the procedures employed for recording vaccinations. NCK, which had the highest match (96-98%), uses research personnel to audit vaccinations. NWK also has its own vaccination auditing system, with data being entered by clinic personnel. GHC also uses vaccinations entered by clinic staff, but without special auditing procedures.

To compare outcomes in the automated emergency room (ER) database to those identified by chart review, John used outcomes (within the same week of vaccination) identified at GHC. Eighty-nine percent of outcomes matched the autocoder, 85% with chart review finding, and 77% with either. Based on these data, he highlighted the need to improve the autocoder and develop a supplemental system to code ER records.

John also evaluated the ability of ancillary sources to capture neurologic outcomes. Among 348 charts of children who did not have automated inpatient or ER neurologic diagnosis, 45% had a neurologic diagnosis, including rule out diagnoses. These were identified by reviewing diagnostic procedures, mostly EEGs (63%), anti-seizure medications (11%), and referrals (3%). Twenty-three percent were identified from multiple sources.

Use of the pharmacy was highlighted in identifying patients diagnosed with asthma. Among children born between 1/1/90 and 12/31/91, 12% were prescribed anti-asthmatic medications during their first year of life.

John also explained his model for misclassification.

Screening for Association (Phil Rhodes via telephone)

Phil described vaccines, outcomes, and vaccine-outcome combinations and presented analytic results. He also discussed problems and opportunities for future screening analysis and directions for the VSD.

Vaccines: He described the number of vaccinations by age and antigen, including simultaneous administration. He discussed the difficulty of differentiating the separate effects of vaccines, if any, when given simultaneously.

Outcomes: Phil also tabulated visits at which outcomes of interest were diagnosed and compared them with acute events. The frequencies with which events occur after vaccination determine which analyses are possible. In these, medical events rather

than visits should be analyzed. Follow-ups were eliminated by designating "black-out periods" following medical events (e.g., diagnosis of encephalitis) that varied among "items."

Vaccine-outcome: Vaccines were analyzed for association with outcomes in time windows such as 0, 0-1, 0-2, 0-7, and 0-30 days following vaccination. By comparing the risks during these intervals with that 30+ days after vaccination, the relative risks (RR) were estimated using stratified Cox regression models in a manner that resembles matched case-control analyses.

Apparent differences in the risk of seizure following vaccination with DTP, MMR, Hib, and OPV among sites could be attributable to differences in ability to capture outcomes in various settings, in the settings at which outcomes occur or in ICD-9 coding. If enough events occur, site-specific analyses would be appropriate.

Phil illustrated how differences in scheduling and practice among sites could be used to separate associations between events and vaccines given simultaneously. Because DTP and Hib were given simultaneously, for example, risk of seizure in various windows of vaccination with both were similar. If adequate numbers of either vaccine were given on different days, however, one could differentiate the association of seizure with DTP and Hib. More complex analyses could differentiate between associations of simultaneously administered vaccines with outcomes. One such model compared risks of an event following simultaneous and separate administration of several vaccines.

Problems with Screening Analysis:

- ICD-9 codes that fall into multiple items and/or subcategories;
- Different ICD-9 codes for the same event in different settings (e.g., seizure);
- Changes to programs for analysis of vaccine-outcome associations.

Areas Requiring Improvement:

- Difference among sites and settings;
- Difference within sites;
- Difference among sites for outcomes occurring on the same day as vaccination;
- Correspondences and differences among visits, codes, and events.

Areas that Require a More In-Depth Look:

- Explore multiple event issues;
- Relationship among events of different types;
- Examine whether outcomes of interest delay or prohibit use of certain vaccines;
- Analyses looking at more than one vaccine at a time;

- Look within the 34 event subcategories to see if vaccines may be associated with portions of them;
- Controlling for other information (e.g., sex, information from birth certificate, geocoding) or looking for interactions.

We must decide who will perform each task; input from physicians and data managers will be essential.

Future Directions -- Possible Restructuring of:

1. Quality control activities

- Not enough focus on or information about cases;
- Over sample children appearing as cases or do separate quality control on cases;
- Could focus the quality control sampling so as to over sample those ages at which vaccination is likely to occur, over sample children during ages which they should be receiving vaccinations, but do not appear to be doing so.

2. Intensive studies (e.g., neurologic outcomes)

- Most neurologic outcomes are rare, which could allow to look at all charts in some depth;

- Seizures are not rare

  Do we want to look at all charts?
  Do we want to look at all charts in a cursory manner?
  Look at some sample of charts in depth?
  How to sample?

- ALL CASES ARE EQUAL EXCEPT SOME ARE MORE EQUAL THAN OTHERS; e.g., for seizures, cases occurring shortly after vaccination are the most important to explore in depth, 'unexposed' cases occurring at ages where vaccination is common may be next most important, etc.

Discussion:

Steve Hadler suggested assigning several outcomes to each investigator, and there was a general understanding of the need for this considering the work to be accomplished. The investigators agreed to review their interests and ability to study outcomes to facilitate such assignments.

Ascertainment of Deaths in Non-Medical Settings:

Bob Wise opened this discussion by describing the importance of including death as a study outcome to ensure public confidence. His opening statement was followed by summaries from the PIs

regarding their collection of data from death certificates.

Robert Thompson said that 80% of GHC's deaths are known to his group. He also stated that they will receive death certificates from the State Coroner's office with a three month lag. They plan quarterly linkage with their data and could match death certificates with birth certificates. Furthermore, they plan to use the SIDS registry as a back up.

John Mullooly reported that NWK will obtain data from the State of Oregon, and link it to their database themselves.

Steve Black stated that NCK is cooperating with five counties to study SIDS, and will link county death and HMO membership records. He mentioned two other sources of information about deaths: (1) SIDS registry in Sacramento and (2) monthly tapes from the CA Maternal and Child Health Office, from which autopsy reports also are available.

Joel Ward cautioned against concentrating too much on SIDS and duplicating efforts by looking at any subset if we are interested in all deaths. He stated that SIDS could be studied in a pilot to evaluate the utility of a broader approach. He also stated that methods should be standardized because causes of death on death certificates are unreliable.

Joint Session, January 13th, p.m.

The meeting resumed with Emmett Swint's presentation of data management activities. Discussion on the definition of non-neurological outcomes by Jessica Tuttle, via phone, was canceled due to lack of time.

Data management activities in 1993 (Emmett Swint)

Emmett recapped his activities in FY 1993: editing and adjusting tape 1; defining acute events; creating files for vaccine rates, acute outcome rates and association analyses; assisting the quality review committee; establishing a system to classify VSD data sets and documentation; identifying resources needed to convert from mainframe processing to a minicomputer; and interacting with HMO data managers to specify the data dictionary for the second set of VSD files.

Tape 2 status: Next he reviewed the status of tape 2 submission: all files have been received from GHC and all save Pharmacy and Address from NWK. April is the target date for SCK and NCK to submit their files. Priorities for partial tape submissions were established in the data manager meeting on January 12th: (1) files to perform rates and cohort analyses and identify neurology outcomes for review (CONSTANT, ENROLL, VACCINE and OUTCOME); (2) file to abstract socioeconomic information from census tapes

(GEOCODE); (3) files to perform birth certificate matching (BIRTHMAT and State Birth Certificate files); and (4) ancillary files to identify new cases (PHARMACY, PROCED, LAB).

Data management issues: Data management issues that surfaced during the year and had been discussed with data managers on the previous day also were reviewed:

a. Enrollment dates used to calculate child days were adjusted for start dates after the date of birth and vaccine or outcome dates out of range. Data managers suggested that the impact of these adjustments be reviewed prior to using them with tape 2 files.

b. Many outcomes of interest occur primarily in the outpatient clinic setting and HMOs without outpatient records will miss many outcomes in their automated datasets. Characteristics of outcomes from HMOs with outpatient records (GHC and three clinics at NCK) were shared with the group.

c. The outcome of interest table contains duplicate ICD-9 codes in different items and subcategories. Data managers indicated that the current methodology is very good for selecting specific items, but one must eliminate duplicates when aggregating counts at the subcategory and category levels.

d. The manner in which acute episodes are defined affects the numbers that children have and their dates of occurrence. Data managers felt that designing an algorithm that minimized the misclassification of follow-up visits as acute events was important. PIs offered the following suggestions to improve the definition: (1) examine distributions of visits to determine if other intervals might be more appropriate; (2) some outcomes such as diarrhea should have relatively constant intervals while chronic conditions such as seizures or asthma might have less predictable ones; and (3) the setting of an acute episode should reflect the most serious setting, if the child visited several, even if it was not the first (i.e., hospital, then ER, and then outpatient clinic).

Identifying deaths outside the HMO: Then Emmett presented the structure proposed by data managers to integrate deaths identified from death certificates and other sources. Merits of using SIDS registries and other databases to ensure that all deaths had been identified and to provide provisional causes of death were discussed.

Ancillary files: Finally, he presented several tables, as examples of the relationship between the neurological outcomes of interest and ancillary information, and noted that: (1) NWK has reviewed some charts to identify the percentage of children in the pharmacy file with supporting ICD-9 codes in their medical charts and (2) GHC has approximated the number of medical records that would require review based on the settings and ancillary

files available. During the early part of this year, CDC will examine GHC's second year tape to help define the utility of the ancillary files in identifying new cases, especially at HMOs that do not report outpatient outcomes.

Establishing Priorities (Bob Chen)

Bob distributed a spreadsheet listing outcomes (from the VSD study and IOM report) by vaccine and site that would lead the investigation of possible associations. He indicated that there was agreement between the VSD and IOM lists, excluding chronic events and ones with insidious onset. The only outcome studied by the IOM that is not on the VSD list is erythema multiforme (which was on an earlier list, but inadvertently dropped). Bob outlined criteria to prioritize the study of each outcome based on specificity of association, frequency or severity of outcome, and interest. He stressed the importance of dividing the lead among sites in investigating these outcomes, and instructed each PI to rank the entire list of outcomes according to their interests and ability to obtain the necessary data.

Discussion:

Steve Hadler suggested that we should concentrate initially on a few outcomes (e.g., with frequencies exceeding 1000 events, of which there are less than 10) and ask systematic questions as a specific focus. These questions will be assembled by CDC and disseminated to the sites for discussion. Participants agreed to discuss this issue further during the next conference call, scheduled for February 15, 1994 at 11 a.m. Pacific time.

Addition of adolescents and adults: Bob Chen stated that older children and adults would be added to the study eventually, but with modifications of methodology. Insofar as adults are concerned, for example, retrospective case-control studies seem most appropriate.

Questions on budgeting and future activities: Robert Thompson raised several questions in regard to budgeting of such unanticipated activities as:

- What did we miss in the last 4-5 years (e.g., no budget for controls)?
- What would it take to include adults?
- What is the extent of reviewing neurologic events?
- What level of chart review is necessary to obtain reliable information on cause of death?

After these questions were presented for further discussion at another time, the meeting was concluded and adjourned by John Glasser.

E. Durry

Analytical Group -- Bill Barlow (GHC); John Mullooly (NWK); Bruce Fireman, Paula Ray (NCK); Peter Christenson, Marlene Lugg (SCK); Suresh Rastogi, Henry Hsu (FDA); Phil Rhodes, John Glasser (CDC)

We spent the morning conversing with Phil in Atlanta via telephone about solutions to problems that he had encountered in screening our 34 outcomes of interest for association with the common childhood vaccines, and most of the afternoon discussing the packaging these results for various audiences, dealing with automated data of variable quality (e.g., whether we should plan on case-cohort analyses or not, and if so, whether or not everyone should extract additional information the next time that they reviewed the 1-2% samples) and complementary analyses that other statisticians could perform (e.g., Poisson regression at NCK with misclassification corrections from NWK).

Phil employed a Cox model stratified on HMO, whether or not outpatient visits were captured and date of birth (within 3 days, but indicated that this could be modified as data accumulated or varied among sites to maintain strata of similar size), with calendar time as the temporal dimension and allowing for multiple entries, exits and events. Whenever events occurred, times since most recent exposure to common childhood vaccines were calculated for every member of the risk set (same values of the stratifying variables) and whether or not each individual was in various risk intervals and windows of particular vaccinations determined.

Our original plan, formulated before Phil joined this project, was to perform cohort analyses if the automated data sufficed for this purpose and case-cohort ones, using augmented records of cases and members of the 1-2% samples, otherwise. Phil's choice was based on computational ease without much loss of efficiency, but won't be as easy to communicate to our primary audience, pediatricians and parents. We decided that Bruce would pursue a modification of the original course, namely use information about misclassification from John Mullooly's assessments of the automated data quality to correct his analytical results.

Phil had advocated reviewing the records of more children who appear to have experienced outcomes of interest, particularly those exposed on the same day as their event (to ensure that exposures preceded these outcomes), but generally because our 1-2% samples contain far less information about rare outcomes than common exposures. In particular, he suggested oversampling such children in the age ranges when they are likely to have been recently exposed. The value of learning more about outcome data quality notwithstanding, it wasn't clear how this would inform Cox analyses. Should we stratify on whether records were reviewed or sample what appeared to be informative strata (i.e., case and risk set discordant in exposure) by virtue of the automated data alone, ...? The neurological case ascertainment provides an opportunity to review the records of children with one-third of our outcomes of interest; should we subject them to the same protocol as we have members of the 1-2% samples?

Dr. BERNIER. I don't know if this is the appropriate time or if you want to finish this but I would like to recommend or suggest that we defer questions about the compensation program to representatives from HRSA. There is not a HRSA representative here today and we were asked if any questions did come up, could we ask for them to be sent to HRSA so they could respond for the record.

Mr. BURTON. I think the Secretary should be made aware of the definition that is currently being used. It should be changed. I will be glad to send a memo to him as well but I would like you to go back and ask him to review that along with you to see if that is in order.

Dr. BERNIER. We would be happy to do that.

Mr. BURTON. We will prepare a memo to that effect.

We have some more questions I would like to submit for the record but I am tired and I am sure that you are tired and we don't want to keep beating on this ad infinitum.

Dr. DeStefano, you worked with Dr. Verstraten on the thimerosal study, didn't you?

Dr. DESTEFANO. Yes.

Mr. BURTON. Would you turn to exhibit No. 14 and read the results in the conclusions section, please?

[Exhibit 14 follows:]

DRAFT – MAY CONTAIN ERROR OF FACT OR OMISSION

Risk of neurologic and renal impairment associated with thimerosal-containing vaccines.

Thomas Verstraeten, Robert Davis, Frank DeStefano, and the VSD team

Abstract

Background: Thimerosal is a mercury-based preservative in vaccines. Theoretical concerns have been raised that, through vaccinations, infants were being exposed to mercury levels exceeding Environmental Protection Agency guidelines. We used automated data from two health maintenance organizations, prospectively collected for vaccine safety studies, to assess the risk of neurologic and renal impairment associated with exposure to thimerosal-containing vaccines.

Methods: Cumulative exposure to mercury from thimerosal was evaluated at 1, 2, 3 and 6 months of age for 213,185 infants born between 1992 and 1997. Using proportional hazards models, we compared the risk of 16 neurologic disorders and 1 renal disorder to the cumulative exposure levels.

Results: We identified 3517 children with neurologic disorders, and 106 with renal disorders. We found a statistically significant positive correlation between the following measures of exposure and outcomes:

- the cumulative exposure at 2 months of age and unspecified developmental delay
- the cumulative exposure at 3 months of age and tics
- the cumulative exposure at 6 months of age and attention deficit disorder
- the cumulative exposure at 1, 3 and 6 months of age and language and speech delay
- the cumulative exposure at 1, 3 and 6 months of age and neurodevelopmental delays in general.

Conclusion: This analysis suggests that in our study population, the risks of tics, ADD, language and speech delays, and developmental delays in general may be increased by exposures to mercury from thimerosal containing vaccines during the first six months of life. Confirmation of these findings in a different population and further quantification of the dose response effect are needed.

Dr. DEESTEFANO. "Results, we identified 3,517 children with neurologic disorders and 106 with renal disorders. We found a statistically significant positive correlation between the following measures of exposures and outcomes, cumulative exposure at 2 months of age and unspecified developmental delay, cumulative exposure at 3 months of age at TICS, a cumulative exposure at 6 months of age in attention deficit disorder, a cumulative exposure at 1, 3 and 6 months of age in language and speech delay, a cumulative exposure at 1, 3 and 6 months of age in neurodevelopmental delays in general. Conclusion, this analysis suggests that in our study population, the risk of TICS, ADD, language and speech delays and developmental delays in general may be increased by exposures to mercury from thimerosal containing vaccines during the first 6 months of life, confirmation of these findings in a different population and further quantification of the dose response effect are needed."

Mr. BURTON. Do you recall the date of that? We don't have the date.

Dr. DEESTEFANO. It must have been like probably winter, later winter, early spring of 2000.

Mr. BURTON. Has that study been published?

Dr. DEESTEFANO. This was presented, I believe, at the Epidemic Intelligence Service Conference in April of that year.

Mr. BURTON. Was it published?

Dr. DEESTEFANO. No, those are not published proceedings.

Mr. BURTON. They are not.

Dr. DEESTEFANO. This was a training program and this is usually the conference where the Epidemic Intelligence Service officers in training present their research but they are not published.

Mr. BURTON. It showed there was a problem, didn't it?

Dr. DEESTEFANO. This is the analysis that the autism figures come from that was displayed earlier.

Mr. BURTON. What was Dr. Verstraten's role at the CDC when the study was conducted?

Dr. DEESTEFANO. He was an Epidemic Intelligence Service officer, so he was there to obtain training in applied epidemiology.

Mr. BURTON. He is no longer with the CDC, correct?

Dr. DEESTEFANO. No, he is not.

Mr. BURTON. Isn't it true that shortly after the study Dr. Verstraten left the CDC and took a job with a vaccine manufacturer?

Dr. DEESTEFANO. Yes.

Mr. BURTON. In June 2000, the VSD project held a meeting, Exhibit No. 16. Could you look at exhibit No. 16? In June 2000, VSD project held a meeting at the Simpson Wood Retreat Center, correct?

Dr. DEESTEFANO. Yes.

Mr. BURTON. Would you explain the purpose of that meeting?

Dr. DEESTEFANO. I could explain but Dr. Bernier organized it and he would be better able to explain.

Mr. BURTON. It was to discuss the thimerosal study, was it not?

Dr. DEESTEFANO. Right.

Mr. BURTON. Was that correct?

Dr. BERNIER. That is correct.

Mr. BURTON. As you can see, exhibit No. 16 is an internal memo from Dr. Harold Guess at Merck to Merck employees distributing the thimerosal information from the Simpsonwood meeting. Isn't it correct that all the vaccine manufacturers had representatives at that meeting?

[Exhibit 16 follows:]

MERCK
Research Laboratories

CONFIDENTIAL

NOT FOR DISTRIBUTION

MEMO

TO: Please See List DATE. June 9, 2000

FROM: Dr. H. A. Guess

SUBJECT: Scientific Review of Vaccine Safety
Datalink Information

For your information.

H. A. G. - 2422

Attachment

TO:

John Boslego	UNC -141
Isabelle Claxton	WP97-B346
Edward Sargent	WS2F-45
Alan Shaw	WP16-100
Robert Sharrar	BLB-30
Robert Trinkle	WP53C-310
Henrietta Ukwu	UN-B121
Thomas Vernon	WP97-A337

Scientific Review of Vaccine Safety Datalink Information
June 7-8, 2000
Simpsonwood Retreat Center

Agenda

Day One – North Georgia Room
Wednesday, June 7th

10:00	Welcome	Walter Orenstein
10:05	Introductions	All
10:15	Chronology of Events & Charge to the Consultants	Roger Bernier
10:30	Summary of Thimerosal Workshop in August 1999	Martin Myers
10:45	Introduction to Vaccine Safety Datalink Study	Frank DeStefano
11:00	Presentation of Vaccine Safety Datalink Information	Tom Verstraeten
11:30	Discussion	
12:30	***LUNCH***	
2:00	Results from Chart Reviews	Bob Davis
2:15	Discussion	
2:30	Presentation of an Independent Review of the Data	Phil Rhodes
2:45	Discussion	
3:00	Comments on Biologic Plausibility and Consistency	Loren Koller
3:30	Discussion	
3:45	*** BREAK***	
4:15	Open Discussion	All
6:00	Adjourn	

Scientific Review of Vaccine Safety Datalink Information
June 7-8, 2000
Simpsonwood Retreat Center

Agenda

Day Two - Watson Room
Thursday, June 8th

8:00	Open Discussion Continued	All
9:00	Individual Consultant Opinions on the Data (Round I)	Consultants
10:00	***BREAK***	
10:30	Presentation of Potential Next Steps for Research	Frank DeStefano/ Bob Davis
11:00	Individual Consultant Opinions on Research Needs (Round II)	Consultants
12:00	Rapporteur's Summary	Paul Stehr-Green
12:30	Adjourn	

Risk of neurologic and renal impairment associated with thimerosal-containing vaccines.

Thomas Verstraeten, Robert Davis, Frank DeStefano, and the VSD team

Abstract

Background: Thimerosal is a mercury-based preservative in vaccines. Theoretical concerns have been raised that, through vaccinations, infants were being exposed to mercury levels exceeding Environmental Protection Agency guidelines. We used automated data from two health maintenance organizations, prospectively collected for vaccine safety studies, to assess the risk of neurologic and renal impairment associated with exposure to thimerosal-containing vaccines.

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Results: We identified 3517 children with neurologic disorders, and 106 with renal disorders. We found a statistically significant positive correlation between the following measures of exposure and outcomes:

- the cumulative exposure at 2 months of age and unspecified developmental delay
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- the cumulative exposure at 6 months of age and attention deficit disorder
- the cumulative exposure at 1, 3 and 6 months of age and language and speech delay
- the cumulative exposure at 1, 3 and 6 months of age and neurodevelopmental delays in general.

Conclusion: This analysis suggests that in our study population, the risks of tics, ADD, language and speech delays, and developmental delays in general may be increased by exposures to mercury from thimerosal containing vaccines during the first six months of life. Confirmation of these findings in a different population and further quantification of the dose response effect are needed.

Introduction

Thimerosal has been used as an additive to biologics and vaccines since the 1930's for preventing bacterial contamination, particularly in opened multi-dose containers. Some but not all of the vaccines recommended routinely for children in the United States contain thimerosal. Thimerosal consists by weight of 49% mercury in the form of ethylmercury.

Mercury exists in metallic, inorganic or organic form. Ethylmercury belongs to the organic group, which includes methylmercury, a better known compound mostly found in fish. As little is known on the pharmacokinetics and toxicology of ethylmercury, and although some argue that ethylmercury behaves more like an inorganic, it is probably most conservative to assume that ethylmercury behaves like methylmercury.

Mercury is known to target mostly the neurologic and renal systems. The effects range over a wide variety of conditions, depending on mode of exposure and form of mercury. All research so far has focused on exposure either through inhalation or oral ingestion. Any knowledge on the effects of injection of mercury compounds in humans comes from anecdotal case reports.

Two prospective cohort studies, undertaken to assess the impact of prenatal exposure to methylmercury from fish consumption on the neurophysiological and neuropsychological development in children, have resulted in conflicting findings. In the Faroe Islands, Grandjean et al found an association with cognitive development at 7 years of age, whereas Davidson et al found no association in the Seychelles.
The current study is to our knowledge the first epidemiologic study to study the effect of thimerosal in vaccines on long-term neurologic and renal outcomes.

Methods and materials

Study participants

We selected a cohort of infants from the Vaccine Safety Datalink (VSD) database. VSD was created in 1991 by the National Immunization Program of the Centers for Disease Control and Prevention (CDC). The project links medical event information, vaccine history, and selected demographic information from the computerized clinical databases of four staff model health maintenance organizations (HMO)s: Group Health

Cooperative of Puget Sound (GHC) in Seattle, Washington; Kaiser Permanente Northwest (NWK) in Portland, Oregon; Kaiser Permanente Medical Care Program of Northern California (NCK) in Oakland, California; and Southern California Kaiser Permanente (SCK) in Los Angeles, California. HMO members have unique HMO identification numbers that can be used to link data on their medical services within the HMO. Vaccination data are derived from computerized immunization tracking systems that are maintained by each of the HMOs. Quality control comparisons of the computerized immunization data with information recorded in paper medical records have shown high levels of agreement. For medical encounters, each of the HMOs maintains computerized databases on all hospital discharges and emergency room visits; diagnoses from outpatient clinic encounters are available from some of the HMOs for certain years.

We have restricted our cohort to children born between 1992 and 1997 into one of the two HMOs with the most complete automated outpatient data set (GHC and NCK). For these two HMOs we have follow-up data to the end of 1998. Children in the cohort thus have a follow-up time of 1 to 7 years.

To ensure capture of all vaccinations in the first year of life within the HMO, we restricted the cohort to children that were born into the HMO, continuously enrolled for the first year of life and that received at least 2 polio vaccines within the HMO by the age of 1 year. We excluded infants with ICD9 codes indicative of congenital disorders, severe perinatal disorders, recipients of HepB immunoglobulins, and gestational age less than 38 completed weeks. For this last group we performed separate analyses.

Exposure assessment

We calculated the cumulative exposure to ethylmercury from individual automated vaccination records, assuming each vaccine to contain the mean dose reported by manufacturers to the FDA. We assessed this cumulative exposure at the end of the first, second, third and sixth months of life. The Thimerosal content of childhood vaccines used in the two HMOs is as follows:

Hepatitis B: 25 µg (12.5 µg ethylmercury)

Haemophilus Influezae: 50 µg (25 µg ethylmercury)

Diphtheria Tetanus Pertussis (whle cell or acellular): 50 µg (25 µg ethylmercury)

Polio, Measles, Mumps, Rubella, Varicella and Pneumococcal: 0 µg

Outcome assessment

A case was defined as any child that was assigned one of the ICD9 codes, listed below. No distinction was made on whether a code was assigned after a clinic visit or hospital stay.

1. Degenerative disorders:

Code	Description
330.x	Cerebral degenerations usually manifest in childhood
331.x	Other cerebral degenerative disease
333.x	Other extrapyramidal disease and abnormal movement disorders
334.x	Spinocerebellar disease
335.x	Anterior horn cell disease

2. Developmental disabilities:

Code	Description
299.0	Autism
299.8	Other childhood psychosis
299.9	Other unspecified childhood psychosis
307.0	Stammering
307.2	Tics
307.3	Repetitive movements
307.4	Sleep disorders
307.5	Eating disorders
307.6	Enuresis
313	Disturbance of emotions specific to childhood and adolescence
314.0	Attention deficit disorder
315.x	Specific delays in development
317-319	Mental retardation

3. Other neurologic conditions:

Code	Description
343.x	Infantile cerebral palsy
345	Epilepsy
346	Migraine
348.x	Other conditions of brain (cysts, encephalopathy, compression, edema)
349.82	Toxic encephalopathy
349.9	Unspecified disorders of nervous system
356.4, 356.8, 356.9	Idiopathic progressive and unspecified polyneuropathy
357.8, 357.9	Other and unspecified polyneuropathies

358.2, 358.8, 358.9	Toxic and other myoneural disorders
359.4, 359.8, 359.9	Toxic and other myopathies

4. Renal conditions

Code	Description
580 (exc. 580.81)	Acute glomerulonephritis
581 (exc. 581.81)	Nephrotic Syndrome
582 (exc 582.81)	Chronic glomerulonephritis
583 (exc. 583.81)	Not specified as acute or chronic nephritis and nephropathy
584, 585	Acute and chronic renal failure
586	Unspecified renal failure
593.9	Unspecified disease of kidney and ureter

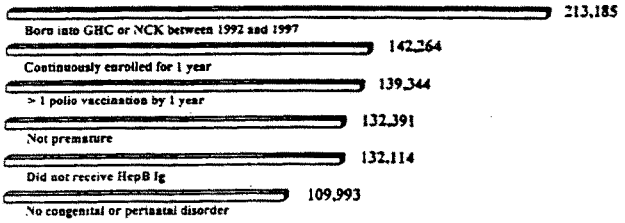
Statistical analyses

We used a Cox proportional hazard model to compare risk of developing any of the outcomes among different levels of exposure. By stratifying on HMO, year and month of birth, we compared children born within the same month at the same HMO. We adjusted the models for gender only. By using age of the child as the time variable in the PH model we also ensured comparison of children of equal age. As endpoint we used whichever of the following occurred first: the date of first diagnosis, the date of first disenrollment from the HMO or the last day of the follow-up period, December 31, 1998. To obtain 80% power in identifying a minimal relative risk of 2, we estimated the minimal number of cases for any outcome to be 50. We subsequently evaluated the impact of increased mercury exposure on the risk of any individual outcome for which we identified at least 50 cases. Because of different coding practices between HMOs and uncertainty on the specific neurologic and renal outcomes related to mercury exposure, we also assessed the risk for the entire categories of neurologic degenerative, neurodevelopmental and renal disorders, respectively. The category of other neurologic disorders was felt to be too heterogeneous for a similar approach. For the disorders of which we identified at least 50 cases among premature infants, we performed separate analyses for premature infants.

Results

The following table illustrates the number of children included in the cohort and the effect of the different eligibility criteria:

Table1. Number of children included:



The final number of children thus included in our cohort was 109,993.

The following graph shows the distribution of the cumulative mercury exposure at 1,2,3 and 6 months of age

Graph 1. Distribution of the cumulative mercury exposure at 1,2,3 and 6 months of age

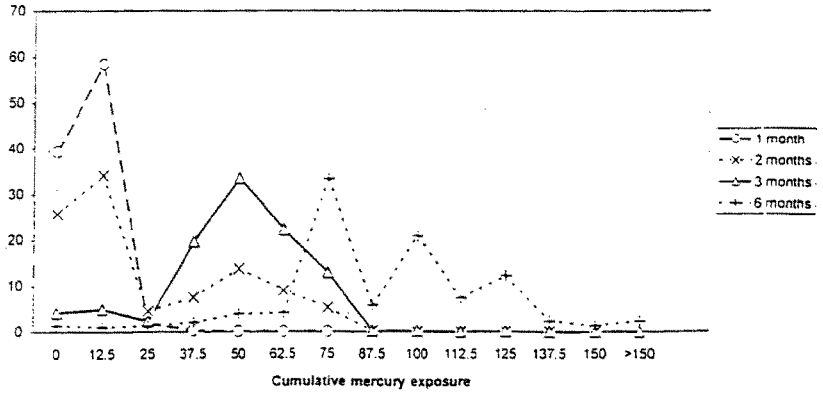


Table 2 shows the number of cases encountered for each disorder, the mean age at first diagnosis, the distribution over the two HMOs and the percentage males among cases.

Table 2. Number of children identified per disorder and some characteristics

				Site (%)		Male (%)
Code	Description	Total	Age *	GHC	NCK	
ALL kids		109,993		14	86	51
Neurologic degenerative disorders:		112	28	27	73	68
330.x	Cerebral degenerations usually	4	25	25	75	50
331.x	Other cerebral degenerative disease	35	19	17	83	69
333.x	Other extrapyramidal disease and	63	33	35	65	70
334.x	Spinocerebellar disease	9	27	11	89	44
335.x	Anterior horn cell disease	9	21	25	75	50
Neurologic developmental disabilities:		3114	32	36	64	69
299.0	Autism	127	42	14	86	83
299.8	Other childhood psychosis	51	49	22	78	92
299.9	Other unspecified psychosis	31	45	100	0	84
307.0	Stammering & stuttering	105	40	51	49	71
307.2	Tics	104	44	36	64	67
307.3	Repetitive movements	2	20	100	0	50
307.4	Sleep disorders	150	27	42	58	57
307.5	Eating disorders	78	21	9	91	53
307.6	Enuresis	20	59	10	90	70
313	Disturbance of emotions specific to	28	35	54	46	66
314.0	Attention deficit Sy	374	49	20	80	80
31531	Developmental language delay	351	34	4	96	74
31539	Developmental speech delay	1533	33	38	62	71
3159	Unspecified developmental delay	555	25	50	50	65
317-319	Mental retardation	17	48	12	88	63
Other neurologic conditions:		442	28	15	85	54
343.x	Infantile cerebral palsy	98	22	17	83	56
345	Epilepsy	236	26	9	91	56
346	Migraine	50	48	22	78	50
348.x	Other conditions of brain	30	23	30	70	51
349.82	Toxic encephalopathy	0				
349.9	Unspecified disorders of nervous	49	29	14	86	53
356.x	Idiopathic polyneuropathy	3	32	0	100	100
357.x	Other polyneuropathies	0				
358.x	Toxic and other myoneural	6	26	67	33	67
359.x	Toxic and other myopathies	8	25	13	87	63
Renal conditions:		151	23	17	87	50
580	Acute glomerulonephritis	3	57	67	33	67

581	Nephrotic Sy	17	31	6	94	71
582	Chronic glomerulonephritis	8	21	75	25	88
583	Not specified as d nephropathy	43	21	16	84	51
584	Acute renal failure	10	24	10	90	50
585	Chronic renal failure	7	44	14	86	57
586	Unspecified renal failure	11	31	45	55	73
593.9	Unspecified disease of kidney	95	25	13	87	54

* at first diagnosis, in months

Results for risk estimates are given first for the cumulative mercury exposure as a continuous variable assessed at 1,2, 3 and 6 months of age. Table 3 shows the number of cases occurring any time after the point at which the exposure is assessed, the relative risk estimate, and its 95% confidence intervals, associated with an increase of 1 microgram of cumulative mercury exposure at 1, 2 ,3 or 6 months of age.

For illustrative purposes we also show the relative risks for categories of increasing mercury exposure at three months of age. These are given in graphs 1 – 20 with their 95% confidence intervals and interconnected to illustrate potential trends. Note that the Y axis can be on a linear or logarithmic scale, depending on the magnitude of the CIs. For most of these analyses the reference category is the group with less then 37.5 µg of ethylmercury cumulative exposure at three months. For the most frequent disorders, the reference category is the 0 exposure group.

For completeness we also add the results of analyses of the cumulative exposure at 1 and 3 months of age compared to EPA guidelines in table 4.

Table 5 gives these results for premature infants, not excluding those with congenital or perinatal disorders, and restricted to neurodevelopmental disorders, speech and unspecified delay, for sample size purposes.

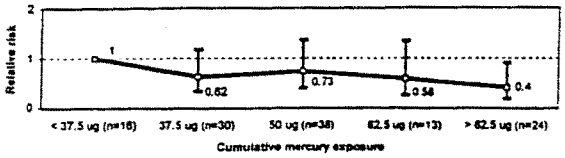
In the following tables, statistically significant results (not adjusting for multiple comparisons) are bolded.

Table 3 Relative Risk associated with an increase at 1, 2 ,3 or 6 months of age of 1 microgram of cumulative mercury exposure and its 95% confidence intervals.

Code	Description	Cases*	RR + 95% CI			
			1 month	2 months	3 months	6 months
Neurologic Degenerative Disorders		121	0.991 (0.964, 1.020)	0.994 (0.986, 1.010)	**0.987 (0.976, 0.999)**	0.994 (0.986, 1.001)
333	Extrapyradianal disease	63	1.003 (0.966, 1.042)	1.004 (0.993, 1.014)	1.003 (0.985, 1.022)	1.000 (0.990, 1.011)
Neurologic Developmental Disorders		3179	**1.007 (1.002, 1.012)**	1.001 (1.000, 1.002)	**1.007 (1.004, 1.010)**	**1.003 (1.001, 1.004)**
299.0	Autism	127	1.008 (0.983, 1.034)	1.003 (0.996, 1.011)	1.005 (0.991, 1.019)	0.999 (0.992, 1.007)
2998	Childhood psychosis	51	0.987 (0.946, 1.030)	1.000 (0.988, 1.012)	1.002 (0.980, 1.022)	1.001 (0.989, 1.013)
307.0	Stammering	105	0.983 (0.951, 1.017)	1.004 (0.996, 1.012)	1.007 (0.989, 1.025)	1.005 (0.997, 1.013)
307.2	Tics	104	1.05 (0.986, 1.045)	1.006 (0.998, 1.014)	**1.021 (1.004, 1.039)**	1.008 (1.000, 1.015)
307.4	Sleep disorders	151	1.003 (0.977, 1.028)	1.002 (0.995, 1.008)	1.004 (0.991, 1.018)	1.000 (0.994, 1.007)
307.5	Eating disorders	78	0.994 (0.961, 1.027)	0.997 (0.986, 1.007)	1.004 (0.986, 1.022)	1.000 (0.991, 1.060)
313.1	Misery disorder	158	1.016 (0.990, 1.044)	1.003 (0.995, 1.008)	1.005 (0.989, 1.021)	0.997 (0.989, 1.006)
313.8	Mixed emotional	156	0.991 (0.916, 1.016)	0.996 (0.989, 1.002)	1.000 (0.988, 1.012)	1.002 (0.996, 1.009)
314.0	Attention deficit Sy	377	1.006 (0.990, 1.021)	1.000 (0.996, 1.005)	1.008 (1.000, 1.016)	**1.006 (1.001, 1.010)**
315.31	Language delay	351	**1.019 (1.004, 1.034)**	1.003 (0.999, 1.008)	**1.021 (1.012, 1.030)**	**1.006 (1.002, 1.011)**
315.39	Speech delay	1533	**1.011 (1.004, 1.019)**	1.001 (0.999, 1.003)	**1.008 (1.004, 1.013)**	**1.002 (1.000, 1.004)**
315.9	Unspecified delays	555	1.005 (0.992, 1.019)	**1.005 (1.001, 1.008)**	**1.007 (1.000, 1.014)**	1.001 (0.997, 1.005)
Other neurologic conditions:						
343.x	Infantile cerebral palsy	98	0.976 (0.945, 1.008)	0.995 (0.985, 1.002)	0.993 (0.979, 1.007)	1.000 (0.992, 1.009)
345	Epilepsy	240	1.011 (0.993, 1.030)	1.002 (0.997, 1.008)	1.004 (0.994, 1.014)	1.000 (0.994, 1.005)
346	Migraine	50	0.981 (0.945, 1.028)	1.001 (0.990, 1.012)	1.018 (0.995, 1.042)	0.994 (0.983, 1.005)
Renal conditions:		164	0.992 (0.969, 1.016)	1.000 (0.994, 1.007)	0.994 (0.983, 1.006)	1.000 (0.993, 1.006)
593.9	Unspecified	106	1.003 (0.975, 1.032)	1.004 (0.995, 1.013)	1.003 (0.987, 1.019)	1.003 (0.994, 1.012)

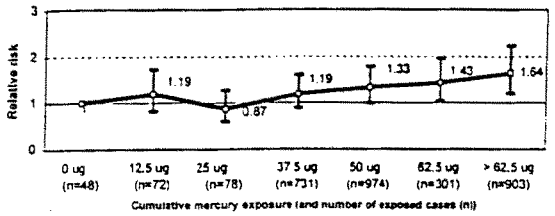
* occurring after 1 month of age

Graph 1: Relative risk + 95 % *CI* of Degenerative neurologic disorders after different exposure levels of thimerosal at 3 months of age, NCK &GHC, Cycle 7



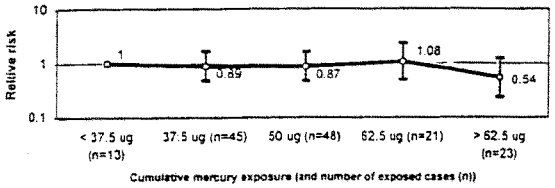
Trend:
0.987/ug
p = 0.03

Graph 2: Relative risk + 95 % *CI* of Developmental neurologic disorders after different exposure levels of thimerosal at 3 months of age, NCK &GHC, Cycle 7



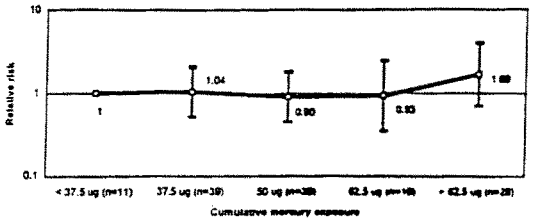
Trend:
1.007/ug
p < 0.01

Graph 3: Relative risk + 95 % *CI* of Renal disorders after different exposure levels of thimerosal at 3 months of age, NCK &GHC, Cycle 7



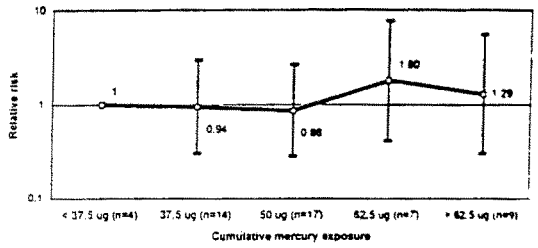
Trend:
0.994/ug
p = 0.71

Graph 4: Relative risk + 95 % *CI* of Autism after different exposure levels of thimerosal at 3 months of age, NCK &GHC, cycle 7



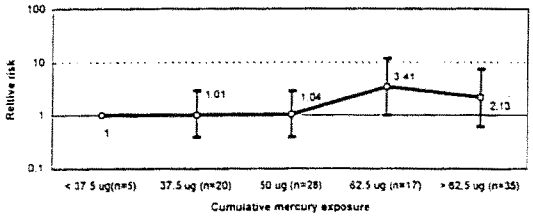
Trend:
1.005/ug
p = 0.48

Graph 5: Relative risk + 95 % *CI* of Childhood psychosis after different exposure levels of thimerosal at 3 months of age, NCK &GHC, cycle 7



Trend:
1.002/ug
p=0.94

Graph 6: Relative risk + 95 % *CI* of Stammering after different exposure levels of thimerosal at 3 months of age, NCK &GHC, cycle 7



Trend:
1.007/ug
p = 0.45

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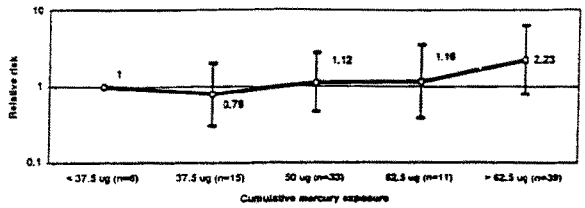
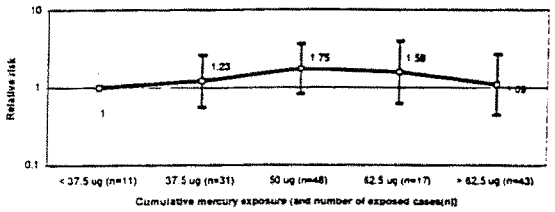
Graph 7: Relative risk + 95 % *CI* of Tics after different exposure levels of thimerosal at 3 months of age, NCK &GHC, cycle 7



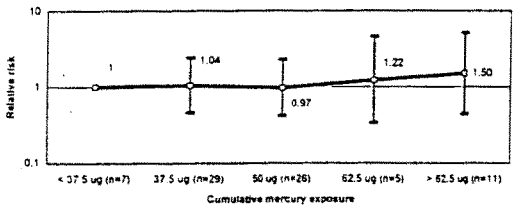
Trend:
1.021/ug
p = 0.02

Graph 8: Relative risk + 95 % *CI* of Sleep disorders after different exposure levels of thimerosal at 3 months of age, NCK &GHC, cycle 7



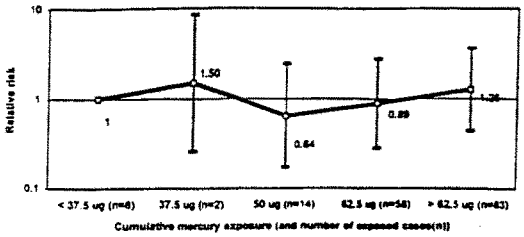
Trend:
1.004/ug
p = 0.51

Graph 9: Relative risk + 95 % *CI* of Eating disorders after different exposure levels of thimerosal at 3 months of age, NCK &GHC, cycle 7



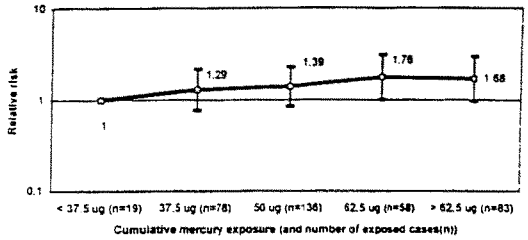
Trend
1.004/ug
p = 0.66

Graph 10: Relative risk + 95 % *CI* of Misery and Unhappiness Disorder after different exposure levels of thimerosal at 3 months of age, NCK &GHC, cycle 7



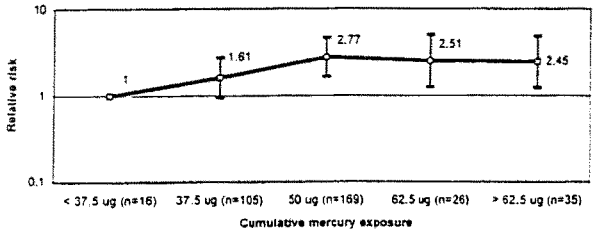
Trend
1.005/ug
p = 0.54

Graph 11: Relative risk + 95 % *CI* of Attention Deficit Disorder after different exposure levels of thimerosal at 3 months of age, NCK &GHC, cycle 7



Trend
1.008/ug
p = 0.06

Graph 12: Relative risk + 95 % *CI* of Developmental language disorder after different exposure levels of thimerosal at 3 months of age, NCK &GHC, cycle 7



Trend
1.021
p < 0.01

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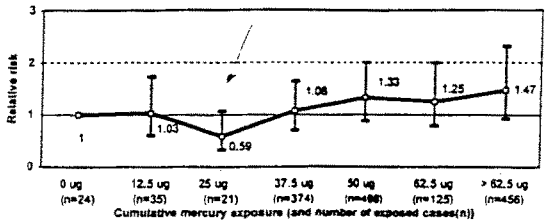
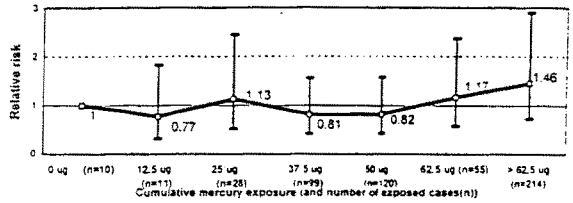
Graph 13: Relative risk + 95 % CI of Developmental speech disorder after different exposure levels of thimerosal at 3 months of age, NCK &GHC, cycle 7



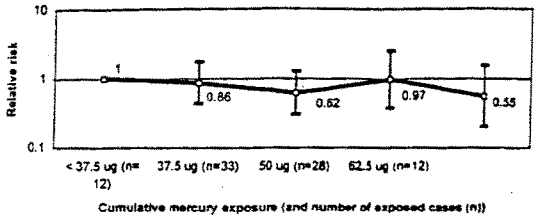
Trend
1.008/ug
p < 0.01

Graph 14: Relative risk + 95 % CI of Unspecified delay in development after different exposure levels of thimerosal at 3 months of age, NCK &GHC, cycle 7



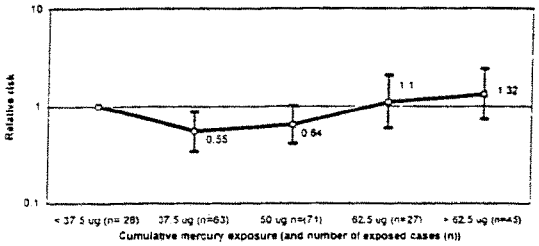
Trend
1.007/ug
p = 0.07

Graph 15: Relative risk + 95 % *CI* of Infantile cerbral palsy after different exposure levels of thimerosal at 3 months of age, NCK &GHC



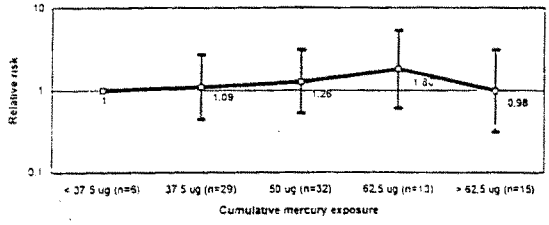
Trend
0.993/ug
p = 0.30

Graph 16: Relative risk + 95 % *CI* of Epilepsy after different exposure levels of thimerosal at 3 months of age, NCK &GHC



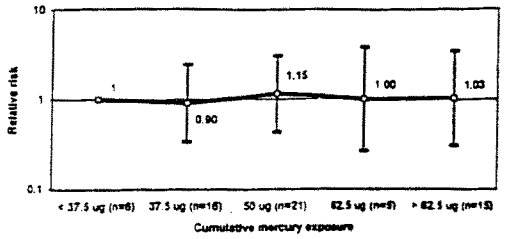
Trend
1.004/ug
p = 0.45

Graph 17: Relative risk + 95 % *CI* of Unspecified kidney or ureter disorder after different exposure levels of thimerosal at 3 months of age, NCK &GHC



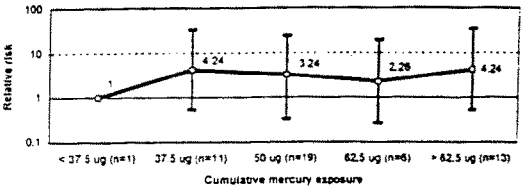
Trend
1.003/ug
p = 0.71

Graph 18: Relative risk + 95 % CI of Extrapyramidal disorders after different exposure levels of thimerosal at 3 months of age, GHC & NCK, Cycle7



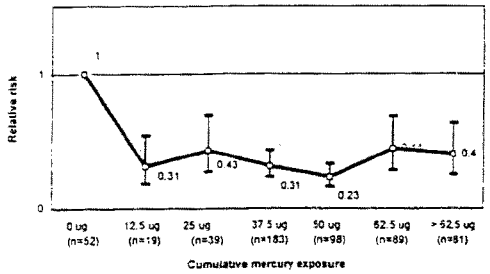
Trend
1.003/ug
p = 0.75

Graph 19: Relative risk + 95 % CI of Migraine after different exposure levels of thimerosal at 3 months of age, GHC & NCK, Cycle 7



Trend
1.018/ug
p = 0.13

Graph20: Relative risk + 95 % CI of Developmental neurologic disorders among prematures after different exposure levels of thimerosal at 3 months of age



Trend
0.985/ug
p < 0.01

Table 4. Relative risk + 95 % confidence intervals for exposure assessed as exceeding or not the EPA guideline at 1 and 3 months of age (reference category not exceeding guideline)

Code	Description	Cases	RR – 95% CI	
			1 month	3 months
Neurologic Degenerative Diorders		121	0.92 (0.62, 1.35)	0.92 (0.59, 1.43)
333	Extrapyramidal disorders	63	1.12 (0.65, 1.94)	1.22 (0.66, 2.24)
Neurologic Developmental Disorders		3179	**1.14 (1.05, 1.24)**	**1.19 (1.08, 1.30)**
299.0	Autism	127	1.01 (0.71, 1.48)	0.94 (0.62, 1.42)
299.8	Childhood psychosis	51	0.85 (0.47, 1.56)	0.99 (0.50, 1.95)
307.0	Stammering	105	0.87 (0.55, 1.37)	1.14 (0.65, 2.01)
307.2	Tics	104	1.28 (0.82, 2.01)	1.46 (0.85, 2.58)
307.4	Sleep disorders	151	1.03 (0.71, 1.48)	1.43 (0.93, 2.19)
307.5	Eating disorders	78	0.87 (0.55, 1.39)	0.99 (0.60, 1.62)
313.1	Misery disorder	158	**1.96 (1.09, 3.52)**	0.98 (0.58, 2.55)
313.8	Mixed emotional	156	0.88 (0.62, 1.25)	0.76 (0.50, 1.14)
314.0	Attention deficit Sy	377	1.04 (0.83, 1.30)	1.20 (0.91, 1.57)
315.31	Language delay	351	**1.44 (1.16, 1.78)**	**1.85 (1.46, 2.33)**
315.39	Speech delay	1533	**1.21 (1.08, 1.35)**	**1.30 (1.14, 1.48)**
315.9	Unspecified delays	555	1.17 (0.91, 1.36)	1.09 (0.86, 1.39)
Other neurologic conditions:				
343.x	Infantile cerebral palsy	98	0.75 (0.48, 1.16)	0.72 (0.44, 1.16)
345	Epilepsy	240	1.20 (0.92, 1.57)	1.13 (0.84, 1.52)
346	Migraine	50	0.84 (0.44, 1.61)	1.05 (0.48, 2.29)
Renal conditions:		164	0.93 (0.66, 1.29)	0.84 (0.58, 1.22)
593.9	Unspecified	106	1.11 (0.73, 1.70)	1.18 (0.74, 1.90)

Table 5. Relative Risk associated with an increase at 1, 2 ,3 or 6 months of age of 1 microgram of cumulative mercury exposure and its 95% confidence intervals among premature infants.

Code	Description	Cases	RR – 95% CI	
			1 month	2 months
NDD		582	**0.968 (0.955, 0.983)**	**0.994 (0.990, 0.998)**
315.39	speech delay	155	0.995 (0.971, 1.019)	0.994 (0.986, 1.002)
315.9	Unspecified delays	300	**0.951 (0.930, 0.974)**	**0.994 (0.988, 0.999)**

Code	Description	Cases	RR + 95% CI	
			3 months	6 months
NDD			**0.985 (0.980, 0.991)**	0.998 (0.995, 1.02)
315.39	speech delay		0.994 (0.982, 1.005)	0.999 (0.992, 1.007)
315.9	Unspecified delays		**0.980 (0.973, 0.987)**	0.997 (0.991, 1.002)

Code	Description	Cases	RR + 95% CI	
			EPA at 1 month	EPA at 3 months
NDD			**0.58 (0.47, 0.71)**	**0.69 (0.56, 0.85)**
315.39	speech delay		0.89 (0.62, 1.27)	0.95 (0.65, 1.40)
315.9	Unspecified delays		**0.44 (0.31, 0.60)**	**0.65 (0.48, 0.88)**

Discussion

Limitations

- Some misclassification errors may have occurred in the assessment of the inclusion/exclusion criteria: some HepB Ig administrations may be missed, some premature children may not be classified as such. In case of a true effect of thimerosal, this error is likely to cause a bias towards the null hypothesis.

- A lack of specificity in the ICD9 codes for congenital or perinatal disorders may have caused exclusion of children that were not at higher risk for developmental disorders and/or lower risk for vaccination. This error is likely to have decreased the power. Including all children regardless of these disorders results in moderate changes in results towards the null.

- Some misclassification error may have occurred in the exposure assessment: some vaccinations, particularly the neonatal HepB dose may not have been reported. We estimated that approximately 4 and 18 % of these are missed at NCK and GHC respectively. In case of a true effect of thimerosal, this error is likely to cause a bias towards the null hypothesis.

- We were not able to differentiate, using the available automated data, between single dose thimerosal free Hib vaccines and multi-dose thimerosal containing Hib vaccines. The analyses were done assuming all vaccines to come from multi-dose vials. An

analysis assuming all Hib vaccines to come from single dose-vials did not substantially alter the results. An ongoing FDA effort to resolve this question based upon the lot numbers has revealed that about 1 % of the Hib vaccines may be Thimerosal free. In case of a true effect of thimerosal, this error would cause a bias towards the null hypothesis.

- We did not assess the exposure by bodyweight. The birthweight is available only for a subset of 10% of the cohort. We shall present analyses including birthweight at the June 7-8 meeting.

- Some misclassification error may have occurred in the outcome assessment: we used ICD9 codes from automated data that lack specificity for certain disorders and are prone to errors by the person (often administrative) coding and at data entry level. This error is likely to cause an error in the findings for some specific ICD9 codes that may not have an obvious clinical correlate such as 31539 (other developmental speech or language disorder) or 3159 (unspecified delay in development). There is no reason to think that this error would occur differentially among the exposure categories and it is therefore unlikely to affect the estimates.

- We had no information on potential predisposing factors, such as maternal smoking, lead exposure or fish consumption. It is not clear, however, how these factors would be related to the exposure measure and are felt to be unlikely to cause any bias.

- In the analyses using the cumulative mercury exposure, we could not differentiate between the difference in effect from the preservative or other component in the vaccines. Exposure to thimerosal from vaccines is invariably linked to the likelihood of being vaccinated with Hepatitis B, DTP or Hib. An analysis of DTP & Hib in combination vs separate suggests a thimerosal effect for at least a few disorders, particularly among prematures.

- We have limited our analyses to a list of potential outcomes based on prior knowledge of adverse conditions found in infants exposed to high doses of methylmercury. We cannot rule out other disorders potentially related to exposure to ethylmercury.

- We were able to evaluate only relatively severe conditions that come to medical attention, and not possibly more subtle effects. Such an evaluation would require neuropsychological testing.
- The study was underpowered for some conditions, particularly the renal outcomes.
- Additional analyses addressing these limitations will be presented at the June 7-8 meeting.

Methylmercury

Neurotoxic Symptoms

- Tremors (initially hands)
- Emotional lability (irritable, shy)
- Insomnia
- Memory loss
- Neuromuscular (weakness, twitching, atrophy)
- Headaches
- Polyneuropathy
  - Parathesias
  - Stocking glove sensory loss
  - Hyperactive tendon reflexes
  - slowed sensory
  - motor nerve conduction velocities
- Performance deficits (cognitive & motor function tests)
- Hearing & visual loss hallucinations
- Photophobia (children)

Methylmercury

Typical Daily Consumption

- Infants (6-11mm) 0.49µg/day
- Children (2 yr.) 1.30 µg/day
- Females (25-30 yrs.) 2.90 µg/day
- Males (25-30 yrs.) 3.9 µg/day

Per Body weight basis, intake for all age groups

- ~ 0.05 µg/Kg/day (except 2 yr old)

120,000 Health Professions

- Females 8.2 µg/day (0.37-203) = 0.126 µg/Kg/day
- Males 8.6 µg/day (0.22-165) = 0.123 µg/Kg/day

Canadian

- Toddlers (3-4 yrs) 3.3 µg/day
- 5-11 yrs old 5.6 µg/day
- Teens 6.7 µg/day
- Adults 9.4 µg/day

FDA estimates average intake of total mercury is 50-100 µg/Kg/day.

Methylmercury

Seychellosis Child Development Study

- 700 mother-infant pairs tested from parturition through 66 months of age.
- Mercury levels 10-20 times US
- Seychelles pristine environment
- Population highly literate
- Healthy population, low alcohol/tabacco use
- Developing fetuses exposed in utero
- Neonates exposed via breast feeding
- 6.8 ppm (0.5-26.7) mean maternal hair during pregnancy
- 6.5 ppm (0.9-25.8) mean child hair at 66 month age
- Six Neurobehavioral Tests conducted

"None of the tests indicated an adverse effect of methylmercury exposure".

"Four of the six measures showed better scores in the highest methylmercury-exposed groups.

Methylmercury

Seychellois Neurobehavioral Tests

- (1) General; Cognitive Index (GCI) of the McCarthy Scales of Children's Abilities (to estimate cognitive ability);
- (2) the Preschool Language Scale (PLS) total score (to measure both expressive and receptive language ability);
- (3) the Letter and Word Recognition and
- (4) Applied Problems subtests of the Woodcock-Johnson (W-J) Tests of Achievement (to measure reading and arithmetic achievement);
- (5) the Bender Gestalt test (to measure visual-spatial ability); and
- (6) the total T score from the Child Behavior Checklist (CBCL) (to measure the child's social and adaptive behavior).

Methylmercury

Faroe Islands

- 917 children 7 years of age tested
- The neuropsychological testing indicated mercury-related dysfunction of language, attention-memory, and visuospatial and motor function remained after the children and women with maternal hair mercury above 10 ppm were excluded.

Amazon River Basin

- 91 Adults (15-31 yrs) with hair mercury <50ppm
- Clinical examinations normal
- Displayed disorganized movements (alternating movement task)
- Highest mercury levels-some restricted visual fields

Mancora Peru

- 131 infant-mother pairs
- Maternal hair 8.3 ppm (1.2-30)
- No neurodevelopment abnormalities in children

Methylmercury

Hair: Blood Ratios

- 250 (140-416)
- One-half life methylmercury blood ~ 50 days
  - ✓4 week lag in hair
- Seychellosis

  15.3 ppm hair (parturition) (12-26.7)
  - ✓0.061 mg/L blood (ppm)
  - ✓0.075 mg/day daily intake equal to blood
  - ✓0.0013 mg/Kg.day

  6.8 ppm hair
  - ✓0.027 mg/l blood (ppm)
  - ✓0.034 mg/day
  - ✓0.0006 mg/Kg/day

- Thimerosal (12.5 –25 µg/day ethylmercury)
  - ✓Seychellosis = 27 µg/l
  - ✓Daily intake .50 – 1.3 µg/day (0.05 µg/Kg/day)

Mercury

Stajich et al (2000) (term)

Blood Mercury	
Newborn pre-vac	48-72 hr post-vac.
0.09 ug/l	2.24 ug/l

Ethyl mercury

12.5 ug	≠ 2.25 ug/l	Cumulative?
25.10 ug	≠ 5.5 ug/l	
50 ug	≠ 11.0 ug/l	

Seychellosis (Continuous Exposure - In Utero, Neonate (breastfed))

Mothers	Daily Intake	Blood (calculated)
6.8 ppm hair (mean)	34 ug/day	27 ug/l
15 ppm hair (high grp)	75 ug/day	61 ug/l
children		
6.5 ppm hair (mean)		~25 ug/l

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Assessment of neurologic and renal impairment associated with Thimerosal-containing vaccines.

Thomas Verstraeten
National Immunization Program

CDC

1

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Study phases & objectives

- Phase I: Screen automated data for signals
- Phase II: Hypothesis testing through:
  - case-control involving chart reviews
  - cohort study involving neuropsychological testing
  - alternative data bases

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Study design Phase I

- Cohort study of automated VSD data
- Exposure: mercury from thimerosal-containing childhood vaccines at different ages
- Outcomes: range of plausible neurologic and renal disorders

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3

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Study population

- Born between 1992 and 1997
- Born into one of two HMOs of VSD:
  - Northern California Kaiser
  - Group Health Cooperative
- Continuously enrolled first year
- Received at least 2 polio vaccinations by 1 year of age *

*: added to original protocol

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Study population: excluded infants

- Prematures (separate analyses)
- Recipients of HepB immunoglobulins *
- Congenital or severe perinatal disorders *

*: added to original protocol

5

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Exposure assessment

- Cumulative mercury exposure calculated from individual automated vaccination records
- Assessed at 1,2,3,and 6 months of age
- Categorized by levels of 12.5 ug mercury
- Assumption: all conjugate Hib vaccine thimerosal containing

6

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Outcome definition

Neurologic Developmental disorders (NDD)

ICD9 codes & disorders

- 299: childhood psychosis (incl. autism)
- 307: specific psychopathological symptoms (incl. stammering, tics)
- 313: emotional disturbances
- 314: hyperkinetic syndrome
- 315: specific developmental delays (incl. speech and coordination disorders)
- 317 - 319: mental retardation

} largest group

} very small group

CDC

1

also of "degenerative" neuro disorders & "other" neuro disorders

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Outcome definition

Renal disorders } lumped into one category.

ICD9 codes & disorders

- 580, 581, 583: acute, chronic and unspecified glomerulonephritis
- 582: nephrotic syndrome
- 584 - 586: acute, chronic and unspecified renal failure
- 593.9: unspecified kidney and ureter disease

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Statistical analyses

- Proportional hazards models
- Stratified on HMO, year and month* of birth
- Adjusted for gender – (the only adjustment factor)
- Separate analysis for each disorder with n >=50

*: added to original protocol

compare cases & controls in same HMO & same birth month

9

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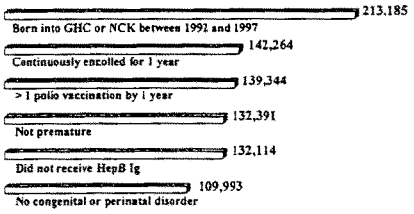
Results: eligible children



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Vaccines contributing to mercury distribution at three months

Category	Frequency	Combinations
0 ug	2493 (2.3%)	No vaccines
12.5 ug	3039 (2.8%)	1 HepB only
25 ug	3863 (3.5%)	2 HepB, 0 DTP, 0 Hib (25%) 0 HepB, 1 DTP-Hib (75%)
37.5 ug	33839 (30.8%)	1 HepB, 1 DTP-Hib
50 ug	35951 (32.7%)	2 HepB, 1 DTP-Hib (75%) 0 HepB, 1 DTP, 1 Hib (25%)
62.5 ug	11635 (10.6%)	1 HepB, 1 DTP, 1 Hib
75 ug	18855 (17.1%)	2 HepB, 1 DTP, 1 Hib
> 75 ug	299 (0.3%)	> 1 DTP, > 1 Hib, + flu

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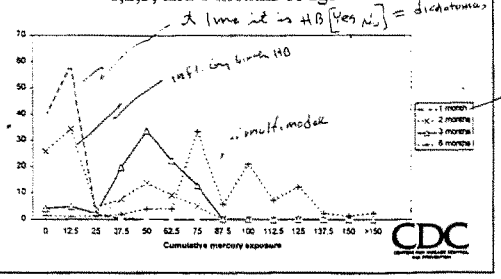
Cumulative ethylmercury exposure from thimerosal-containing vaccines: 1,2,3, and 6 months of age



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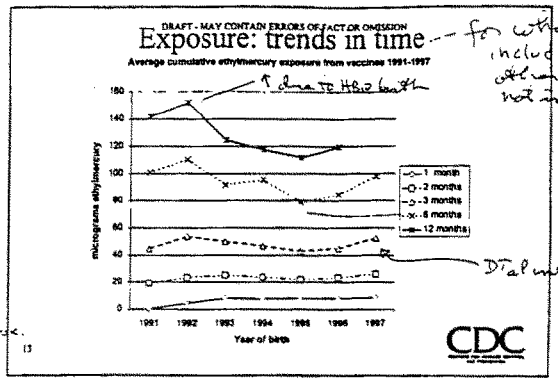

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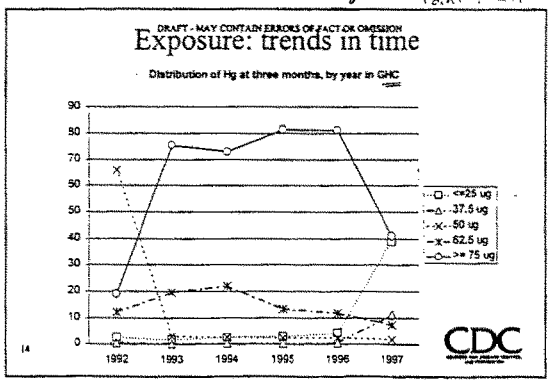

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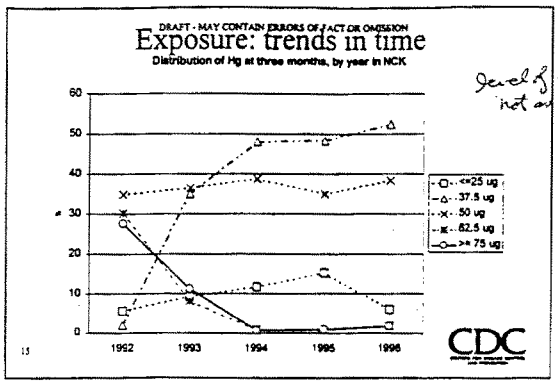

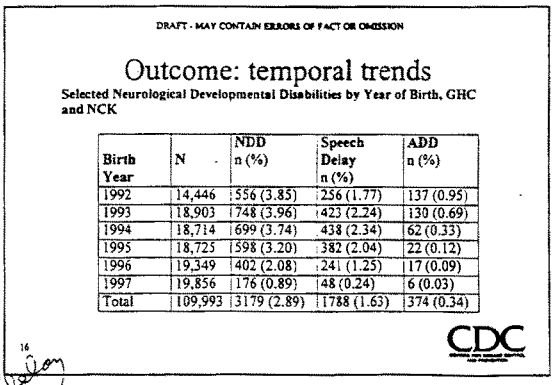

Birth Year	N	NDD n (%)	Speech Delay n (%)	ADD n (%)
1992	14,446	556 (3.85)	256 (1.77)	137 (0.95)
1993	18,903	748 (3.96)	423 (2.24)	130 (0.69)
1994	18,714	699 (3.74)	438 (2.34)	62 (0.33)
1995	18,725	598 (3.20)	382 (2.04)	22 (0.12)
1996	19,349	402 (2.08)	241 (1.25)	17 (0.09)
1997	19,856	176 (0.89)	48 (0.24)	6 (0.03)
Total	109,993	3179 (2.89)	1788 (1.63)	374 (0.34)

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Outcome vs exposure: crude incidence rates

Selected Neurological Developmental Disabilities by Cumulative Hg Exposure at 3 months, GHC and NCK

Cumulative Hg exposure	N	NDD n (rate*)	Speech Delay n (rate*)	ADD n (rate*)
0	2,493	49 (7.5)	26 (4.0)	
12.5	3,035	73 (8.6)	40 (4.4)	19 (1.0)
25	3,864	84 (8.6)	25 (2.4)	
37.5	33,832	734 (7.9)	453 (4.8)	78 (0.8
50	35,940	983 (9.9)	611 (6.0)	136 (1.4)
62.5	11,631	310 (11.5)	149 (5.4)	58 (2.1)
>75	19,148	946 (19.0)	484 (9.4)	83 (1.6)

* per 1,000 person-year

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Outcome vs exposure: crude incidence rates by HMO

Incidence Rates of Neurological Developmental Disabilities and Speech Delay by Cumulative Mercury Exposure at 3 Months

Cumulative Hg exposure	Speech Delay (rate per 1,000 child-years)		ADD (rate per 1,000 child-years)	
	NCK	GHC	NCK	GHC
0	4.7	13.0	0.7	4.1
12.5	5.4	13.8	1.1	1.7
25	2.8	8.3	0.5	0.8
37.5	6.4	5.0	0.8	0.0
50	7.0	14.7	1.3	2.5
62.5	4.5	14.9	2.7	0.8
>75	4.6	19.0	1.9	1.5
Total	6.1	17.2	1.2	1.6

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Summary of Descriptive Analyses

- Exposure varies by HMO and time
- Outcomes vary by HMO and time
- Difficult to interpret crude results
- Need to account for temporal trends and differences by HMO in analysis

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So 2x2 tables would have lots of potential confounding

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Results: risk calculations

- Compared in total 17 individual (out of 38 "plausible") and 3 grouped outcomes to 7 measures of exposure
- Statistically significant relationships:
  - exposure at 2 months of age and unspecified developmental delay
  - exposure at 3 months of age and tics
  - exposure at 6 months of age and attention deficit disorder
  - exposure at 1, 3 and 6 months of age and language and speech delay
  - exposure at 1, 3 and 6 months of age and neurodevelopmental delays in general.

20

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those with ≥ 50 cases

cont @ 1, 7, C

categor @ 3 mo

dichot 1 mo, 3 mo using EPA cut off to define Hi/Low

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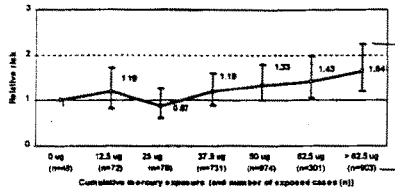
Relative risk associated with exposure at 3 months of age: neurologic developmental disorders (NDD)



Trend: 1.007 (1.004, 1.010), p < 0.01

21

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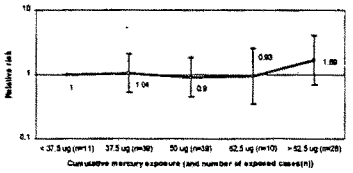
Relative risk associated with exposure at 3 months of age (NDD): Autism (ICD9 2990)



Trend:1.005 (0.991, 1.019), p = 0.48

22

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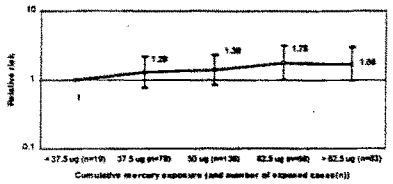
Relative risk associated with exposure at 3 months of age (NDD): attention deficit disorder (ICD9 3140)



Trend: 1.008 (1.000, 1.016), p = 0.06

23

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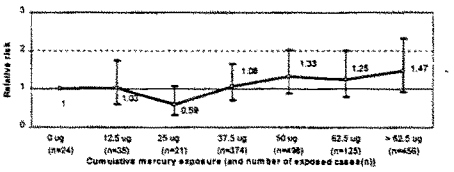
Relative risk associated with exposure at 3 months of age (NDD): speech delays (ICD9 31539)



Trend: 1.008 (1.004, 1.013), p = 0.0004

24

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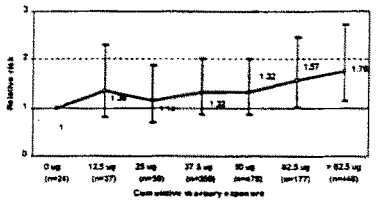
Relative risk associated with exposure at 3 months of age (NDD): All excluding speech delay



Trend:1.005 (1.001, 1.009)

25

this is NDD minus the speech delay dx

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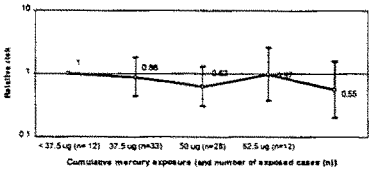
Relative risk associated with exposure at 3 months of age :Cerebral palsy(ICD9 343)



Trend:0.993 (0.979, 1.007), p = 0.30

26

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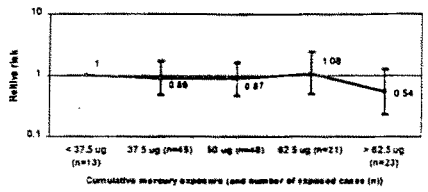
Relative risk associated with exposure at 3 months of age: renal disorders



Trend: 0.994 (0.983, 1.006), p = 0.71

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27

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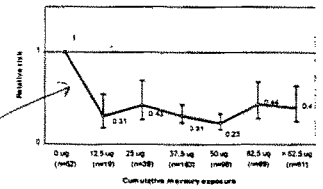
Relative risk associated with exposure at 3 months of age *among prematures*: neurologic developmental disorders (NDD)



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28

test for trent is 55 negative driven by the 0µg vs > 0µg

his conclusion — those @ high risk are not getting vaccinated.

B01297

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Exposure: by birthweight

- Based on linkage to state birth files
- Only at Group health Cooperative
- Only for approx 10,000 children

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Exposure: by birthweight

Selected Neurological Developmental Disabilities by Cumulative Hg Exposure at 3 months / Birthweight GHC

Cumulative Hg / birthweight exposure	N (%)	NDD n (%)	Speech Delay n (%)	ADD n (%)
0-14 ug/kg	1651 (17)	148 (9.0)	90 (5.5)	17 (1.0)
15-17 ug/kg	1807 (19)	131 (7.3)	80 (4.3)	6 (0.4)
18-20 ug/kg	2707 (28)	256 (9.5)	159 (5.9)	17 (0.6)
21-23 ug/kg	2088 (22)	148 (7.1)	82 (3.9)	13 (0.6)
>23 ug/kg	1376 (14)	140 (10.3)	57 (4.1)	9 (0.7)

approximating birth weight quintiles

30

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B01298

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Exposure: by birthweight

ICD9	Exposure	Sub-analysis	RR + 95% CI
3140	Birthweight in kilos		0.86 (0.53, 1.37)
(ADD)	Cumulative at 3 months	Stratified on BW (categories of 250g)	1.006 (0.982, 1.030)
	Cumulative/Birthweight		1.025 (0.872, 1.081)
31539	Birthweight in kilos		1.20 (1.06, 1.36)
(speech)	Cumulative at 3 months	Stratified on BW (categories of 250g)	1.006 (0.998, 1.015)
	Cumulative/Birthweight		0.987 (0.968, 1.006)
NDD	Birthweight in kilos		0.92 (0.81, 1.05)
	Cumulative at 3 months	Stratified on BW (categories of 250g)	1.007 (1.001, 1.014)
	Cumulative/Birthweight		1.025 (1.010, 1.040)

31

CDC

expected

unexpected heavier babies more speech delayed

strat. on Bw ↑ not effected — by Bw - it does effect relative

DRAFT - MAY CONTAIN ERRORS OF FACT OR OMISSION

Limitations

- Misclassification exposure
  - HepB birthdose
  - Thimerosal free Hib
  - Limited (birth) weight information
- Misclassification outcome: ICD9 codes
- Unknown: medical care utilization factors
- Only conditions that come to medical attention
- Insufficient power for some conditions

32

CDC

more thing have lots of Hib = FDA has said that ± 1% of Hib was thimerosal free

the speaker said

The same parents who bring children for vaccination may be more likely to have developmental delay strat - SAME can be said for providers differing in some way

This is a central concern of mine & of theirs

a person Alec Walton also asked this

B01299

6/6/00

DRAFT
May contain error of fact or omission

DRAFT - MAY CONTAIN ERRORS OF FACT OR OMISSION

Discussion

- Inconsistency:
  - No association among premature infants
- Exclusion congenital & perinatal disorders
- Variation in exposure
- Effect thimerosal vs other (aluminum, number antigens ...)

33

CDC

thus the association could be argued to be not due to Hg but due to number of antigens given

DRAFT - MAY CONTAIN ERRORS OF FACT OR OMISSION

Discussion

- This screening analysis suggests a possible association between certain neurologic developmental disorders (i.e. tics, ADD, speech and language disorders) and exposure to mercury from thimerosal containing vaccines before the age of 6 months
- No association was found for renal disorders

34

CDC

B01300

these are visits

Exp	Well Child < 3m	Well child < 12	~~OR~~ < 3	~~OR~~ visits < 12
1 →	0.7 →	2.6 →	1.6 →	8.0
2	1.3	41 35	2.6 31	11.8 11.7
3	1.3	4.0	2.7	
4	1.4	35	2.4	10.5
5 6		32	30	9.5
7 →	1.6 →	36 →	36 →	10.5 11.5

these are diagnostic codes; not visits

Bob Davis
2 wk
2 mo
4 6
9 mo
12
than 2 URI's
.. get 12

he put this in model & did not affect

Paul Stehr Green – this won't control anterity bec correl dry siblings; answer could do in database

Draft - may contain error of fact or omission

Thimerosal - VSD study

Additional analyses

CDC

Areas of concern

- Exposure ascertainment
- Outcome ascertainment
- Cohort selection
- Confounders - Biases

CDC

Exposure - HepB birthdose

Assumed missing if:

- only 2 doses of Hep B by the age of 2 yrs, but all 4 DTP and Hib and 3 polio

3.8% and 16.5% missed at NCK and GHC

- only 1 dose of HepB by 6 months, but 2 DTP, Hib and Polio

4.2 % and 17.9% missed at NCK and GHC

CDC

Exposure - HepB birthdose

3 months results: stratification by HepB birth dose:

	HepB birth = 1	HepB birth = 0	Stratified
ADD	1.014 (0.998, 1.031)	1.007 (0.995, 1.019)	1.010 (1.000, 1.020)
Speech delay	1.004 (0.997, 1.012)	1.006 (0.999, 1.014)	1.005 (1.000, 1.011)
Unspecified delay	1.011 (0.998, 1.023)	1.002 (0.991, 1.014)	1.006 (0.998, 1.015)

CDC

Exposure - Thimerosal content Hib:
sensitivity analysis for 3m results

	Hibtiter Thimerosal containing	Hibtiter Thimerosal free
ADD	1.008 (1.000, 1.016)	1.009 (1.001, 1.018)
Speech delay	1.008 (1.004, 1.011)	1.007 (1.003, 1.011)
Unspecified delay	1.007 (1.000, 1.014)	1.008 (1.000, 1.015)

CDC

Exposure - influence high categories at 3 months

Code	Descripcion	RR + 95% CI (Ref. = 0 ug)	
		Hg <= 50 ug	
		n	RR
Neurologic developmental disabilities		1903	1.006 (1.002, 1.011)
299.0	Autism	89	0.997 (0.979, 1.014)
307.0	Stammering & stuttering	33	1.005 (0.976, 1.030)
307.4	Sleep disorders	90	1.018 (0.997, 1.039)
313	Disturbance of emotions specific to	132	0.994 (0.980, 1.009)
313.1	Misery and unhappiness disorder	24	Not estimated
313.8	Mixed emotional disturbances	102	0.994 (0.978, 1.009)
314.0	Attention deficit Sy	233	1.006 (0.994, 1.019)
315	Specific delays in development	1349	1.008 (1.003, 1.013)
315.39	Developmental speech delay	952	1.010 (1.004, 1.017)
315.9	Unspecified delays o development	268	0.997 (0.986, 1.007)
Other neurologic conditions			
343.x	Infantile cerebral palsy	73	0.993 (0.875, 1.012)
345	Epilepsy	162	0.991 (0.979, 1.004)
Renal conditions			
593.9	Unspecified disease of kidney	67	1.009 (0.985, 1.033)

CDC

Draft - may contain error of fact or omission

Exposure - influence high categories at 3 months

Code	Description	RR + 95% CI (Ref = 0 ug)	
		No HepB in first month	
		n	RR
Neurologic developmental disabilities:		1416	1.007 (1.002, 1.012)
299.0	Autism	69	1.001 (0.981, 1.022)
307.0	Stammering & stuttering	51	1.029 (0.999, 1.060)
307.4	Sleep disorders	67	1.009 (0.987, 1.031)
313	Disturbance of emotions specific to	126	1.500 (0.973, 1.035)
313.1	Misery and unhappiness disorder	31	Not estimated
313.8	Mixed emotional disturbances		1.000 (0.973, 1.035)
314.0	Attention deficit Sy	208	1.007 (0.995, 1.014)
315	Specific delays in development	1001	1.008 (1.002, 1.014)
315.39	Developmental speech delay	663	1.006 (0.991, 1.014)
315.9	Unspecified delays in development	224	1.002 (0.991, 1.014)
Other neurologic conditions:			
343.x	Infantile cerebral palsy	60	1.007/0.985, 1.029)
345	Epilepsy	116	1.000 (0.985, 1.016)
Renal conditions:			
593.9	Unspecified disease of kidney	46	Not estimated

CDC

Exposure - influence 0 category at 3 months

Code	Description	RR + 95% CI (Ref. = 0 ug)	
		Excluding 0 exposure	
		n	RR
Neurologic developmental disabilities:		3130	1.007 (1.004,1.011)
307.2	Tics	103	1.022 (1.003, 1.042)
314.0	Attention deficit Sy	367	1.009 (1.000, 1.019)
31531	Language delay	348	1.020 (1.010, 1.030)
315.39	Speech delay	1509	1.009 (1.001, 1.017)
315.9	Unspecified delays	527	1.009 (1.001, 1.017)

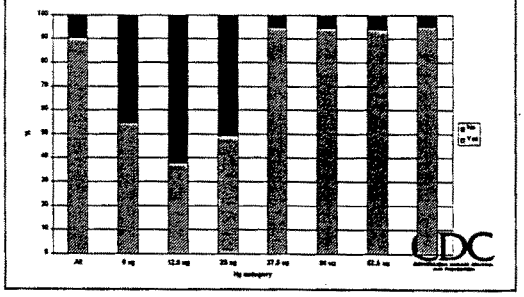
CDC

Exposure: correlation between exposure measures

	1 month	2 months	3 months	6 months	12 months
1 month	1	0.36	0.45	0.16	0.16
2 months		1	0.41	0.34	0.28
3 months			1	0.71	0.74
6 months				1	0.80
12 months					1

CDC

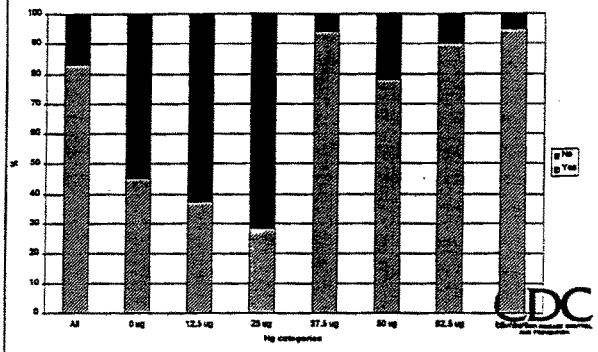
Exposure: Variation in exposure



Draft - may contain error of fact or omission

Exposure: Variation in exposure

Proportion of completion of recommended vaccine schedule by end of first year, including Hepatitis B, by categories of Hg exposure at three months of age



Exposure: by birthweight NDD

Exposure	Sub-analysis	RR + 95% CI
Cumulative at 3 months		1.005 (0.999, 1.012)
Cumulative at 3 months	Stratified on BW (categories of 250g)	**1.007 (1.001, 1.014)**
Birthweight in kilos		0.92 (0.81, 1.05)
Cumulative/Birthweight		**1.025 (1.010, 1.040)**
Cumulative/Birthweight	Stratified on BW (categories of 250g)	**1.024 (1.003, 1.046)**

CDC

Exposure: by birthweight ADD

Exposure	Sub-analysis	RR + 95% CI
Cumulative at 3 months		1.005 (0.982, 1.020)
Cumulative at 3 months	Stratified on BW (categories of 250g)	1.006 (0.982, 1.030)
Birthweight in kilos		0.86 (0.53, 1.37)
Cumulative/Birthweight		1.025 (0.872, 1.081)
Cumulative/Birthweight	Stratified on BW (categories of 250g)	1.025 (0.948, 1.112)

CDC

Exposure: by birthweight Speech

Exposure	Sub-analysis	RR + 95% CI
Cumulative at 3 months		1.005 (0.996, 1.014)
Cumulative at 3 months	Stratified on BW (categories of 250g)	1.006 (0.998, 1.015)
Birthweight in kilos		1.20 (1.06, 1.36)
Cumulative/Birthweight		0.987 (0.968, 1.006)
Cumulative/Birthweight	Stratified on BW (categories of 250g)	1.011 (0.985, 1.037)

CDC

Exposure: by birthweight Unspecified delay

Exposure	Sub-analysis	RR + 95% CI
Cumulative at 3 months		1.018 (1.001, 1.035)
Cumulative at 3 months	Stratified on BW (categories of 250g)	1.019 (1.003, 1.036)
Birthweight in kilos		0.51 (0.38, 0.68)
Cumulative/Birthweight		1.057 (1.039, 1.076)
Cumulative/Birthweight	Stratified on BW (categories of 250g)	1.067 (1.014, 1.122)

CDC

Outcome - multiple diagnoses

Number of common cases in some disorders (cycle 6)

	2990	3070	3140	31539
2990	66	0	7	23
3070		59	2	15
3140			158	20
31539				830

CDC

Outcome repeated diagnoses

- Diagnosed more then once:
- Autism: 40%
  - (GHC: 22%, NCK: 43%)
- Speech delay: 37%
  - (GHC: 64%, NCK: 22%)
- ADD: 39%
  - (GHC: 24%, NCK: 48%)

CDC

RRs repeated diagnoses

Code	Description	RR + 95% CI (Ref. = 0 ug)	
		Diagnosed more than once	
		n	RR
Neurologic developmental disabilities:			
307.2	Tics		
314.0	Attention deficit Sy	190	1.008 (0.996, 1.019)
31531	Language delay		
315.39	Speech delay	618	1.013 (1.005, 1.021)
315.9	Unspecified delays		

CDC

Cohort selection -
Excluded congenital - perinatal disorders

Main exclusion codes:

7469: Unspecified heart anomaly

7708: Other respiratory problems after birth

7706: Transitory tachypnea of newborn

7671: Scalp injury

7793: Feeding problems newborn

CDC

Cohort selection -
Excluded congenital - perinatal disorders

	Excluded infants	ALL infants
NDD	1.001(0.996, 1.006) (n = 953)	1.005 (1.002, 1.008) (n = 4060)
ADD	1.001(0.986, 1.016) (n = 91)	1.006 (0.999, 1.013) (n = 486)
Speech delay	1.005 (0.996, 1.014) (n = 349)	1.007 (1.003, 1.011) (n = 1882)
Unspecified delay	1.005 (0.997, 1.013) (n = 366)	1.005 (1.002, 1.008) (n = 903)

CDC

Cohort selection -
Excluding recipients of < 2 polio by 1 yr

Code	Description	RR + 95% CI (Ref. = 0 µg)	
		Any number of polio	
		n	RR
Neurologic developmental disabilities:		3340	**1.007 (1.004, 1.010)**
307.2	Tics	105	**1.023 (1.006, 1.040)**
314.0	Attention deficit Sy	376	**1.010 (1.002, 1.009)**
31531	Language delay	356	**1.021 (1.012, 1.030)**
315.39	Speech delay	1557	**1.007 (1.003, 1.012)**
315.9	Unspecified delays	587	1.006 (1.000, 1.012)

CDC

Bias: medical care utilization

Exposure category	Well child <3m	Well child <12m	All <3m	All < 12m
1	0.7	2.6	1.6	8.0
2	1.3	4.1	2.6	11.8
3	1.3	3.5	3.1	10.9
4	1.6	4.0	2.7	10.5
5	1.4	3.5	2.4	9.5
6	1.4	3.2	3.0	10.5
7	1.6	3.6	3.6	11.9

CDC

Bias: medical care utilization

Number of outpatient visits per additional 12.5 µg of cumulative mercury exposure at 3 months

Year of birth	GHC	NCK
1992	0.4	0.2
1993	2.7	-0.5
1994	1.7	0.5
1995	1.5	0.0
1996	0.9	0.7
1997	1.4	0.3

Linear model of the above, adjusted for HMO, year and month of birth:
All outpatient visits: 0.55 per 12.5 µg of cumulative mercury at 3 months

CDC

Bias: medical care utilization

Number of well child visits per additional 12.5 µg of cumulative mercury exposure at 3 months

Year of birth	GHC	NCK
1992	0.1	0.0
1993	0.5	-0.1
1994	0.4	0.0
1995	0.4	0.1
1996	0.4	0.2
1997	0.1	0.0

Linear model of the above, adjusted for HMO, year and month of birth:
Well child visits: 0.15 per 12.5 µg of cumulative mercury at 3 months

CDC

Bias: medical care utilization

	Number well visits	Hg 3 mo adjusted	Hg 3 mo stratified
ADD	1.07 (1.02, 1.13)	1.007 (0.999, 1.016)	1.008 (1.000, 1.016)
Speech delay	1.16 (1.13, 1.19)	1.007 (1.003, 1.012)	1.006 (1.002, 1.011)

CDC

Bias: medical care utilization

- SES :Race - ethnicity

category	Mean cumulative exposure at 3 months (ug)	% of total
Asian	48.8	6.5
Black	45.7	3.7
Hispanic	46.5	6.9
Native	62.5	0.0 (n=3)
White	49.5	82.8

CDC

Bias: medical care utilization

- SES :Yearly Household Income

category	Mean cumulative exposure at 3 months (ug)	% of total
< 15K	48.4	6.8
15 – 24 K	47.7	1.1
25 – 49 K	49.7	66.9
50 – 74 K	48.1	10.8
>= 75 K	47.9	14.3

CDC

Bias: temporal trend:
Relative risk associated with exposure at 3 months of age: tests for trend by calendar year

	Speech delay	ADD
1992	1.004 (0.993, 1.016) n = 201	1.009 (0.997, 1.022) n = 137
1993	1.013 (1.003, 1.023) n = 354	1.014 (0.999, 1.029) n = 130
1994	1.013 (1.003, 1.023) n = 378	1.007 (0.983, 1.030) n = 62
1995	1.003 (0.994, 1.012) n = 334	1.005 (0.970, 1.041) n = 22
1996	1.006 (0.993, 1.019) n = 217	0.981 (0.952, 1.011) n = 17
1997	1.009 (0.987, 1.032) n = 39	0.981 (0.939, 1.025) n = 6

CDC

Bias: temporal trend:
tests for trend by calendar year by logistic regression (speech delay)

- For all ages : RR 1.006 (1.004, 1.010)
- Under 1 year: 1.006 (0.985, 1.027)
- 1 – 2 years: 1.010 (1.000, 1.020)
- 2 – 3 years: 1.007 (0.999, 1.014)
- 3 - 4 years: 1.009 (0.999, 1.019)
- > 4 years: 1.002 (0.990, 1.014)

CDC

Alternative diagnoses

Code	Diagnosis	Cases	Mean age
37230	Unspecified conjunctivitis	16805	
5589	Non-infectious gastro-enteritis	23018	
9599	Unspecified injury	3369	
V655	Worried well	1141	20
734	Flat feet	379	32

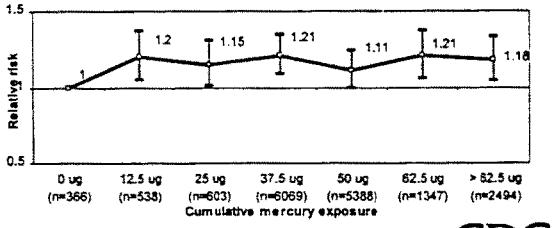
CDC

Alternative diagnoses

Description	RR + 95% CI		
	1 month	3 months	Hib combined - sep
Conjunctivitis		1.001 (1.000, 1.001)	0.93 (0.85, 1.02)
Gastro-enteritis		1.001 (1.001, 1.002)	0.94 (0.87, 1.03)
Injury		0.997 (0.995, 0.998)	0.86 (0.66, 1.04)
Worried well	0.992 (0.981, 1.002)	0.998 (0.995, 1.004)	1.05 (0.26, 4.48)
Flat foot	0.989 (0.974, 1.004)	0.997 (0.989, 1.004)	0.96 (0.36, 2.54)

CDC

Relative risk associated with exposure at 3 months of age: Unspecified conjunctivitis (ICD9 37230)

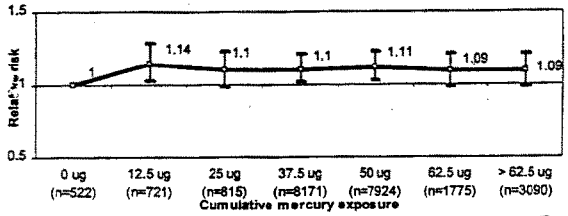


Trend: 1.001 (1.000, 1.001)

CDC

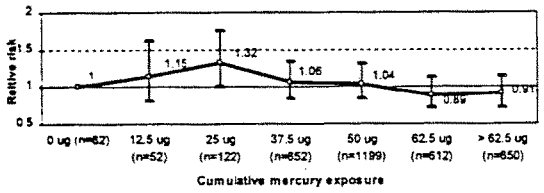
Draft - may contain error of fact or omission

Relative risk associated with exposure at 3 months of age : Non specific non-infectious Gastro-enteritis (ICD9 5589)



Trend: 1.001 (1.001, 1.002)

Relative risk associated with exposure at 3 months of age : Unspecified injury (ICD9 9599)



Trend: 0.997 (0.995, 0.998)

Draft - may contain error of fact or omission

Prematures

Code	Description	Cases	RR + 95% CI		
Prematures: (n = 6953)			1 month	2 months	3 months
Neurologic Developmental Disorders		562	0.970 (0.956, 0.985)	0.994 (0.990, 0.998)	0.986 (0.980, 0.992)
315.39	Speech delay	155	0.995 (0.971, 1.019)	0.994 (0.986, 1.002)	0.994 (0.982, 1.005)
315.9	Unspecified delays	300	0.951 (0.930, 0.973)	0.994 (0.988, 0.999)	0.980 (0.973, 0.987)

Code	Description	Cases	RR + 95% CI	
Prematures: (n = 6953)			6 months	Hib comb -sep
Neurologic Developmental Disorders		562	0.998 (0.995, 1.002)	2.89 (1.35 – 6.18)
315.39	Speech delay	155	0.999 (0.992, 1.007)	0.77 (0.10, 5.86)
315.9	Unspecified delays	300	0.997 (0.992, 1.002)	4.46 (1.81, 10.94)

CDC

Thimerosal or other effect:

DTP separate vs combined

Code	Descripuon	RR + 95% CI (Ref. = DTP-Hib combination)
Neurologic developmental disabilities		1.20 (0.84, 1.72)
299.0	Autism	1.25 (0.36, 4.35)
307.0	Stammering & stuttering	2.05 (0.25, 18.63)
307.4	Sleep disorders	2.15 (0.43, 10.86)
313	Disturbance of emotions specific to	1.50 (0.40, 5.67)
313.1	Misery and unhappiness disorder	Not estimable
313.8	Mixed emotional disturbances	1.53 (0.40, 5.67)
314.0	Attention deficit Sy	1.79 (0.70, 4.58)
315	Specific delays in development	1.17 (0.77, 1.78)
315.39	Developmental speech delay	1.28 (0.78, 2.10)
315.9	Unspecified delays in devesoproent	0.81 (0.29, 2.24)
Other neurologic conditoons		
343.x	Infantile cerebral palsy	1.95 (0.48, 7.87)
345	Epilepsy	1.66 (0.58, 4.73)
Renal conditoons		0.13 (0.00, 4.05)
593.9	Unspecified disease of kidney	0.01 (0.00, 7.31)

CDC

Draft - may contain error of fact or omission

Thimerosal or other effect:
Number of antigens as exposure

	Antigens 1 month	Antigens 3 months
NDD	1.07 (1.01, 1.13)	1.04 (1.02, 1.06)
Tics	1.11 (0.82, 1.52)	1.16 (1.01, 1.34)
ADD	1.06 (0.88, 1.26)	1.06 (0.99, 1.14)
Speech delay	1.11 (1.02, 1.20)	1.04 (1.01, 1.08)
Unspecified delay	1.04 (0.90, 1.21)	1.04 (0.98, 1.10)

CDC

Thimerosal or other effect:
Number of shots as exposure

	Shots 1 month	Shots 3 months
NDD	1.09 (1.02, 1.17)	1.10 (1.05, 1.15)
Tics	1.18 (0.81, 1.72)	1.39 (1.07, 1.81)
ADD	1.06 (0.87, 1.29)	1.13 (1.00, 1.27)
Speech delay	1.15 (1.04, 1.27)	1.10 (1.03, 1.18)
Unspecified delay	1.07 (0.90, 1.28)	1.10 (0.98, 1.21)

CDC

RRs for HepB and Hib thimerosal free

Disorder	At 3 months	at 6 months
ADD	Not estimable	1.07 (0.50, 2.29)
Language delay	Not estimable	**2.78 (1.08, 7.20)**
Speech delay	0.71 (0.44, 1.38)	1.28 (0.89, 1.84)
Speech or language delay	0.75 (0.49, 1.16)	**1.43 (1.00, 2.03)** p = 0.05
Unspecified delay	1.48 (0.74, 2.97)	1.42 (0.77, 2.63)
NDD	0.92 (0.67, 1.26)	1.25 (0.98, 1.61) p = 0.08

CDC

0 at 1-3 - (ref) vs 2? at 1-3

0 - 3-6 - (ref) vs 5? - 3-6

regardless of what they got at birth

[a reluctantly performing analysis ...]

Draft - may contain error of fact or omission

Discussion of Initial Analyses and Re-Analyses of Thimerisol and Developmental Delay in the Vaccine Safety Datalink Cohort

Philip Rhodes
Centers for Disease Control

June 7, 2000

Draft - may contain error of fact or omission

Outline

VSD Study

Evaluating thimerisol effects vs other effects

Difficulties with early analyses
- Exclusion criteria
- Uncertainties about low exposure groups
- Importance of clinic practices at NCK

Re-definition of cohort to be studied
- At one month
- At three months

Re-analyses of exposure-outcome relationships

Conclusions

Limitations/ Further Efforts

Draft - may contain error of fact or omission

Vaccine Safety Datalink Study

Good at evaluating exposures-- outcomes where

1) Outcome is acute, medically well defined, high probability of coming to medical attention and has a clear onset occurring a short time after the exposure

2) Effect of the exposure on the outcome is transitory

3) Exposures are nearly universal but there is sufficient variation in the age at exposure

e.g. seizures after DTP or MMR

Hard to evaluate exposures-- outcomes where

1) Outcome is chronic, not medically well-defined or onset is not well-defined

2) Exposure is nearly universal, i.e. only a small unrepresentative sub-group do not have the exposure

e.g. Attention deficit disorder after MMR

Draft - may contain error of fact or omission

Vaccine Safety Datalink Study

Where is thimerisol - developmental delay on this continuum?

Outcomes studied here vary on their medical certainty and likelihood of coming to medical attention

autism vs speech delay

Outcomes are chronic and onset is not well defined

Exposure is nearly universal and completely unvaccinated form an unrepresentative sub-group

Hopeless?

No – there is variation in the amount of thimerisol by type and manufacturer of vaccine

Important to distinguish whether differences in cumulative thimerisol exposure at some age are due to: 1) policy vs 2) self-selection (e.g. lateness in getting vaccinated, reluctance to accept vaccination and/or other medical care)

Original Exclusion Criteria

Born into HMO
Followed continuously for > 1 yr, first follow-up only

Not premature or low birth weight
Not have one of many possible perinatal conditions

No HBIG
Two or more polio vaccines by age 1

All exclusions had good intent

Prematures/ low birth weight may be less likely to receive HepB or other vaccines at an early age and may be more likely to have some outcomes of interest

Children receiving less than two polio vaccines in first year may not be accessing system as often as others

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Problems with Exclusion Criteria

Perinatal Exclusion Codes

Differential usage by HMO

NCK 19.2 %
GHC 6.7 %

Also differential usage or occurrence across birth f facilities in NCK : Range 13 - 36 %

Some of the ICD-9 codes likely represent fairly minor events e.g.

767.1 Scalp injury at birth
6060 at NCK
24 at GHC

779.3 Feeding Problems
3895 at NCK
548 at GHC

Problems with Exclusion Criteria

Prematurity Codes 765

Different usage of prematurity/ low-birth weight code

NCK 5.3 %
GHC 1.8 %

36% of those excluded at NCK > 2.5 kg
5% for GHC

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Original Exclusion Criteria

Two or more polio vaccines at 1 yr
First enrollment > 1yr

Some events occur by 1 year of age
Need to exclude these or have odd situation where exclusion follows event of interest

OK for events such as speech/lang delay that occur after one year

Polio exclusion is a reasonable attempt to control for HMO usage

Enrollment Date Problems

NCK has moderate number of children with multiple enrollment periods

Second or later periods not used in current study

Substantial numbers of events/vaccines are recorded at times where children are not 'enrolled

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Thimerisol Status at 100 and 107 Days
Children <=25 at 93 Days in Original Cohort

Per Cent Changing after 7 or 14 Days Further Follow-up

	93 days	N	100 days	107 days
NCK	0	2302	27%	42%
	12.5	2826	18 %	27%
	25	2989	6%	11%
GHC	0	181	19%	31%
	12.5	215	27%	38%
	25	894	1%	2%

Mean Time Since Last Well Child Visit (ICD9 V20.*)
By Length of Follow-up and Hg at 3 Months
GHC - Original Cohort

	Hg at 3 Months							
	0-25		37.5-50		62.5		>=75	
	N	Avg Lag	N	Avg Lag	N	Avg Lag	N	Avg Lag
First Follow-up								
12-18 m	888	104	6129	96	2754	81	2961	88
19-24 m	675	158	7446	143	1359	127	1368	130
25-36 m	1098	250	14832	225	264	164	255	201
37-48 m	1783	382	12072	348	81	370	105	370
>48 m	1513	455	10978	439	84	460	74	413

VSD Cycle 7
DRAFT

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Clinics at NCK

NCK has clinics over a wide geographic area in Northern California

Birth facilities and clinics often have different policies

Use of Hep B vaccine in first month of life
For all children born into HMO 1992-1998

Range : 4% – 85% Mean 43%

Great differences in exposure groups at three months by clinic e.g. Four clinics listed below, all > 4000

Clinic	I	II	III	IV	V
11	54	5	7	23	10
31	22	13	41	15	9
35	24	6	52	5	12
72	25	1	48	2	24

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Clinics at NCK

Variations in outcome by clinic

All Developmental Delays

In all children followed longer than 4 years
Overall 4.4%

32 clinics : Range 1.6 – 8.7%

	# Clinics
< 3 %	3
3 – 4%	9
4 – 5%	11
5 – 6%	3
6 – 7%	1
> 7 %	4

Common Combinations at 3 Months and Numbers of Children in Original Cohort

	Hep	DTP*	HIB	Hg	NCK	GHC
I	1	Comb		37.5	33,004	—
II	0	1	1	50	4,328	1,990
III	2	Comb		50	28,628	—
IV	1	1	1	62.5	9,199	2,213
V	2	1	1	75	9,427	9,165
Total					**84,586**	**13,368**

Five Exposure Group Approach:

Clarifies questions that may be answerable by the current data and where the information may be obtained

Thimerisol Difference = 37.5

I vs V – Differ on 1 vs 2 HepB and DTP-HIB combination vs separate DTP (or DTaP), HIB
Only possible at NCK

Thimerisol difference = 25

I vs IV – Both have 1 HepB, differ on DTP-HIB combination separate DTP (or DTaP) , HIB
Only possible at NCK

III vs V – Both have 2 HepB, differ on DTP-HIB combination separate DTP (or DTaP) , HIB
Only possible at NCK

II vs V – Both have separate DTP , HIB , differ by 2 HepB
Possible at both NCK and GHC

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Reanalyze Data Based on:

1) Five exposure groups

2) At one month, consider exclusions based on Hep B usage within the group considered for exclusion , for outcomes occurring mostly after one year consider two polio exclusion

3) At three months base exclusion primarily on ability to get into one of the five exposure groups
– Except exclude children receiving DT by three months

4) Use clinic as an additional stratification variable at NCK

5) Consider data quality issues e.g. some children at NCK receive unusual vaccines based on their month of birth i.e. separate DTP and HIB during calendar periods when >99% of the rest receive DTP-HIB combination

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NCK + GHC
Outcome = Speech/Lang Delay 315.3*
Relative Rates and P-values

Analysis	Thimerisol at One Month		
	RR	Chi-Sq	P-value
Original	1.20	12.1	0.005
+ Clinic	1.15	4.1	0.04
+ Exclus	1.09	2.1	0.14
- Prem (<1.75 kg)	1.14	5.4	0.02
- Polio <2 At 1 year	1.09	2.2	0.14

Stratify by month of birth, Control for gender
Reference Group = No thimerisol in first month

NCK

Outcome = All Developmental Disorders
Relative Rates and P-values

	Thimerisol at Three Months			
	(50)	(50)	(62.5)	(75)
Analysis	II	III	IV	V
Original	1.34	1.12	1.41	1.35
	(0.13)	(0.03)	(0.03)	(0.06)
+ Excl	1.46	0.97	1.48	1.29
	(0.01)	(0.49)	(0.006)	(0.03)
+ Clinic	1.22	0.97	1.30	1.18
	(0.25)	(0.64)	(0.05)	(0.21)
– Odd Codes	1.19	0.96	1.24	1.17
	(0.42)	(0.52)	(0.20)	(0.35)

Stratify by month of birth, Control for gender
Reference Group = I (37.5)

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NCK

Outcome = Speech/Lang Delay 315.3*

Relative Rates and P-values

	Thimerisol at Three Months			
	(50)	(50)	(62.5)	(75)
Analysis	II	III	IV	V
Original	1.64	1.25	1.30	1.21
	(0.07)	(0.001)	(0.25)	(0.38)
Final	1.13	1.04	0.96	1.14
	(0.72)	(0.60)	(0.90)	(0.65)

Stratify by month of birth, Control for gender

Reference Group = I (37.5)

GHC

Outcome = All Neurologic Devel Delay
Relative Rates and P-values

	Thimerisol at Three Months	
	(62.5)	(75)
Analysis	IV	V
Original	0.97	1.23
	(0.89)	(0.30)
Final	1.30	1.28
	(0.14)	(0.16)

Stratify by month of birth, Control for gender
Reference Group = II (50)

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NCK + GHC
Outcome = All Neurologic Devel Delay
Relative Rates and P-values

	Thimerisol at Three Months	
	(62.5)	(75)
Analysis	IV	V
Original	0.99	1.13
	(0.96)	(0.31)
Final	1.10	1.06
	(0.45)	(0.68)

Stratify by month of birth, Control for gender
Reference Group = II (50)

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Conclusions from Re-Analysis

Strong uncertainties about fairness of low exposure groups

Much less concern about exposure groups 37.5 – 75

Evaluation still tricky because of several issues:

1) Small amount of calendar overlap of use of the different policies that lead to the various exposure groups

   May have resulted in a small number of mis-coded children having an undue influence on the results

2) Original exclusion criteria were too extreme

3) Importance of accounting for clinic practices at NCK

Overall: Slight tendency for higher exposure groups to have higher rates but p-values unimpressive (i.e. mostly > .20)

Draft - may contain error of fact or omission

Limitations / Extensions of Current Analyses

Complete rejection of the 0, 12.5 and 25 groups at three months may be too severe -- try to refine assessment of the possible biases in these groups

Conclusions of little or no effect of thimerisol at three months on developmental delay outcomes must be confined here to the restricted range 37.5 - 75

i.e. No way to 'fairly compare' 0 with 50-75 or higher

Better definition of clinic at NCK, i.e. change over time

Check assumption that at NCK children with unusual combinations for their birth cohort are in fact mis-coded

Continue analyses looking at whether relative dose or age at receipt of doses is related to outcomes

Use data from chart reviews to refine case definitions

Re-do analyses as more data becomes available from these two and/ or other sources

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Dr. BERNIER. I can't say that all of them did but they were invited.

Mr. BURTON. But most of them were there?

Dr. BERNIER. I believe that is correct.

Mr. BURTON. What were the industry's recommendations or concerns about the study? We are going to find out so I hope you will give us the whole story here. What was the industry's concerns about that study?

Dr. BERNIER. I am not sure that I can characterize industry's concerns separate from the concerns of epidemiologists or other members of the group that were there. We didn't segregate out peoples' views by their affiliations.

Mr. BURTON. So the views of CDC or FDA or the health agencies would be incorporated in with the pharmaceutical representatives that were there?

Dr. BERNIER. No. The pharmaceutical representatives were not there as consultants. The Simpson Wood meeting was called together on short notice by CDC because these results had caused concern on our part and we wanted to consult with expert opinion outside the agency. As a result, we invited somewhere in the neighborhood of 12 or 15 individuals.

Mr. BURTON. Where were they all from?

Dr. BERNIER. They came from academia, they came from I am not exactly sure. We did it more by expertise. We were looking for pediatricians, neurologists, epidemiologists, that kind of thing.

Mr. BURTON. Were most of them from the pharmaceutical companies?

Dr. BERNIER. Oh, no. They were just a minority. The members from the vaccine companies were not there as consultants. They were there as observers because their products were the subject of the conversation, so CDC felt it was appropriate for them to be aware of these data so they could have an opportunity to assess them along with others who were looking at them.

Mr. BURTON. Did any of the industry representatives make any recommendations or anything while they were there? Did they say we have a problem with this report?

Dr. BERNIER. It is difficult to deal with things on two sides. They were free to talk. If they were at the meeting, they were observers in the sense that they were not the consultants per se but if they had an opinion about the data or about anything going on, I am sure the chairman of the group would have recognized them and would have allowed them to express their views.

Mr. BURTON. Were there minutes taken at the meeting?

Dr. BERNIER. Yes, there were. I don't know about minutes but I believe there is a transcript and report that was written.

Mr. BURTON. I would like to have that transcript, post haste and if need be, I will give you a subpoena for it. I want a transcript of that, I want to read it. I want to find out if the pharmaceutical industry had any influence over the decisionmaking process of our health agencies because if that is the case, there is going to be a big, big problem. How soon can I have that transcript?

Dr. BERNIER. I believe the transcript is available. It should not take a long time. I would think a matter of days if we can put our hands on it.

Mr. BURTON. I sure hope you can put your hands on it.

Dr. BERNIER. That shouldn't be a problem, Mr. Chairman.

Mr. BURTON. Why haven't you submitted that information I read to you a few minutes ago, Dr. DeStefano, for peer review?

Dr. DESTEFANO. That is part of the manuscript that was developed from this. I think its current status perhaps Dr. Chen could talk about. I am no longer involved.

Mr. BURTON. Dr. Chen.

Dr. CHEN. Unusual to most scientific studies, in fact because of the importance of this study, the analyses of the VSD have been shared publicly in multiple forums, at Simpsonwood, at the ACIP, and at the IOM. At each of the meetings, several interested parties on both sides of the equation have raised many concerns about how they want the study improved or analyzed and we have been trying to address those concerns. We have finished that and we expect to submit the paper for peer review shortly.

Mr. BURTON. I think I will let you fellows go for the time being. I am sure we will be together again before long. I appreciate your being here.

If you are still here, can I have the first panel come back to the table, I have a few more questions. I really don't have any questions, I just want each of you, as people who have worked on this subject a long time, I would like to have any of your thoughts on what you just heard regarding all this questioning. We are talking about kids who have been harmed, so if you have any comments you would like to make, I would like to hear them for the record. If you don't, that is fine as well.

Dr. BRADSTREET. As a parent of a child with autism, as a physician, it would have been wonderful, absolutely grand to have the information that has been kept largely behind closed doors for years available to me both as a parent and as a physician to guide my decisionmaking about vaccine administration.

Mr. BURTON. Amen.

Dr. BRADSTREET. I think it is appalling that some of their answers were clearly evasive and fly in the face of reality—where we just received evidence that in fact there was abundant information that thimerosal associated itself with a variety of different problems, all of which for the most part would be associated with neurodevelopmental disorders typical of autism with speech language delay, general overall neurodevelopmental disorders.

To then take that data and say there is no relationship to autism where most of those constituents are part of the spectrum of autism, seems hypothetically almost impossible and statistically almost impossible. I think we have been done a disservice in the way in which this data has been withheld for 2, 3, 4 years. I think it has and should have been the cause of a recall of thimerosal immediately. I think we have seen some of the issues they were concerned about: whether or not we would continue to have the uptake of vaccines, if the parents would continue to submit to voluntary vaccination programs, and I realize some of the driving forces behind that.

The problem is in the process of attempting to cover this up they haven't done a very good job. Parents have found out the truth. They have multiple access, whether it is through Freedom of Infor-

mation or through various other resources, to find out the toxicology of mercury and find out the problems with persistent viral infections.

I think it is incredibly valuable for this committee to continue its work trying to expose the truth. I thank you very much for it.

Mr. BURTON. You don't have any doubt about that do you?

Dr. BRADSTREET. No, I don't.

Mr. BURTON. There are a lot of reasons I am concerned about the health and safety of the entire population of America but I am so ticked off about my grandson and my granddaughter just like you are that I can't see and to find that our health agencies have, as Dr. Weldon said, circled the wagons trying to keep us from knowing the facts just makes me want to vomit.

Dr. BRADSTREET. Do you think it is any coincidence that the rise and the use of ritalin, which I think various other government agencies have had hearings on the use of ritalin, absolutely corresponds to the rise in the use of mercury and that they find a statistically significant increase in ADHD?

Mr. BURTON. Those are things that we will continue to beat on and try to get to the bottom of with your help and others.

Anybody else have any comments?

Dr. WAKEFIELD. One comment and that is my third occasion here. It underscores for me the overwhelming need to disassociate those who mandate and endorse vaccines from those who monitor safety. You cannot referee your own soccer matches. It is like asking an Italian referee to take over the game of Italy between South Korea. It doesn't work, can't do it. You have to separate those agencies that endorse and mandate vaccines and those who monitor safety. One needs to be on the back of the other all the time in order to check on safety.

It also underscores the value of your Freedom of Information Act which we do not have in the United Kingdom. It is enormously to this committee's credit that it has gotten as far as it has. The work clearly must continue.

Mr. BURTON. Al Jolson used to sing and they would bring the curtain down and the audience would be up pounding the floor and clapping because he was such a great entertainer. He would get down on one knee and say, you ain't seen nothing yet. Other comments? Dr. Spitzer.

Dr. SPITZER. I would like to say as a Canadian epidemiologist I am also a member of the Institute of Medicine of the USA, that if one had to make a choice between epidemiology and the clinical and laboratory disciplines looking at all of this, one sets epidemiology aside and one goes to the clinic, one goes to the labs and some of the work that has been done in Britain and here and we have heard about today.

Nevertheless, having said that, I would urge thoughtful, responsible colleagues such as those in the committee and leadership in this country and elsewhere, that we need to push the answers in parallel, in three or four areas, the biological mechanisms such as have been done by Dr. Friedman and Professor O'Leary; the epidemiology which so far has been noncontributory, the Institute of Medicine says there is no evidence and that is very different than saying the evidence demonstrates there is no relationship. You can

see the itty bitty study we saw today and that is the kind of epidemiology that we find when we go and look plus others and we really need to do serious work.

We were talking about sample size. The study we designed internationally to get some answers has 3,500 cases and 7,000 controls. Why? Suppose 10 percent of the children are affected by one product, say MMR, that subset also has to be statistically significant or we are going to have to use another 5 years. I will make that my own example.

I want to thank you as one who benefits from the fact I have no family members involved or anything that the support by this committee and its staff to those trying to look at this seriously in various country and I think this hearing was extremely important to many of us involved.

Mr. BURTON. Ladies first, Dr. Krigsman.

Dr. STEJSKAL. You have an admirer in Sweden for your work with this issue of chemical toxicity. As an immunologist working for a long time in pharmaceutical industry at toxicology laboratory, I am still shocked regarding risk benefit assessment of this additive thimerosal. I don't see the reason why it wasn't changed and replaced by other additives like, for example, chloride. For me this is astonishing and shocking. I think your explanation of money is the right one.

I also hope you will continue with your work to remove all mercury from the body and out of the fillings. I want to tell you that in Europe, the nickel is already banished and prohibited as a part of metal alloys used in dentistry while unfortunately here in America, you still have high nickel rich metal alloys allowed. Nickel is another mutagen and carcinogen and so on.

We will help you in any way we can. I hope you will go on with your work.

Mr. BURTON. Thank you.

Dr. Krigsman.

Dr. KRIGSMAN. I would like to conclude by saying what has happened in the past and what this committee is interested in looking into is one issue. I want to project to the future and I would invite the governmental agencies to show and demonstrate their commitment to research in this area by providing funding for those people who are pursuing those answers. Thank you.

Mr. BURTON. Thank you very much. I want to thank all of you for being so patient. You have been here since 10 a.m. I really appreciate that. You are doing the good Lord's work. Hopefully there will be a lot of children and people that will grow up a bit safer because you are willing to come and testify.

Dr. Wakefield, hang in there, buddy.

Thank you.

[Whereupon, at 2:40 p.m., the committee was adjourned, to reconvene at the call of the Chair.]

[The prepared statements of Hon. Constance A. Morella, Hon. Edolphus Towns, Hon. Dennis J. Kucinich, additional information submitted for the record, and the complete set of exhibits follow:]

Statement of Congresswoman Constance A. Morella
Government Reform Committee Hearing
Full Committee Hearing:
"The Status of Research Into Vaccine Safety and Autism"
Wednesday, June 19, 2002 at 11:00
2154 Rayburn House Office Building

Constance Morella

Mr. Chairman, I want to thank you for holding this hearing today to examine the many issues surrounding the vaccines and autism.

I look forward to hearing the testimony of the witnesses. Specifically, learning more about the Vaccine Safety Datalink (VSD) and what this program has accomplished to date in serving the needs of the research community Is it working, and that it is doing what Congress intended for it to do.

Before we being hearing the testimony of the witnesses I would like to say that I do believe that our Nation's vaccine program is first and foremost about the protection of our citizens, particularly our children.

Vaccines are about the promotion of health. Vaccines are often cited as one of, if not the greatest, achievement of biomedical science and public health in the 20th century. There has been remarkable success in controlling many other infectious diseases. We have been very successful in controlling vaccine preventable diseases in the United States, and without these diseases as reminders in our daily lives, we can easily forget how serious and even how deadly these diseases are.

This fact however should not make us complacent. I am aware, and concerned about some of the negative reactions to vaccines we have heard about in previous testimony.

This Committee has held numerous hearings on the anthrax vaccines as well as childhood vaccines and its possible relationship to autism. We have as a Committee reviewed ongoing concerns about vaccine safety, vaccine adverse events tracking, and the National

Vaccine Injury Compensation Program.

So I welcome the witnesses today, thank you for coming, and I look forward to hearing your testimony.

Thank you.

Statement of Congressman Ed Towns
House Government Reform Committee
"The Status of Research Into Vaccine Safety and Autism"
Wednesday, June 19

Mr. Chairman, thank you for holding this important hearing. Autism is a developmental disorder that usually manifests itself within the first three years of a child's life through symptoms such as deficits in sociability, in verbal and non-verbal communication, and in the range of the child's interests and activities. There is no known cure for autism. This has left many parents, doctors and researchers searching for answers. While I believe we must do everything within our power to assist in this effort, we must avoid the natural inclination to accept well intentioned though flawed theories and rely on sound science to provide these answers.

Compounding the mysteries around autism is the issue of prevalence. Studies conducted in Brick Township, New Jersey, and Atlanta, Georgia, the Center for Disease Control and Prevention (CDC) has found that 6.7 per 1000 children have disorders within the autistic spectrum. Other autism advocates use the increased demand for services for autistic children as proof of an "epidemic" of autism currently spreading in America. Yet, others say that these figures represent, not the increased incidence of autism, but rather, the use of a much broader definition of autism.

Additionally, the causes of autism have also been the subject of much debate. While the precise causes are unknown, the National Institute of Health (NIH) reached a consensus in 1995 that autism probably results from a genetic susceptibility that involves multiple genes. Conversely, there are parents and researches who believe that autism is caused by vaccinations.

As evidence, they use the fact that children begin manifesting autistic symptoms between the ages of 15 and 18 months, around the same time as they receive their vaccinations. Yet, for all their claims, the proponents of this theory have yet to corroborate their assertions with scientific evidence. Nevertheless, in 1997, NIH launched a five-year $27 million international collaborative effort to study the neurobiology and genetics of autism.

I look forward to hearing the witnesses' testimony, and I hope that the findings of this hearing prove constructive and helpful in our fight to cure autism and help America's youth.

Opening Statement
Rep. Dennis Kucinich
June 19, 2002
"The Status of Research into Vaccine Safety and Autism"

I would like to begin by thanking Chairman Burton for his dedication and persistence on the issue of autism. His commitment to the search for a cause for autism has provided leadership toward a goal that will eventually help not only his own family, but also thousands of individuals with autism throughout the world. My thanks also to the witnesses, who have researched, studied, and experienced firsthand the effects of autism.

As you all know, autism spectrum disorders present a significant problem to our youth. The Center for Disease Control estimates that almost 400,000 children are affected by autism; equally disturbing are estimates by the International Child Development Resource Center that autism-related costs will exceed $1 trillion in the next fifty years. As the rates of autism appear to be increasing in many states, autism presents a problem of profound significance to all of us. It is essential that we continue to address this issue.

More than a year ago, this committee explored the issue of increasing autism rates. In addressing these concerns, I noted that the scope of the research should be broadened to include as many professional resources and as much informed testimony as possible. I also made it clear that Congress should allocate more funds to autism research. These statements still stand. Autism represents a

complex disorder that should be taken seriously by this government. Clear answers and conclusions will take both research and funding.

Today, over a year later, we are here examining vaccine safety as it relates to autism. Chairman Burton and the committee have raised interesting and intriguing points about the connection between the measles, mumps, and rubella vaccine and autism. Is there a link between the vaccine and this terrible affliction? At present time, we do not have sufficient evidence to conclude that a clear correlation exists. Research must continue.

The National Institutes of Health has taken significant steps to find answers with an international effort that has brought together researchers from Canada, Britain, France, and Germany to study causes and mechanisms of autism. From this research, theories about the connection between autism and vaccines are being developed, providing possible clues that bring us closer to the answers we seek. The NIH should be applauded for these efforts.

Perhaps the most comprehensive effort to look at possible adverse effects of vaccines has come from the Vaccine Safety Datalink, a joint effort between the Center for Disease Control and seven HMOs. Since 1990, the health records of more than six million people have been entered into a database to investigate the effects of vaccines. A preliminary conclusion of CDC researchers has found that thimerosal exposure does not directly cause developmental delays such as autism.

Of course, when dealing with live viruses, as those contained in the MMR vaccine, we must be careful. Indeed, interesting evidence has come up that shows that

perhaps the combination of thimerosal and the live virus in the MMR vaccine is to blame. This would suggest that each is not harmful in its own right; however, when combined, they bring about harmful effects such as autism. Vera Stejskal is a researcher from the University of Stockholm who has researched this issue extensively and continues to shed light on the issue.

As technology gets better throughout the world, so does the expectation that the world's citizens will be better protected against diseases. Therefore, it is disturbing to hear allegations that vaccines - the miracles that are supposed to cure our diseases - are actually in turn creating problems. At this point, vaccines are still helping more people than they are purportedly adversely affecting. Indeed, they are incredibly beneficial to the population as a whole. Circulation and use of the MMR vaccine should still be encouraged, as its benefits have been proven to greatly outweigh possible costs in the past. According to the American Academy for Pediatrics, vaccines have saved millions of lives and have succeeded in virtually wiping out worldwide epidemics such as polio and smallpox. With this in mind, they should still be considered a viable option in the fight against many childhood and early developmental diseases.

However, the source of the negative effects of vaccines must be ascertained through further research and funding. Once again, I am happy to see that many of these issues have been brought to the forefront and addressed by the members in attendance. I applaud this committee, the researchers who have worked with autism, and the families who have lived with it. Finally, to those individuals who struggle daily with autism, I applaud your determination and I praise your courage.

[redacted]

confidential
fax

To: **The Honorable Dan Burton**
Fax Number: [redacted]

From: **Amy A. Blodgett**
Fax Number: [redacted]
Business Phone:
Home Phone: [redacted]

Pages: 2
Date/Time: 7/23/2002 11:42:13 AM
Subject: MMR in Japan

Many thanks for the work that you are doing in Washington. Although the circumstances are unfortunate, there are those of us who finally feel we have a voice in Washington.

God bless you and keep you in your efforts.

Sincerely,

Amy Blodgett
Spring Lake, MI
(Hoekstra constituent!!)

Japan Bans MMR Vaccine

Japan stopped using the MMR vaccine seven years ago virtually the only developed nation to turn its back on the jab. Government health chiefs claim a four-year experiment with it has had serious financial and human costs.

Of the 3,969 medical compensation claims relating to vaccines in the last 30 years, a quarter had been made by those badly affected by the combined measles, mumps and rubella vaccine, they say.

The triple jab was banned in Japan in 1993 after 1.8 million children had been given two types of MMR and a record number developed non-viral meningitis and other adverse reactions.

Official figures show there were three deaths while eight children were left with permanent handicaps ranging from damaged hearing and blindness to loss of control of limbs.

The government reconsidered using MMR in 1999 but decided it was safer to keep the ban and continue using individual vaccines for measles, mumps and rubella.

The British Department of Health said Japan had used a type of MMR which included a strain of mumps vaccine that had particular problems and was discontinued in the UK because of safety concerns.

The Japanese government realized there was a problem with MMR soon after its introduction in April 1989 when vaccination was compulsory. Parents who refused had to pay a small fine.

An analysis of vaccinations over a three-month period showed one in every 900 children was experiencing problems. This was over 2,000 times higher than the expected rate of one child in every 100,000 to 200,000.

The ministry switched to another MMR vaccine in October 1991 but the incidence was still high with one in 1,755 children affected. No separate record has been kept of claims involving autism.

Tests on the spinal fluid of 125 children affected were carried out to see if the vaccine had got into the children's nervous systems. They found one confirmed case and two further suspected cases.

In 1993, after a public outcry fuelled by worries over the flu vaccine, the government dropped the requirement for children to be vaccinated against measles or rubella.

Dr Hiroki Nakatani, director of the Infectious Disease Division at Japan's Ministry of Health and Welfare said that giving individual vaccines cost twice as much as MMR 'but we believe it is worth it'.

In some areas parents have to pay, while in others health authorities foot the bill. However, he admitted the MMR scare has left its mark. With vaccination rates low, there have been measles outbreaks, which have claimed 94 lives in the last five years.

Data Sharing Principles and System

National Immunization Program (NIP)

Draft Proposal 2/21/02

Background: Science relies on the replication of study findings by independent researchers. The science of epidemiology likewise benefits when different researchers address the same question, examine it from different perspectives, and compare their results. Unlike the basic laboratory sciences, epidemiologic research relies on the complex analyses of large amounts of information obtained directly or indirectly from individuals. Historically, replication of epidemiologic findings has relied on repeating a study in another population. However, given the large number of individual patient records contained in NIP's Vaccine Safety Datalink (VSD), other researchers would need access to the original data set to verify or refute the original results.

The decision to allow access to database involves more than the original researchers' confidence in their results and their willingness to permit replication of the original analyses. Also involved are the confidentiality of individual patient records and the proprietary interest of the companies that collect the information as part of their business practice.

The American College of Epidemiology has proposed 10 principles as a guide to epidemiologists interested in data sharing. Relevant selections from these principles include:

> Under appropriate conditions, data sharing enhances the veracity of epidemiologic findings and enhances science.
> The rights and privacy of people who participate in epidemiologic research must be protected.
> Limited informed consent for future use of data beyond the original study should be obtained.
> Data should be made available for sharing as soon as possible after the completion of the original study, preferably at the time of publication.
>
> Archiving of unique data sets should be encouraged.
> Cost of making data available to secondary users should be borne by the secondary user.
> Data sharing is not always appropriate. The decision to release a data set should be made by an Institutional Review Board after the secondary user has explained precautions to be taken and made a pledge to protect the confidentiality of individually identifiable data.

It is preferable for secondary investigators to work with original investigators (sometimes on site) to understand the nuances involved in data collection, the reliability of variables, and the particularities of the data set.

Co-authorship of the original investigators should not be requirement for release of the data set to other researchers. The secondary analyses should be peer-reviewed by the original researchers.

Established CDC Model - NCHS Research Data Center: CDC's National Center for Health Statistics (NCHS) has established a system to permit access to potentially confidential data collected through their national surveys using their Research Data Center (RDC). The RDC is a physical space where researchers are allowed controlled access to restricted data files. Access depends on NCHS approval of a research proposal, as outlined below.

NCHS reviews projects based on their scientific and technical feasibility, availability of RDC resources, risk of disclosure of confidential or restrained information and whether each proposal meets NCHS's mission to provide statistical information that will guide policies to improve the health of the American people. The review board consists of the RDC director, the NCHS Confidentiality Officer, staff involved in the original survey, and a RDC staff person assigned to oversee the project. This board meets within 3-4 weeks of receipt of a proposal and if it is approved, the RDC prepares a data set containing the requested variables. On-site use of data sets at the RDC costs $1,000 per week. More than one researcher may work on the project at the RDC site.

NIP Proposed system: Based on the American College of Epidemiology's principles and the NCHS model, NIP proposes to make VSD data available for the independent re-evaluation of publically reported VSD research studies as described below.

Research proposals would be submitted to NIP and contain the following:

Cover letter
Project Title
Abstract
Full personal identification and institutional affiliation of researchers
Current resume or *Curriculum vitae* of the principal investigator
Proposed dates for conducting the analyses at the RDC (or equivalent)
Source of funding
Detailed summary of the

proposed research

Complete list of requested data including fields, variables, years etc. Details of any data that may be merged with the data provided by NIP. This includes documentation, file layout, and number of records

Software requirements

NIP will review the submitted proposal for its completeness and feasibility and to determine which HMOs' data will be necessary to complete the project. If these conditions are met, NIP will send the proposal to the IRBs of each involved HMO.

Each HMO's IRB must review and approve the proposal.
Once approval is obtained from each involved HMO's IRB, the principal investigator will make arrangements with NIP to conduct the analyses at NCHS RDC (or equivalent). NIP will prepare the necessary files.

Before using the files, each researcher must sign a 308(d) Assurance of Confidentiality Agreement.
Each researcher will conduct the approved analyses at the established RDC (or equivalent.
Researchers will be allowed to leave only with copies of their summary results after they have been reviewed for confidential information.

Researchers will be charged a fee, dependent upon the costs of the study.

Clay, Beth

From: Crain, Michael (HHS/OS) [Michael.Crain@hhs.gov]
Sent: Tuesday, June 04, 2002 3:05 PM
To: Clay, Beth
Subject: Fw: Address for submission of VSD data sharing proposals

Beth-

Here is the address where proposals can be sent to gain access to the VSD data for research purposes.

MDC

Sent from my BlackBerry Wireless Handheld (www.BlackBerry.net)

-----Original Message-----
From: Boll, Deborah A. (CDC) <daa4@CDC.GOV>
To: Crain, Michael (HHS/OS) <Michael.Crain@hhs.gov>
Sent: Tue Jun 04 14:01:12 2002
Subject: Address for submission of VSD data sharing proposals

They should be sent to:

Robert T. Chen, MD
Chief, Vaccine Safety and Development Activity
Epidemiology and Surveillance Division
National Immunization Program
Centers for Disease Control and Prevention
Mailstop E-61
1600 Clifton Road
Atlanta, GA 30333
(404) 639-8256

FedEx address:

Robert T. Chen, MD
Chief, Vaccine Safety and Development Activity
Epidemiology and Surveillance Division
National Immunization Program
Centers for Disease Control and Prevention
Corporate Square Facility
Building 12, Room 3314
Corporate Square Boulevard
Atlanta, GA 30329

Deborah A. Boll

CDC Washington Office
Phone 202-690-8598
Fax 202-690-7519
www.cdc.gov/washington

LLDB Study of Vaccine Safety
Data Managers' Meeting
January 12, 1993
UCLA Center for Vaccine Research

Present: Emmett Swint, Centers for Disease Control/National Immunization Program (NIP); Virginia Immanuel, Group Health Cooperative (GHC), Seattle; Loie Drew, Northwest Kaiser-Permanente (NWK), Portland; Ned Lewis, Northern California Kaiser-Permanente (NCK), Oakland; Pat Osbourne, Southern California Kaiser-Permantente (SCK), Pasadena; Connie Vadheim, Ph.D., UCLA Center for Vaccine Research (SCK), Los Angeles; Eilleen ;

Review of 1993 LLDB data management activities
Emmett distributed the agenda materials. The group reviewed the major data management components that were addressed during the year, including tape 1 edits, creation of an analysis file, adjustments for child-days, definition of acute events, and creation of a file to calculate acute outcome rates and vaccine rates. Preliminary work has been done for conducting geocoding and birth certificate matches when tape 2 files are submitted and local data management has been involved in quality control study activities. A major goal in the tape 1 edits and analysis was to become more familiar with the similarities and differences among HMOs for each of the files.

Status of tape 2
Tape 2 files were initially targeted for December, 1993 submission. The status among sites is as follows:

- GHC All files have been submitted.
- NWK All files but the PHARMACY and ADDRESS files have been submitted.
- NCK The target date for submission is April, 1994 due to the difficulties in identifying the study population.
- SCK The target date for submission is April, 1994.

Both NCK and SCK indicated they may be able to submit some files earlier. The following priorities was established:

(1) CONSTANT, ENROLL, OUTCOME, and VACCINE files -- these files would provide information for identifying the study population and calculating enrollment days, vaccine and outcome rates, and performing the cohort analyses relating vaccine exposures to adverse outcome events.

(2) GEOCODING and ADDRESS file -- The GEOCODING file contains the specific street addresses and zip codes that are used for a contracted geocoding facility to add census tape identifiers. These identifiers are used to merge with census tapes for abstraction of socio-economic status (SES) variables. The ADDRESS file contains other child demographic data.

(3) BIRTHMAT file and state birth certificate files -- These files enable NIP to perform birth certificate

matching for the abstraction of additional demographic data and for identifying antecedent conditions.

(4) Ancillary files (LAB, PHARMACY, PROCED as available) -- These files allow for verification of outcome events and new case findings. Until these files arrive, NIP will use the GHC outcome and ancillary files to explore how these files can best be utilized.

LLDB data management goals and activities for 1994

The group discussed the major activities that will be addressed at NIP and/or local HMOs in the following year:

(1) Edit tape 2 files;
(2) Compare tape 1 and tape 2 contents, including additional descriptions of local HMO methods in collecting data;
(3) Assess the need to adjust enrollment intervals;
(4) Update files used to calculate new vaccine and outcome rates;
(5) Create file for updated power calculations;
(6) Assess the method for computing acute outcome events;
(7) Create new analysis files for updating the cohort analysis;
(8) Work with the quality review committee to:
    (a) Finalize the SAMPLE file and submit files to NIP;
    (b) Standardize data collection procedures and automated quality review files that are used in any future quality review studies;
    (c) Determine how SAMPLE data can be integrated with existing automated data.
(9) Define, create and submit DEATH files resulting from linking study participants with state death files or other sources of deaths not occurring within the HMO.
(10) Work with the neurologists and statisticians to:
    (a) Review the methods proposed to verify neurology outcomes and insure they are consistent with current data flow at the HMO;
    (b) Define the data structure for the REVIEW file;
    (c) Determine how REVIEW data can be integrated with existing automated data.
(11) Incorporate ancillary data into analysis files:
    (a) Review the relationships of ancillary data with outcomes identified in various settings using GHC data;
    (b) Define the data structure for reporting new cases identified in ancillary data files;
    (c) Determine how new case data can be integrated with existing automated data.
(12) Identify SES identifiers from the geocoding process
    (a) Obtain census file indicators from geocoder.
    (b) Identify variables from census files that are to be used in the LLDB study for SES indicators;
    (c) Define the data structure for the SES file;
    (d) Incorporate SES variables into the cohort analysis files.

(13) Perform birth matching activities;
  (a) Match child identifiers with state birth files;
  (b) Refine the demographic, antecedent and underlying condition variables and data structure of items that are to be obtained from the birth certificates;
  (c) Incorporate birth certificate variables into the cohort analysis files.

(14) Expand and/or improve local collection procedures:
  (a) Enhance the software that defines of ICD-9 codes in the emergency room and urgent care and make available to all HMOs (NCK);
  (b) Implement outpatient outcome system in all clinics that reports ICD-9 codes for all visits (NCK);
  (c) Implement optical scanning outpatient coding sheet in clinics to identify reasons for visits (SCK);
  (d) Develop new automated files from local automated data systems:
    NWK -- LAB, PHARMACY (inpatient)
    NCK -- LAB, PHARMACY (inpatient and outpatient)
    SCK -- LAB, PHARMACY (inpatient and outpatient)

(15) Improve documentation of LLDB data management activities
  (a) Document data collection differences at different HMOs (supplemental to quality control booklets);
  (b) Document structure and characteristics of original automated files for NIP and HMO staff who wish to utilize LLDB data;
  (c) Document any adjustments made to the original automated files and the data structure of new analysis, rate and special study files;
  (d) Document and standardize naming of LLDB files on the mainframe and LAN;

(16) Provide technical support to NIP and HMO users who wish to use LLDB data for special vaccine safety studies:
  (a) Develop generic programs that can be used for study of specific vaccine-adverse event relationships;
  (b) Develop documentation for users not familiar with LLDB activities;
  (c) Provide consultation on LLDB file data structures and methods for SAS programming;

(17) Identify and implement hardware personnel and equipment resources to perform LLDB activities in a more efficient manner:
  (a) Acquire equipment to transfer from mainframe to local data processing;
  (b) Explore the ability to transfer large files between HMO sites and NIP via Internet NTP;
  (c) Hire contract personnel to help perform geocoding, birth certificate matching and other LLDB functions.

Issues surfacing during the past year
Emmett presented several data management issues that resulted in adjustments or special explanations. Data managers shared similar experiences at their HMO.

(1) Adjustment of enrollment dates
Three adjustments were used: (a) first start date was extended to the date of birth at NCK if the child was born in the HMO and had continuous HMO coverage; (b) enrollment dates were extended to a vaccine date that occurred outside the start and stop dates; and (c) enrollment dates were extended to an outcome date that occurred outside the start and stop dates;

Ned indicated that children within NCK are free to go to any outpatient clinic they choose and the first adjustment is no guarantee that the child received care at a LLDB study clinic. He hoped that tape 2 would be improved because children will be receiving HEP-B vaccine at a very early age. Eventually, as all clinic facilities implement the immunization and outpatient clinic outcome modules, defining the study population will be similar to other HMOs.

There was a caution about extending enrollment dates because of vaccine and outcome dates that are out-of-range. There was one suggestion that the amount of adjustment should be limited to a relatively small value (e.g., 30 days) equivalent to the number of days of error that might be introduced by the membership and other administrative files used to define the start and stop dates.

The problem of creating a zero-day target window in the cohort analysis file when a stop date to an out-of-range vaccine date was discussed. This adjustment probably should not be done unless there are also outcomes that fall after the stop date.

(2) Methods of combining vaccines into vaccine groups
Emmett explained that vaccines may be grouped differently in several types of LLDB analyses that were conducted. For example, vaccine rates for DTP components would combine all vaccines that have a vaccine component offering protection against diptheria, pertussis and tetanus while the cohort analysis would limited the DTP group to vaccines that only contained the same type of vaccine (i.e, DTP and DTPHIB but not DT(a)P or DT(a)PH). Documentation should identify how vaccine groups are formed.

(3) Impact of missing outpatient clinic outcomes
The group reviewed a table showing health care setting characteristics of the 34 outcomes of interest. Caution was made about using HMOs that do not report outpatient clinic visits to study outcomes of interest whose predominant setting is "CLINIC". Ancillary files would be used to help identify some of the children who have outcome events that could be not identified in the OUTCOME files.

(4) Overlap of ICD-9 code in outcomes of interest table

ICD-9 codes that appear in more that outcome of interest category, subcategory and item were reviewed and data managers indicated that there is probably not a way to define the categories so no overlap occurs. The overlap occurred in part because PIs are interested in viewing a specific subsets of a particular outcome (e.g., allergic purpura <287.0>, primary thrombocytopenia (287.3) and secondary thrombocytopenia <287.4> and unspecified thrombocytopenia <287.5> as subsets of purpura and other hemorrhagic conditions <287.*>) and partly because PIs were interested in viewing data from different classifications (e.g., mumps meningitis <072.1> as an Aseptic Meningitis outcome and mumps <072.*> as an Other Vaccine-Preventable outcome and epidemic or infectious parotitis <072.*> as an Parotitis outcome). Data managers felt the classification scheme was useful because it helps capture general as well as specific outcomes of interest, but one has to be aware where duplications occur when analyses are conducted and results are presented. A table was distributed identifying one method of removing duplicated ICD-9 codes at different classification levels.

(5) Definition of acute episodes.

Problems encountered with defining acute episodes were discussed. In general, data managers felt that any definition used should minimize separation of follow-up visits associated with an acute event. This could probably be accomplished more by adding the acute interval (or some number of days smaller than the acute interval) to the most recent event when defining the end of the episode rather than just the first one. Specific interval distribution analysis would be needed to refine acute interval values since many of those were best estimates based on clinical experience of the PIs.

(6) Same-day outcome and exposure records.

Data managers were to check the time stamp of records having ICD-9 codes occurring on the same day in the same setting to be sure they were from separate health care encounters. It was more difficult to determine the order of events when a child has a vaccine and outcome on the same day unless they occur in different settings. In some cases the time-stamp in the immunization module is the time of data entry, not time of shot.

(7) Clinic facilities are not known for vaccines and outcomes.

In tapes 1 and 2, NCK has only three clinics reporting outpatient visits and new clinics were added to the study once immunization modules were implemented at the clinic. About ten percent of the children with outpatient visits in the OUTCOME file were not from the clinics with automated outpatient records. This occurred because children are able to attend multiple clinics. Ned said facility codes were available for both vaccine and outcomes and will be added to the VACCINE and OUTCOME file to help determine give a better account of child-days for children with outpatient records in the OUTCOME file and help identify the amount of inter-clinic usage within the HMO.

Clarification of tape 2 data structure

(1) Enrollment of children who die near birth.

Connie (SCK) inquired whether other data managers enroll children in the LLDB study if they die at or near birth prior to any vaccine being given. NWK considers the child as being covered under the parent's membership for the first month of life and they would be excluded from the study because they would never appear in the membership file. GHC has an inactive membership file that would pick up new births who die or are terminated. NCK would include anyone receiving a vaccine on that date and probably would include others. This problem should be minimized in the future because children are being HEP-B vaccine within hours of birth and there is an interest in capturing all deaths, even if a vaccine is not given.

(2) New medications for the PHARMACY file.

Loie (NWK), Virginia (GHC) and Emmett (NIP) met after the meeting to discuss how to categorize medications that were not on the medication list.

New developments at local HMOs and CDC

Hardware (NCK). Ned reported that NCK purchased a new SUN-SPARK computer that allows up eight users, connects directly into the LAN, has 6.5 gigobytes of hard disk storage, 64 MB of memory, and a tape drive to read 1/2 inch cartridge tapes; has SAS BASIC and STAT programs running in the UNIX environment; and has an Internet connection to transfer large files rapidly. The processing time benchmarks are impressive when compared to mainframe, PC SAS and SAS for WINDOWS. Ned indicated that its main strength is analysis of large files very quickly while its drawbacks are printing to LAN printers, which requires special set-ups or copying the output back to the LAN system. An outside service contracts is essential. Ned will share specs to those that are interested.

Linking death and birth files (NCK). Ned indicated that NCK has purchased FORTRAN software to link death and birth files. The State of Washington performs this linkage on request at a small amount. NWK has several references and algorithms for matching birth certificate records.

Software for assigning ICD-9 codes to ER visits. Ned is developing a software package at NCK that assigns ICD-9 codes from text-strings and is supplemental to the existing autocoder. Other HMOs with Internet FTP capability will be able to transfer their text files and have ICD-9 codes assigned on a short time-frame.

Automated outpatient system (NCK). NCK is planning to implement an automated outpatient records system that will capture and assign ICD-9 outcomes to outpatient visits at all HMO clinics.

Guidelines to using LLDB files. Data managers indicated

that a growing number of people are expressing interest in using LLDB files for specific vaccine safety and other types of studies. Because the files are so complex, it is important to develop written guidelines, write model programs, and provide SAS and/or consultation for other users in order to insure the files are being used correctly. This may become very resource intensive, especially as the datasets grow and LLDB results are presented.

Identifying deaths outside of the HMO

(1) Methods of timely capture of non-hospital deaths.
Non-hospital deaths are missing from the OUTCOME files and often unknown at the HMO. The State Death Certificate can have a lag time of up to 18 months in some states. HMOs have explored ways to capture these deaths in a timely fashion from non-HMO data systems, such as the state death registry and SIDS databases.

GHC Monthly provisional tapes from State death certificate, SIDs database
NWK Monthly provisional tapes from State death certificate SIDS database
NCK Monthly provisional tapes from counties within HMO catchment area
Maternal and Health Care record file
SCK Monthly provisional tapes from seven counties within HMO catchment area
Maternal and Health Care record file

These sources identify children but may not contain all the underlying causes of death that is on the finalized Death Certificate. The SIDS registry or Maternal and Health Care record files are probably not good sources for identifying additional names since its source is the same as that used for death certificates but it may have some provisional causes of death that are not known until the death certificate is finalized.

Ned indicated that NCK has other automated data sources that he uses to identify some deaths. The date of death is not available and often these names do not appear in the State death files. These children are kept in the study until some more official record of the death becomes available.

(2) State Death Certificate Data Structures.
Data managers provided copies of the California, Oregon and Washington death certificates and data dictionaries. NIP will compare them to determine what information is common and the format their format. This will enable interested LLDB personnel to know data available for special studies.

(3) LLDB Death file.
Deaths will be reported in the OUTCOME file and not as a

separate file. There will be a different record for each ICD-9 code reported on the death certificate. Preliminary sources of death may have a single record with no DXCODE that is later replaced when ICD-9 codes become available.

Deaths occurring in other outcome settings (hospital, ER, clinic) should be completed as normal with the value of DEATH set to "Y". Additional ICD-9 codes from the death certificate are added, even if they duplicate the records of the other settings.

The variables and the values for death records are as follows:

CDCSITE	HMO code (C, O, S, or W)
STUDYID	Child's assigned study ID
CAREDATE	Date of death.
DURATION	0 (zero)
DXCODE	ICD-9 reported on death certificate. Provisional death records may not have any ICD-9 codes.
RULEOUT	" " (blank) unless an autocoder is used to interpret text strings.
FLAGOCOI	" " (blank) -- code is assigned at CDC.
FLAGACUT	" " (blank) -- code is assigned at CDC.
DXTYPE	Type of ICD-9 code on death certificate: "MC" = Cause of Death "MU" = Underlying cause of death "MO" = Other cause of death
LOCATION	Source of the death record "P" = Preliminary record from State or County death certicate files "F" = Final record from State death certificate "S" = SIDS registry (if used) "M" = Maternal and Health Care records "X" = Other local sources
DEATH	"Y" if death occurred

If the child died during a hospitalization, ER and clinic visit, the child may have two set of records: the first set is coded like all other outcomes in those settings (DXTYPE="BP", "BS", "HP", "HS", "EP", "ES", "CP", "CS" and LOCATION="I" or "O", DURATION=0 or hospital LOS, etc.) with DEATH set to "Y". The second set will be generated, using the variables codes above, when the death record is found in either the preliminary or final death certificate files.

All deaths are identified by subsetting on DEATH="Y". A given STUDYID may have more than one record with the same DXCODE (e.g., one from hospitalization and one from death certificate). All unique DXCODES associated with the death are found by sorting on STUDYID then DXCODE and selecting the first unique DXCODE. Unique children are found by sorting on STUDYID and selecting the first unique STUDYID record.

Automated versus non-automated data

Emmett provided an overview of how several LLDB components interact with each other. Basic to this model is the concept of automated data versus non-automated data. The LLDB files (CONSTANT, ENROLL, VACCINE, OUTCOME, etc.) represent data from automated sources. They are used initially for the cohort analyses, vaccine and outcome rates, etc. Information abstracted from birth certificates and from census tapes during the geocoding process are also part of the automated data.

The quality review process is the examination of 1%-2% of the records to estimate the accuracy of the automated data. It identifies the quality of specific automated systems at each of the HMOs and gives an indication whether the automated data can be used alone or whether case-cohort or case-control studies are needed. Associated with the quality review process is the SAMPLE file. It contains variables in the same format as the automated data but the values are those from the medical record or other document to which the automated data is compared. This file is submitted to CDC and may be used to replace the automated data in special analyses involving the 1%-2% sample. In addition other data not in the automated data, but collected during the quality control review audits, may be submitted and used to supplement the automated data in special studies.

The neurology review process is for verification of ICD-9 codes in the automated OUTCOME file. The results of the medical chart review are entered into the REVIEW file (e.g., reviewed/not reviewed, verified/not verified, period of review, new ICD-9 codes, etc.). This information is compared to the OUTCOME record to determine if the outcome is kept, deleted or modified. At that point the neurology outcome is considered verified automated data. Any additional information not in the automated files but collected during the neurology review process can be submitted to CDC to supplement the automated files when special studies are performed. This information may be general information applicable to all neurology outcomes, or specific information applicable to the ICD-9 code(s) being reviewed. At the same time, if the child were not already in the 1-2% sample, the quality control review could be done to provide additional verified automated data. NOTE: Collection of additional data and quality control reviews would depend on recommendations by the neurologist and statisticians group.

The automated ancillary files contain information that either

helps verify outcomes already in the automated OUTCOME file or indicate that a child has had an outcome of interest that was not reported in the OUTCOME file. These ancillary indicators may identify specific outcomes (e.g., insulin med and diabetes outcome) or general outcomes that would need medical chart review (e.g., EEGs, MRI, neurology referrals without any ICD-9 code in the OUTCOME file). These reviews would generate an outcome record that is in the same format as the OUTCOME file. When added to the OUTCOME file, they become outcome events that may be associated with vaccine exposures in cohort analyses. During the chart reviews, additional information and quality control review data may be collected and submitted in the same manner as in the REVIEW process.

Quality review process and the SAMPLE file
Data managers reviewed the status of the different components of the quality review process.

(1) Quality review analysis. Ned indicated he had tables for John Mullooly to help complete the analysis.

(2) SAMPLE file. Emmett requested data dictionaries from all HMOs describing the automated files they have developed during the first quality control review. The data should fall into several categories: (a) data that is equivalent to the automated files (e.g., vaccine and outcome codes and dates); (b) data that describes the confidence, source and review ranges of the data; (c) data that does not correspond to our current automated data but useful to have available for special studies with the 1%-2% sample; and (d) data that has local use but not submitted to CDC. Emmett will refine the spreadsheets begun in November of 1993 and develop the first format for the SAMPLE process.

(3) Future quality review studies. Data managers will assist the Quality Review committee in developing the procedures for conducting any future quality review studies. This includes (a) standardizing the procedure across sites; (b) identifying variables about the process (e.g., confidence and source of data) that need to be collected; and (c) standardizing the databases that are used to store the quality review findings. Some of this work has already been reported in the quality review committee minutes.

Neurology reviews and the REVIEW file.
The general process was discussed but the specifics could not be determined until the recommendations of the neurology meeting are known.

The REVIEW file would use the information from the OUTCOME file to identify the neurology outcome records that need to be verified. Emmett indicated that it is possible to other automated LLDB information could be printed with this if desired (e.g., other outcomes, ancillary information, demographics, etc.).

Variables in the file would fall into several types:
(1) Variables identifying the outcome record being reviewed
e.g., CDCSITE, STUDYID, CAREDATE, DXCODE and DXTYPE.
(2) Variables identifying the review status, e.g.,

NEEDREVW	Record needs review
REVIEWED	Flag indicating review is complete
DATERVWD	Date reviewed decision was made
RESULTS	Code describing if verification is positive or not supported.
DONEBY	Code describing who/how decision was made
TRIGGER	="N" to indicate neurology review

(3) Variables refining the outcome record

NEWICD9	New ICD9 (DXCODE) if RESULTS indicate the ICD9 code was incorrect in the automated data
ONSET	Probable onset date of the case, if different from the CAREDATE.

If other general data not in the automated file is collected during neurology review, it can be included as variables in this file. If data specific to the neurology outcome is collected in can be reported in separate files.

Ancillary reviews and the NEWCASE (?REVIEW) file.

(1) Uses of the ancillary files.
Loie described some of their work done at NWK to identify children with seizures and asthma from medications in the ancillary file. Virginia (GHC) reviewed the process they used to estimate the number of cases that would be identified at each HMO based on the outcome and ancillary sources available at that HMO. Emmett indicated that GHC's tape 2 data contains outcomes from all settings and has all ancillary components. CDC will compare the cases identified as outcomes with those cases in the ancillary file to determine how the ancillary files can best be used.

(2) Process to review cases from the ancillary files.
The general process was discussed but the specifics could not be determined until the recommendations of the neurology meeting are known.
The NEWCASE (?REVIEW) file would use the information from the different ancillary files to identify a specific outcome to be verified or no outcome, in which case, the medical chart would have to be reviewed to specify the ICD-9 code. Emmett indicated that it is possible to other automated LLDB information could be printed with this if desired (e.g., other outcomes, ancillary information, demographics, etc.).

Variables in the file would fall into several types:
(1) Variables identifying the outcome record being reviewed
e.g., CDCSITE, STUDYID, date, ancillary type, ancillary file. The last two variables would depend on the ancillary file used.
(2) Variables identifying the review status, e.g.,

	NEEDREVW	Record needs review
	REVIEWED	Flag indicating review is complete
	DATERVWD	Date reviewed decision was made
	RESULTS	Code describing if ICD-9 outcome was found or not supported.
	DONEBY	Code describing who/how decision was made
	TRIGGER	="A", to indicate Ancillary file
(3)	Variables	corresponding to variables in the outcome record:
	NEWICD9	New ICD9 (DXCODE) if ICD-9 code was found in the medical record.
	ONSET	Probable onset date of the case. It is equivalent to the CAREDATE.
	OSETTING	Setting where ICD9 was found in medical chart.
	OLOCATION	Location where ICD9 was found in medical chart.

If other general data not in the automated file are collected during ancillary review, it can be included as variables in this file. (?) If the child is not already in the 1%-2% sample, the quality review could be done in order to provide verified data of additional data.

Emmett indicated that Jessica Tuttle, M.D., at CDC has cross-referenced the different ancillary files to non-neurological reviews. PIs will need to specify the specific type of records are to have medical record chart reviews.

Narrative Summary:
Vaccine Safety Data Link Meeting
March 31-April 1, 1992
Atlanta, Georgia

Objectives
The objectives of this fourth meeting of the CDC and contract investigators were to discuss 1) the power of study to reach study objectives; 2) approaches to an analysis plan; 3) the role of automated covariates; 4) clinical issues of defining outcomes of interest and record review; 5) data entry, quality control and quality assurance; and 6) progress and findings in delivery of test data tapes.

Participants
NCK: S. Black, B. Fireman, H. Shinefield; NWK: J. Mullooly; GHC: W. Barlow, T. Payne, R. Thompson. FDA: R. Kapit. CDC: B. Chen, J. Glasser, J. Mullen, P. Rhodes, E. Swint, S. Wassilak.

Introduction
After the meeting was called to order, Drs. Walter Orenstein and Stephen Hadler welcomed the group and iterated the importance of the project as a major source of scientific evaluations of vaccine safety, as well as serving as a resource for generating hypotheses and objective surveillance of adverse events following vaccination. The project is anticipated to be ongoing and serve as a cornerstone for future vaccine evaluations.

S. Wassilak reviewed some recent events and actions related to vaccine safety:

- Following a WHO study in Senegal, in which Edmonston-Zagreb measles was administered at 6 months of age, an apparent increase in delayed mortality in girls following high-dose EZ measles vaccine was observed and has led to discontinuation of routine EZ vaccination there. These findings have apparently been corroborated in other countries and are under further evaluation.

- Canada has implemented an active immunization system to track adverse events as a result of the experience there of aseptic meningitis following MMR administration with Urabe strain mumps vaccine.

- Representatives of several developed and developing nations met in Ottawa in October to standardize case definitions related to adverse events following immunization, although the objectives of adverse event surveillance differ in the developed and developing world settings.

- In Taiwan, recent reports of deaths following vaccination with a particular lot of Connaught Laboratories, Ltd. (Canada) DTP vaccine prompted an invitation to CDC to participate in a investigation, for which B. Chen subsequently traveled.

- J. Glasser is working with Michigan and Massachusetts health departments in an attempt to develop methods to detect vaccine lots associated with truly higher frequencies of reported adverse events.

- There has been a recent report of two cases in the medical literature and direct reports from a physician in Wisconsin suggesting an association between hepatitis B vaccination of adults and demyelinating neurologic conditions. Examination of this issue within the current project may be pursued.

Status Reports

Northwest Kaiser: J. Mullooly reviewed the following:
In an examination of the frequency of outcomes which were generated by a combination of different automated means--i.e., outpatient anticonvulsant prescriptions, inpatient and outpatient procedures (EEGs, MRIs, CTs) and outpatient neurologist referrals--compared to inpatient and ER ICD codes, these means together identified 176 more children than the 99 identified by inpatient and ER neurologic outcome codes. NWK considers this important to continue since they are unable to obtain automated outpatient clinic outcomes. The utility and accuracy of these identification methods will depend on the results of chart review. It was suggested that the 2% sample and the routine NWK 5% OPUS sample should be used to validate these types of results rather than to have special chart reviews, and examine the relationship of date of prescription to date of onset. A similar examination of asthma outcomes indicated little overlap (382 children) of the 2053 children identified by outpatient prescriptions with the 797 children identified by inpatient and ER codes.

A study comparing the completeness of immunization data in the automated immunization database by comparison with medical records showed 100% positive predictive value; there was, however, a 39% negative predictive value, which is likely related in large part to delays in inputing the data. To improve the capture of these events and for accountability reasons, NWK, as a routine procedure goal in 1992, will be routing vaccine sheets to the pharmacies to be entered, including lot information. In the interim, NWK proposes to review the scheduling database to identify likely immunization visits and review the medical charts of those without an immunization entry in the automated file.

Northern California Kaiser: S. Black reported the following:
NCK and GHC have been comparing GHC's autocoder results to NCK's software for reading text fields from Emergency Room reports and assigning ICD9 codes. There was an exact match in 35.4% of the cases, appropriate coding in an additional 61.8% of the cases, and inappropriate codes assigned in 2.8% (1.7% incorrect at NCK and 1.1% incorrect at GHC) of the cases. Of the outcomes of interest to this project, all matched. NCK is further refining their software and will make this available to the other sites. Note that GHC codes, however, are assigned by the autocoder to those text strings of diagnoses not available as check-off diagnoses.

NCK did a comparison of inconsistencies which are present in the automated Immunization Tracking System with immunization logs from another study, in which 21,997 immunizations had been administered. There was a 2% error rate between their two systems, 3/4 of which was omission in ITS; improvements were noted over time. The study revealed a bug in ITS in preventing data entry for vaccines not given simultaneously into ITS which has been corrected.

Soon at NCK, the inpatient ICD codes will specify co-morbidity at the time of presentation versus complications in course of hospitalization.

S. Black distributed a draft of a chart abstraction form which NCK developed to be used in abstracting the medical records for the 2% sample (see below).

Group Health Cooperative: T. Payne cited several recent events:

- GHC is utilizing PCs for data entry which will enable them to more easily incorporate internal edits at the time of entry. Source data is entered at the clinic site, improving the timeliness of data entry.

- The outpatient clinic form for recording outcome diagnoses is being revised and GHC is moving toward an automated problem list.

- Lab and radiology data are being put into a better format to facilitate the review and abstract of data; currently the text for these are captured but purged shortly after entry.

- Washington State will now release the State's entire Birth Records which will enable matching of birth certificates to be done at the project and not the State level.

- Immunization exposure data and immunization rates are being provided to local clinics. This feedback is improving their immunization performance.

- GHC has weekly staff meetings, quarterly meetings of their Advisory Board and has put many files and datasets on the LAN which has improved access to standardized documents used in the study.

- GHC is involved in other programs to improve immunization levels of their clients, e.g., "All Kids Count" and a grant from the Robert Wood Johnson Foundation testing intervention strategies.

- There have been several abstracts developed: (a) tracking system and validation (b) HiB study and (c) comparison of ICD9 codes to child's condition.

R. Thompson added that they have made improvements in their radiology capture, are publishing an Immunization Newsletter, and are repeating studies comparing immunization data in the database to the medical record and direct observation, previously indicating 94% and 99% accuracy, respectively.

GHC also reported they are considering different coding software systems to assign diagnostic codes. They are SNOMED and ICD-10. SNOMED has an advantage of being able to describe a disease on several axes but can be ambiguous; for the outcomes of interest, this system has little import. ICD-10 will not be available for several years. The group discussed the possible use of COSTART or WHOART to provide a standardized coding terminology for adverse reactions, but non-specificity can be a problem, particularly for respiratory illnesses.

Mapping mechanisms for these different coding schemes will be explored in the future.

Power Calculations

E. Swint indicated that the rates for outcomes of events have been input into EXCEL tables. These tables are linked together and age-specific and/or site-specific outcome rates can be calculated. These were used to build curves of incidence rate by age for each of the outcome subclasses/selected outcomes. GHC urged comparison with national rates for the outcomes, which can be done using National Hospital Discharge Survey tapes.

J. Glasser reviewed our most recent power calculations, whose details are described in "Resources...," which was circulated to all participants prior to the meeting. This employed near-actual age-specific exposures and actual age-specific outcome rates as above, together with minimal assumptions about compliance and risk potentially associated with vaccination, to assess -- as realistically as presently possible -- our ability to detect hypothetical hazards. Participants suggested that we consider finer temporal resolution (e.g., days within the week following vaccination), exposure misclassification (e.g., children whose automated vaccination records are incomplete), and that we retain the numbers of exposed and unexposed cases. The spreadsheets that perform these calculations have been since modified in accordance with these recommendations.

The purpose of these assessments is to facilitate planning, particularly resource acquisition and allocation. Participant comments improved the presentation of our case for additional resources to the National Vaccine Program Office. By virtue of our power to detect hypothetical risks after only one year, several outcomes are candidates for early evaluation using automated data: aseptic meningitis; seizures and persistent seizure disorders; asthma; diarrhea; invasive bacterial and other infections of interest; (potentially) site abscesses; and apnea. However, all outcomes will be examined for their relationship to vaccination (see below).

Analysis Plan

Overall Approach: J. Glasser presented a diagram showing the role of the various types of study designs -- cohort, case-cohort and matched case-control. The intent of the study is to use, as much as possible, the automated data in cohort analyses. Our discussion of the analysis plan began with a review of the current situation, in which sites are improving their capture of exposures and outcomes, and CDC is comparing quality-control procedures and scrutinizing the test tapes, striving to ensure that covariates obtained from birth certificates are comparable, and so on. We planned to analyze automated information only if we believed it sufficiently accurate and/or complete, and endeavored to reconsider what criteria to employ in view of John Mullooly's evaluation of exposure misclassification at NWK. We generally agreed that vaccinations must be accurately captured by the automated systems, but deferred precise specification to further exploration of its consequences on power and effect estimates from analyses of hypothetical and test tape data. Misclassification generally reduces power (or increases confidence intervals) and biases generally affect estimates toward the null. The focus now will be on examining the quality of the immunization data in the data bases and implementing means of decreasing error rates. Each site will evaluate their 1-2% sample

to measure error rates so that the impact on power can be determined.

Covariate information: Covariates were excluded from the analysis discussions at the last meeting in view of the dearth of sources by which to evaluate the automated information. Currently, socioeconomic indices are no longer considered appropriate in view of our ability (via multivariate methods) to evaluate the separate contributions of education, occupation, and geocoded income, which various indices weight differently. Similar conclusions undoubtedly apply to indices that might be or routinely are composed of information about prenatal care and exposures in utero, complications of delivery and newborn conditions. We therefore will proceed making the most of the birth certificates, accurately recording addresses for geocoding, and comparing these automated data with whatever other sources are available (document circulated at the meeting in Seattle). Further issues involving covariates are further detailed under data management issues.

Our discussion of the intervals following vaccination during which children would be considered recently exposed began with a review of our objectives. These include (a) evaluating putative mechanisms for known associations, (b) evaluating hypothesized associations, (c) detecting heretofore unknown associations (i.e., risks or benefits), and (d) elucidating risks to develop contraindications. Demyelination as the potential mechanism of GBS following vaccination was used to illustrate the first class of objectives. Insofar as this process is thought to occur in 2 to 3 weeks, it would be inappropriate to consider those cases exposed less than 1 or more than 6 weeks prior to onset (i.e., from half the lower bound to twice the upper one) as having been recently exposed in a study designed to evaluate this putative mechanism. Appropriate window sizes were discussed to capture short-term, delayed and long-term associations. Window sizes of 0-3, 4-7 (or 0-7), 30 and 90 days were proposed.

To evaluate hypothetical associations and enable us to detect ones mediated by processes occurring on a range of time scales, we agreed to be much more generous. But we must set a reasonable limit; else virtually every outcome will be associated with an exposure, however distantly. To elucidate associations, moreover, we ought to evaluate various intervals. Bill Barlow's later presentation of his analysis of seizures following DTP at the GHC was more interesting than the hypothetical one employed and equally to the point: The extremely short onset interval observed portends a particular etiologic mechanism, and--given additional clinical information (e.g., temperature)--may suggest a means of dealing with this problem (i.e., premedication, especially of children disposed to febrile seizures). Much productive discussion ensued as to the details, which will be evaluated using the tape data.

Besides cohort and case-cohort methods, we plan to perform matched case-control studies of any apparent exposure-outcome associations that survive whichever of those analysis methods is deemed appropriate, a decision to be based on the completeness and quality of the automated data. Scrutiny of hypothetical data using a nested, but otherwise ordinary case-control analysis, together with cohort and case-cohort analyses, was circulated to the statisticians prior to the meeting. These and preliminary mock analyses of convulsions, the most common outcome on the test tape, by the methodology appropriate for matched case-

control studies (i.e., conditional logistic regression) were reviewed by the statisticians at a meeting whose minutes are summarized separately. Revised documents have been sent to them, the second now including analyses by the self-control method.

An enlightening discussion of whether or not--with such possible exceptions--we should analyze all possible associations whenever tapes are received ensued. Provided that tentative results do not affect our subsequent behavior (e.g., positive ones preclude further analyses), the conclusion was generally affirmative. The group felt that, as a surveillance system, the data could be examined often because part of the purpose of the project was to explore possible associations between vaccinations and adverse events which were not known before. R. Kapit aptly stated that, as a representative of a regulatory agency, he felt it was as important to know that vaccination has no or only a small risk, as it is to know that there is a large risk present. The group supported this concept as the main objective of seeking high study power. P. Rhodes suggested that there should not be a rush to publish or to cause alarm at the beginning. S. Black said part of the first year's analysis should be to justify continuation of the study and part of this would be to confirm associations which are already known.

Study Designs J. Glasser indicated he is using GLIM software to develop some analyses for the test tape. These will be shown more in depth to the statisticians. B. Barlow showed two analyses he developed on GHC's outcome and vaccine data, to examine the relationship between DTP exposure and seizures. These analyses compared subjects at a given age and time following vaccination for different exposures.

On April 1, 1992, the group divided; clinicians stayed at the Mariott Courtyard while statisticians went to CDC to review study design methodologies.

Medical Record Abstraction

Chart Abstraction Forms for Quality Control: The chart abstraction form would be used to abstract information from the medical record chart on the 1-2% sample. The sample would be those identified from the random number variable SOURCE. Although the frequency of abstraction will be determined after the completing the initial review, the current plan is for annual review updates for children newly entering into the 1-2% sample and at least one subsequent review to obtain new information for the sampled children. Data would be entered and reviewed at each site as part of contract expenses. Results of the first year's review would determine changes needed in the review procedure as well as ways to improve data collection methods, as well as determine the approach of future comparisons. The group reviewed each section of the proposed form from NCK. With this major contribution from NCK, this quality assurance abstraction procedure will begin as soon as possible. NCK subsequently revised the form based on discussion points from the meeting and further experience. This revision includes: (1) adding a section on prenatal/congenital conditions; (2) recording the full immunization history, including data prior to the study beginning and containing route, body site and dosage; (4) exclude diagnoses for URI, viral syndromes and otitis media from ER and outpatient clinic visits; (4) rearrange ER and outpatient clinic visits sections so they are together; (5) keep RESULT of procedures on form.

Clinical Conditions Requiring Medical Record Reviews:

Neurologic outcomes: The group indicated that all neurologic outcomes of interest, excluding febrile seizures and aseptic meningitis should have a full medical review and, potentially, confirmation by a neurologist. Simple febrile seizures should be classified and a certain percentage of these reviewed based on their classification. Other abstractions and potential neurology reviews would be triggered by EEG procedures, presence of specific medications and laboratory results.

Encephalopathy: Outcomes which are likely to have be under close scrutiny should have case information collected so that one could easily display the symptoms displayed, vaccine given, interval between vaccine and onset, etc. There is a need for a clear definition of the outcome, a full review, and copies of their medical record.

Anaphylaxis: Outcomes need a clear case definition. The group suggested that all anaphylaxis and hives ICD9 codes should be reviewed but not all "wheeze" codes.

Additional Considerations: S. Wassilak stated that sites may be interested in comparing side effects following the first and second doses of MMR. Additionally, he reported that the National Vaccine Injury Compensation Program staff reviewed the study protocol and indicated their interest in the occurrence of symptoms of tuberous sclerosis following vaccination.

Data Management Issues

Birth certificates: Each site indicated that they need full access to complete birth record files from their state. E. Swint reviewed each state's birth record tape layout of variables which could be used in the Covariate file. Each site expressed interest in having CDC match their members to the birth certificates in order to have matching to the other states' birth record files for their members born in those states. This must be done in a way that preserves confidentiality while recognizing the need to have a full copy of the birth certificate information for matching records. CDC will refine the submission procedures needed to insure identifying information cannot be merged with other LLDB files, (2) identify site information needed to merge the files, and (3) will develop the standardized coding needed for the covariate files. As currently envisioned, pending approval of site data managers, IRBs and administrators, the process will be complex. In order to protect the privacy of the HMO clients and avoid any opportunity to link at CDC an individual or his/her address with a given medical history, several steps will be taken in handling information with potential identifiers so that privacy will be ensured. Based on the ensuing discussion, a mechanism for merging of birth certificates with clinical data was decided: the public portions of the birth records will be forwarded to CDC for merging with enrollment rosters at all sites based on a combination of the California Medicaid and Vanderbilt merging schema. This matching will include identifying information but not the scrambled ID used for other CDC project merging (STUDYID, but rather a separate scrambled ID (BCRID); following the matching, these files will be returned to the sites for correct identification of individuals and merging of the covariate information on the confidential portions of the birth certificate by birth certificate number before forwarding to CDC with the scrambled STUDYID number.

Geocoding information: The present structure of the ADDRESS file does not allow CDC to know when an address has actually changed from one poll date to another. This is needed to know when an additional geocoding survey is to be done.

Submitting addresses to be geocoded from all sites together will save money (although the process is relatively inexpensive at $750/137,000 matches), particularly additions as members are born into or otherwise join the study population and changes as they move. In order to proceed on this means of obtaining covariate information, similar procedures will be used to protect client privacy. It was proposed to collate address information from all sites at CDC using additional scrambled ID numbers (GEOID) and send to the geocoder. Geocoding will occur at least twice in the 5-year study, for initial then new and moved study clients.

Death Tapes: The State death certificates will have to be assessed. FDA has particular interest in this aspect of vaccine risk evaluation.

Outcomes of Interest: E. Swint presented a list of nine ICD9 codes which were being coded as emergency room visit outcomes but were not on the CDC list of outcomes of interest, which the group reviewed. The following codes were added to the list of study outcomes of interest:

486.* Pneumonia, organism NOS -- added to "other inf. of interest" subcategory
400.* Bronchitis NOS -- added to "Bronchitis and Asthma" subcategory
558.9 Noninfectious Gastroenteritis NEC -- added to "Diarrhea" subcategory.

The other codes reviewed will not be flagged as outcomes of interest.

The group also identified two supplemental files which would be needed to validate and/or supplement birth certificate information and to identify potential underlying medical conditions present before vaccination. Sites should create (1) a local birth record file containing birth record information on all study children born in their HMO hospitals and (2) a file of all hospitalizations and the associated diagnostic codes from birth to the current date.

Edit of Test Tapes: E. Swint presented a brief summary of test tape edits. Handouts were made available which showed missing, unavailable and frequencies of variables on each of the files. Sites indicated that many of the variables unavailable on the test tapes would be available later. The group decided to drop the variable SUBSIZC from the ADDRESS file since none of the sites could create the information.

Standardized File Edits: E. Swint reported that a site by site comparisons of edits in place was part of the handouts. NWK indicated that a single list of edits should be prepared. CDC will provide a list based on each the site's Quality Control documents and distribute to data managers for review.

Pharmacy File: The group decided to use NWK's list of medications for the pharmacy file. This includes medications for anti-convulsant, bronchodilators, asthma, TB, and Oral Gold. Iron prescriptions were added by GHC. The file structure would remain the same as specified in the data dictionary (MED and PHARDATE). Sites should not differentiate between first

medication and refills.

Laboratory File: The use of standardized codes for microbiologic assays by source and type of pathogen was discussed. In addition, specific steps for identifying hemolytic anemia and thrombocytopenia, and using anticonvulsant level assays as a means of case identification were indicated. The data dictionary for this file will be further discussed by conference call.

Future Directions

S. Wassilak indicated CDC interest in adding ancillary studies at minimal additional costs within the HMOs, including studies of varicella incidence and complications and comparative studies of DTaP vaccines. A specific proposal was distributed for the former and will be circulated for the latter for comment by site investigators. S. Wassilak requested interest in the current data for examining acute flaccid paralysis for children in the context of polio elimination.

Additionally, there are several ways in which the project can be enhanced. It is the intention of CDC to have this as an ongoing project, so that the length of study may be extended at some or all existing sites. Other potential enhancements are to: (a) add a new site, (b) add more clinics at NCK, and (c) add additional age-groups at existing sites. Limitations to adding new age-groups is minimal except (a) immunization file is designed only for <7 yr olds at NCK, (b) older people may have immunizations outside the HMO, (c) and outpatient diagnostic codes being used for outcomes might not all be appropriate for older age groups.

LLDB Project funding and expenditures were reviewed by J. Mullen. Projects should make sure they are having enough funds available when chart reviews are needed and should examine areas of high costs.

Miscellaneous

S. Wassilak reminded the group that progress reports were due in May. Sites should share copies with other sites.

B. Barlow (GHC) has written the variance in case-control assessment for a statistical journal. He will select an outcome which does not have significance to use as an example.

S. Black is presenting a paper to the Society for Pediatric Research and requested suggestions. GHC will provide NCK with a copy of vaccine frequencies, by vaccine. CDC will provide additional information to S. Black on exporting the map files to other packages.

J. Glasser summarized the statistical breakout group. They reviewed power calculations, mock analyses and proposed teleconferences.

NCK indicated that some information which is available in automated format but routinely purged could be stored on tape in the event it is needed in the future. This could reduce the need for more costly chart reviews. Examples include radiology dictation tapes, laboratory data, and microbiology results.

Meeting to Discuss Analytical Issues

Bill Barlow, Bruce Fireman, John Glasser, John Mullooly and Phil Rhodes met for several hours while others were discussing clinical issues during the morning of 1 April 1992 to discuss analytical ones, particularly our power calculations, descriptions of three analytical designs and a mock analysis of the test tape via a fourth design.

Our discussion of the power calculations included better ways of presenting the results to different audiences (e.g., minimum detectable rate ratios and differences, and amounts and factors by which increasing the size of one study population, adding another or both affected them), modifications (e.g., altering temporal resolution to accommodate events with very short onset intervals (i.e., from weeks to days, hours, or some combination), weighting the regressions of various outcome rates on age, including the numbers of exposed and unexposed cases), and other potential uses (e.g., to evaluate differential exposure misclassification, particularly children whose automated vaccination records are incomplete).

We reviewed case-control, cohort and case-cohort analyses of hypothetical observations composed of 100 cases and 4900 non-cases, whose ages, times since most recent vaccination and numbers in the unit interval were randomly generated, either uniformly or with more or less appropriate means and variances, and a nested case-control analysis of observations from the test tape composed of 70 cases of the most common outcome (ICD-9 Code 780.3, Convulsions) and age-matched controls. Revisions in response to criticism accompany the copies of this report sent to participants, as does yet another analysis of the test tape using the self-control method, which was mentioned in the Request for Proposals, but inadvertently omitted from subsequent consideration.

Our analyses of hypothetical data will continue as long as these exercises facilitate the communication, if not resolution, of analytical issues. We will exploit the explicitness, versatility and power of GLIM until other software proves sufficiently superior for analyses of particular importance to overcome the virtues of a common analytical tool. Besides this ongoing consideration, forthcoming activities are to determine the sensitivity of various methods to the anticipated misclassification, to explore alternative exposure windows (other aspects of issues mentioned in connection with our power calculations), procedures for integrating data from the three sites, and so on.

We plan to confer periodically between meetings and additionally as the need arises.

John Glasser

Vaccine Safety Datalink (VSD) Meeting
Center for Vaccine Research; Harbor-UCLA Medical Center
Torrance, CA; January 12-13, 1994

Present: Group Health Cooperative (GHC) -- William Barlow, Virginia Immanuel, Thomas Knauss, Angela Salazar, Robert Thompson; Harbor-UCLA Medical Center and Southern California Kaiser (SCK) -- Nancy Goff, Jennie Jing, Marlene Lugg, Michael Marcy, Patricia Osborne, Constance Vadheim, Joel Ward, William Shields; Northern California Kaiser (NCK) -- Steven Black, Bruce Fireman, Jean Hayward, Ned Lewis, Henry Shinefield; Northwest Kaiser (NWK) -- Lois Drew, John Mullooly, John Pearson; Centers for Disease Control and Prevention (CDC) -- Robert Chen, Elias Durry, John Glasser, Stephen Hadler, Steven Rosenthal, Emmett Swint; Food and Drug Administration (FDA) -- Henry Hsu, Suresh Rastogi, Robert Wise; National Institutes of Health (NIH) -- Steven Wassilak.

Joint Session, January 12th, a.m.

John Glasser began the meeting with administrative remarks followed by welcome from Joel Ward. Attending staff members from each group were introduced by Robert Thompson, John Mullooly, Steve Black, Joel Ward, Suresh Rastogi, and Bob Chen.

Bob Chen described some developments relevant to the VSD study, including creation of the National Immunization Program (NIP), which reports to the Director of the CDC, and institution of the Childhood Immunization Initiative (CII). The CII sets goals of 90% vaccine coverage by two years of age for MMR, 3 OPV, 3+ DTP, and 3+ Hib; and 70% coverage of 3 HBV by 1996. It also sets morbidity goals of zero indigenous cases of measles, rubella, wild polio, diphtheria and tetanus among children less than 15 years old, and Haemophilus influenzae type b infection among less than 5-year olds by 1996. Currently the NIP is reorganizing to accomplish these goals, but the VSD probably will be minimally affected. Since July of 1993, two medical epidemiologists and an EIS officer have joined the Vaccine Safety Activity.

Bob also mentioned that the IOM has recently published its study of adverse events following receipt of childhood vaccinations against diseases other than pertussis and rubella (which J. Glasser had sent to the investigators). He highlighted their inability to reach conclusions about vaccine associations with 33 of the 54 studied adverse events due to insufficient evidence. He mentioned three workshops recently conducted on vaccine safety (by the FDA on simultaneous vaccination and harmonizing vaccine adverse event terms, and by the IOM on research strategies) and papers presented at the ISPE and ICAAC meetings.

Among the issues discussed during the IOM workshop was an advisory committee for the VSD and means of sharing with other

investigators this study's methodologies and findings. In regard to creating an external advisory group, Joel asked whether the CDC had decided to form such a committee. John Glasser replied that no such decision, including the necessity for a committee, had been made and that this issue would be discussed thoroughly with all investigators.

Following Bob's presentation, participants dispersed into three concurrent sessions for discussions of neurological outcomes or data management or analysis that lasted throughout the day.

Separate Sessions, January 12th

Neurological Group -- Tom Knauss, Robert Thompson (GHC); John Pearson (NWK); Jean Hayward, Steve Black, Henry Shinefield (NCK); Don Shields, Mike Marcy, Joel Ward (SCK); Steve Rosenthal, Elias Durry, Bob Chen, Steve Hadler (CDC); Steve Wassilak (NIH)

We began by clarifying the purpose of assembling the group. Unlike the other outcomes, the specificity of neurologic ones was deemed insufficient for reliance on automated data in screening for potential vaccine associations. Therefore, it was decided that, with the exception of aseptic meningitis, neurologic outcomes of interest required chart review to ensure that cases met definitions. Based on our results (and others in the literature), we may decide to perform more extensive nested case-control studies with more thorough chart abstraction and case definitions. But this was not the main charge for the day. The group then prioritized its discussion from the most to least difficult neurologic outcomes.

Acute/Persistent Seizures: It was decided that both issues are of interest in this study, but require different case finding methods. For acute seizures, the current method is workable, but for persistent seizure disorders, as much time as possible should be allowed to lapse before these charts are reviewed (e.g., at exit from the study, age 7 or departure from HMO).

Encephalopathy: The definition developed by Jerry Fenichel for revision of the Vaccine Injury Table and published in the Federal Register should be adapted without his distinction by age. Similar to seizures, the acute cases would need follow-up $\geq$1 year later to learn the status of their recovery. Acute episodes require hospitalization, with coma or stupor not attributed to medication or post-ictal state.

Sensorineural Hearing Loss: It was the consensus of the group that onset dates could not be assigned with any degree of accuracy. The diagnosis would be made in many children only when they start performing poorly in school, many years after initial onset. It was decided therefore to exclude this outcome from screening chart validations. Crude screening analysis using other dates (e.g., of diagnosis) may still be possible, but

results will always be questionable.

Ataxia: This outcome should be narrowed to Acute Cerebellar Ataxia.

Polio: Case definition should match that used by the CDC for vaccine-associated polio as closely as possible.

Cranial Nerve Disorders: The only cranial nerve disorder likely to be diagnosed is facial nerve (e.g., Bell's Palsy). There was consensus that the accuracy of this diagnosis is quite good by the average physician, so screening chart abstraction was unnecessary for this outcome.

Increased Intracranial Pressure: This outcome should be renamed Pseudomotor cerebri.

Other Aspects of Neurologic Outcomes: Relatively straightforward discussions were held that improved case definitions, chart abstraction forms, and search methodology.

Steve Rosenthal and Robert Thompson were assigned the responsibility to revise the case definitions and chart abstraction forms taking into account the day's discussion. Drafts are to be circulated in approximately 2 weeks, in time for a conference call among the neurologists in about a month's time.

R. Chen

Analytical Group -- Bill Barlow (GHC); John Mullooly (NWK); Bruce Fireman, Paula Ray (NCK); Peter Christenson, Marlene Lugg (SCK); Suresh Rastogi, Henry Hsu (FDA); Phil Rhodes, John Glasser (CDC)

We spent the morning conversing with Phil in Atlanta via telephone about solutions to problems that he had encountered in screening our 34 outcomes of interest for association with the common childhood vaccines, and most of the afternoon discussing packaging these results for various audiences, dealing with automated data of variable quality (e.g., whether to plan on case-cohort analyses or not, and if so, whether or not everyone should extract additional information the next time that they reviewed their 1-2% samples) and complementary analyses that other statisticians could perform (e.g., Poisson regression at NCK with misclassification corrections from NWK).

Phil employed a Cox model stratified on HMO, whether or not outpatient visits were captured and date of birth (within 3 days, but indicated that this could be modified as data accumulated or varied among sites to maintain comparable strata), with calendar time as the temporal dimension and allowing for multiple entries, exits and events. Whenever events occurred, times since most recent exposure to common childhood vaccines were calculated for every member of the risk set (same values of the stratifying

variables), and whether or not each was in various intervals and windows of particular vaccinations was determined.

Our original plan, formulated before Phil joined this project, was to perform cohort analyses if the automated data sufficed for this purpose and case-cohort ones, using augmented records of cases and members of the 1-2% samples, otherwise. Phil's choice was based on computational ease without much loss of efficiency, but won't be as easy to communicate to our primary audience, pediatricians and parents. We decided that Bruce would pursue a modification of the original course, namely use information about misclassification from John Mullooly's assessments of the automated data quality to correct his analytical results.

Phil advocated reviewing more records of children who appear to have experienced outcomes of interest, particularly those exposed on the same day (to ensure that exposures preceded these outcomes), but generally because our 1-2% samples contain far less information about rare outcomes than common exposures. In particular, he suggested over sampling such children in the age ranges where recent exposures are most likely. The value of learning more about outcome data quality notwithstanding, it wasn't clear how this would inform Cox analyses. Should we stratify on whether records were reviewed or sample what appear to be informative strata (i.e., cases and discordant risk sets) by virtue of the automated data alone, ...? The neurological case ascertainment provides an opportunity to review the records of children with one-third of our outcomes of interest; should we subject them to the 1-2% sample protocols?

J. Glasser

Joint Session, January 13th, a.m.

The meeting resumed with John Glasser highlighting the second day's agenda and announcing that PIs and POs would meet in executive session during lunch. He and Bob Chen summarized the concurrent neurological and analytical sessions on 1/12 (above; minutes of data management session were distributed separately).

ANALYTICAL RESULTS:

Descriptive Epidemiology (John Glasser)

John stated that his purposes in describing the exposures and outcomes were to (a) ensure that the data were sensible, (b) identify differences among sites that might implicate data management versus medical practice, and (c) inform subsequent multivariate modeling. Then he illustrated age-specific vaccination and cumulative vaccination rates (interpretable as average numbers of doses), and suggested that we perceive differences among sites as natural experiments. Defining

coverage as the quotient of these observed and the expected numbers of doses, he illustrated DTP coverage.

With regard to our study population, he illustrated the age distributions of all children and those whose clinic visits were captured, which indicate different population dynamics in the three HMOs. We capture outpatient encounters only at GHC and a similar-sized portion of NCK, but because we don't know which children's outpatient visits will be captured until they seek care at one of three large clinics, recruitment to this portion of NCK's population occurs during the first few months of life.

John also illustrated age-specific rates of selected outcomes among sub-populations whose clinic encounters we do and don't capture by site and setting where different. He assigned visits separated by outcome-specific intervals to sites hierarchically (i.e., children hospitalized following urgent care or clinic encounters were counted only as having been hospitalized) and modeled them using Poisson regression. Because our ability to detect differences among sites and settings varies with the number of observations, only substantive experts (e.g., local clinicians and data processors) can determine whether or not statistical differences are meaningful.

Taking seizures and persistent seizure disorders as an example, he indicated that models ignoring site and setting were superimposed on aggregate rates in the first of three figures; the other two illustrate only modeling results. The less well these models fit those data, the greater the differences among sites or settings. The second figure illustrates age-specific rates in the two sites at which only hospitalizations and urgent care encounters are captured, which pertains to roughly two-thirds of NCK and all of NWK, and the third illustrates them in the two sites at which clinic encounters also are captured, the remainder of NCK and all of GHC.

These rates or age-distributions differ with setting, but the nature of such differences varies among sites, most strikingly between GHC and the others: Children having seizures either present for urgent care or are hospitalized at NCK and NWK, whereas they most commonly seek care at GHC's clinics. The ages of children presenting at NCK's and NWK's facilities suggest that those with febrile seizures present at urgent care facilities while children with afebrile seizures are hospitalized, possibly after presenting elsewhere first, but their age distributions don't differ among settings at GHC.

John suggested that whether or not such differences affect our ability to detect vaccine associations was a matter that Phil Rhodes might discuss. Meanwhile, he asked investigators to study the descriptive results illustrated in his handout and share any insights about the apparent differences in exposure or outcome rates by site and setting.

Automated Data Quality (John Mullooly)

To assess the quality of automated data, John compared automated and conventional records using 1-2% samples of the study cohorts.

When he compared automated vaccination dates with those abstracted, accuracy differed among sites. These differences probably are attributable to the procedures employed for recording vaccinations. NCK, which had the highest match (96-98%), uses research personnel to audit vaccinations. NWK also has its own vaccination auditing system, with data being entered by clinic personnel. GHC also uses vaccinations entered by clinic staff, but without special auditing procedures.

To compare outcomes in the automated emergency room (ER) database to those identified by chart review, John used outcomes (within the same week of vaccination) identified at GHC. Eighty-nine percent of outcomes matched the autocoder, 85% with chart review finding, and 77% with either. Based on these data, he highlighted the need to improve the autocoder and develop a supplemental system to code ER records.

John also evaluated the ability of ancillary sources to capture neurologic outcomes. Among 348 charts of children who did not have automated inpatient or ER neurologic diagnosis, 45% had a neurologic diagnosis, including rule out diagnoses. These were identified by reviewing diagnostic procedures, mostly EEGs (63%), anti-seizure medications (11%), and referrals (3%). Twenty-three percent were identified from multiple sources.

Use of the pharmacy was highlighted in identifying patients diagnosed with asthma. Among children born between 1/1/90 and 12/31/91, 12% were prescribed anti-asthmatic medications during their first year of life.

John also explained his model for misclassification.

Screening for Association (Phil Rhodes via telephone)

Phil described vaccines, outcomes, and vaccine-outcome combinations and presented analytic results. He also discussed problems and opportunities for future screening analysis and directions for the VSD.

Vaccines: He described the number of vaccinations by age and antigen, including simultaneous administration. He discussed the difficulty of differentiating the separate effects of vaccines, if any, when given simultaneously.

Outcomes: Phil also tabulated visits at which outcomes of interest were diagnosed and compared them with acute events. The frequencies with which events occur after vaccination determine which analyses are possible. In these, medical events rather

than visits should be analyzed. Follow-ups were eliminated by designating "black-out periods" following medical events (e.g., diagnosis of encephalitis) that varied among "items."

Vaccine-outcome: Vaccines were analyzed for association with outcomes in time windows such as 0, 0-1, 0-2, 0-7, and 0-30 days following vaccination. By comparing the risks during these intervals with that 30+ days after vaccination, the relative risks (RR) were estimated using stratified Cox regression models in a manner that resembles matched case-control analyses.

Apparent differences in the risk of seizure following vaccination with DTP, MMR, Hib, and OPV among sites could be attributable to differences in ability to capture outcomes in various settings, in the settings at which outcomes occur or in ICD-9 coding. If enough events occur, site-specific analyses would be appropriate.

Phil illustrated how differences in scheduling and practice among sites could be used to separate associations between events and vaccines given simultaneously. Because DTP and Hib were given simultaneously, for example, risk of seizure in various windows of vaccination with both were similar. If adequate numbers of either vaccine were given on different days, however, one could differentiate the association of seizure with DTP and Hib. More complex analyses could differentiate between associations of simultaneously administered vaccines with outcomes. One such model compared risks of an event following simultaneous and separate administration of several vaccines.

Problems with Screening Analysis:

- ICD-9 codes that fall into multiple items and/or subcategories;
- Different ICD-9 codes for the same event in different settings (e.g., seizure);
- Changes to programs for analysis of vaccine-outcome associations.

Areas Requiring Improvement:

- Difference among sites and settings;
- Difference within sites;
- Difference among sites for outcomes occurring on the same day as vaccination;
- Correspondences and differences among visits, codes, and events.

Areas that Require a More In-Depth Look:

- Explore multiple event issues;
- Relationship among events of different types;
- Examine whether outcomes of interest delay or prohibit use of certain vaccines;
- Analyses looking at more than one vaccine at a time;

- Look within the 34 event subcategories to see if vaccines may be associated with portions of them;
- Controlling for other information (e.g., sex, information from birth certificate, geocoding) or looking for interactions.

We must decide who will perform each task; input from physicians and data managers will be essential.

Future Directions -- Possible Restructuring of:

1. Quality control activities

- Not enough focus on or information about cases;
- Over sample children appearing as cases or do separate quality control on cases;
- Could focus the quality control sampling so as to over sample those ages at which vaccination is likely to occur, over sample children during ages which they should be receiving vaccinations, but do not appear to be doing so.

2. Intensive studies (e.g., neurologic outcomes)

- Most neurologic outcomes are rare, which could allow to look at all charts in some depth;

- Seizures are not rare

  Do we want to look at all charts?
  Do we want to look at all charts in a cursory manner?
  Look at some sample of charts in depth?
  How to sample?

- ALL CASES ARE EQUAL EXCEPT SOME ARE MORE EQUAL THAN OTHERS; e.g., for seizures, cases occurring shortly after vaccination are the most important to explore in depth, 'unexposed' cases occurring at ages where vaccination is common may be next most important, etc.

Discussion:

Steve Hadler suggested assigning several outcomes to each investigator, and there was a general understanding of the need for this considering the work to be accomplished. The investigators agreed to review their interests and ability to study outcomes to facilitate such assignments.

Ascertainment of Deaths in Non-Medical Settings:

Bob Wise opened this discussion by describing the importance of including death as a study outcome to ensure public confidence. His opening statement was followed by summaries from the PIs

regarding their collection of data from death certificates.

Robert Thompson said that 80% of GHC's deaths are known to his group. He also stated that they will receive death certificates from the State Coroner's office with a three month lag. They plan quarterly linkage with their data and could match death certificates with birth certificates. Furthermore, they plan to use the SIDS registry as a back up.

John Mullooly reported that NWK will obtain data from the State of Oregon, and link it to their database themselves.

Steve Black stated that NCK is cooperating with five counties to study SIDS, and will link county death and HMO membership records. He mentioned two other sources of information about deaths: (1) SIDS registry in Sacramento and (2) monthly tapes from the CA Maternal and Child Health Office, from which autopsy reports also are available.

Joel Ward cautioned against concentrating too much on SIDS and duplicating efforts by looking at any subset if we are interested in all deaths. He stated that SIDS could be studied in a pilot to evaluate the utility of a broader approach. He also stated that methods should be standardized because causes of death on death certificates are unreliable.

Joint Session, January 13th, p.m.

The meeting resumed with Emmett Swint's presentation of data management activities. Discussion on the definition of non-neurological outcomes by Jessica Tuttle, via phone, was canceled due to lack of time.

Data management activities in 1993 (Emmett Swint)

Emmett recapped his activities in FY 1993: editing and adjusting tape 1; defining acute events; creating files for vaccine rates, acute outcome rates and association analyses; assisting the quality review committee; establishing a system to classify VSD data sets and documentation; identifying resources needed to convert from mainframe processing to a minicomputer; and interacting with HMO data managers to specify the data dictionary for the second set of VSD files.

Tape 2 status: Next he reviewed the status of tape 2 submission: all files have been received from GHC and all save Pharmacy and Address from NWK. April is the target date for SCK and NCK to submit their files. Priorities for partial tape submissions were established in the data manager meeting on January 12th: (1) files to perform rates and cohort analyses and identify neurology outcomes for review (CONSTANT, ENROLL, VACCINE and OUTCOME); (2) file to abstract socioeconomic information from census tapes

(GEOCODE); (3) files to perform birth certificate matching (BIRTHMAT and State Birth Certificate files); and (4) ancillary files to identify new cases (PHARMACY, PROCED, LAB).

Data management issues: Data management issues that surfaced during the year and had been discussed with data managers on the previous day also were reviewed:

a. Enrollment dates used to calculate child days were adjusted for start dates after the date of birth and vaccine or outcome dates out of range. Data managers suggested that the impact of these adjustments be reviewed prior to using them with tape 2 files.

b. Many outcomes of interest occur primarily in the outpatient clinic setting and HMOs without outpatient records will miss many outcomes in their automated datasets. Characteristics of outcomes from HMOs with outpatient records (GHC and three clinics at NCK) were shared with the group.

c. The outcome of interest table contains duplicate ICD-9 codes in different items and subcategories. Data managers indicated that the current methodology is very good for selecting specific items, but one must eliminate duplicates when aggregating counts at the subcategory and category levels.

d. The manner in which acute episodes are defined affects the numbers that children have and their dates of occurrence. Data managers felt that designing an algorithm that minimized the misclassification of follow-up visits as acute events was important. PIs offered the following suggestions to improve the definition: (1) examine distributions of visits to determine if other intervals might be more appropriate; (2) some outcomes such as diarrhea should have relatively constant intervals while chronic conditions such as seizures or asthma might have less predictable ones; and (3) the setting of an acute episode should reflect the most serious setting, if the child visited several, even if it was not the first (i.e., hospital, then ER, and then outpatient clinic).

Identifying deaths outside the HMO: Then Emmett presented the structure proposed by data managers to integrate deaths identified from death certificates and other sources. Merits of using SIDS registries and other databases to ensure that all deaths had been identified and to provide provisional causes of death were discussed.

Ancillary files: Finally, he presented several tables, as examples of the relationship between the neurological outcomes of interest and ancillary information, and noted that: (1) NWK has reviewed some charts to identify the percentage of children in the pharmacy file with supporting ICD-9 codes in their medical charts and (2) GHC has approximated the number of medical records that would require review based on the settings and ancillary

files available. During the early part of this year, CDC will examine GHC's second year tape to help define the utility of the ancillary files in identifying new cases, especially at HMOs that do not report outpatient outcomes.

Establishing Priorities (Bob Chen)

Bob distributed a spreadsheet listing outcomes (from the VSD study and IOM report) by vaccine and site that would lead the investigation of possible associations. He indicated that there was agreement between the VSD and IOM lists, excluding chronic events and ones with insidious onset. The only outcome studied by the IOM that is not on the VSD list is erythema multiforme (which was on an earlier list, but inadvertently dropped). Bob outlined criteria to prioritize the study of each outcome based on specificity of association, frequency or severity of outcome, and interest. He stressed the importance of dividing the lead among sites in investigating these outcomes, and instructed each PI to rank the entire list of outcomes according to their interests and ability to obtain the necessary data.

Discussion:

Steve Hadler suggested that we should concentrate initially on a few outcomes (e.g., with frequencies exceeding 1000 events, of which there are less than 10) and ask systematic questions as a specific focus. These questions will be assembled by CDC and disseminated to the sites for discussion. Participants agreed to discuss this issue further during the next conference call, scheduled for February 15, 1994 at 11 a.m. Pacific time.

Addition of adolescents and adults: Bob Chen stated that older children and adults would be added to the study eventually, but with modifications of methodology. Insofar as adults are concerned, for example, retrospective case-control studies seem most appropriate.

Questions on budgeting and future activities: Robert Thompson raised several questions in regard to budgeting of such unanticipated activities as:

- What did we miss in the last 4-5 years (e.g., no budget for controls)?
- What would it take to include adults?
- What is the extent of reviewing neurologic events?
- What level of chart review is necessary to obtain reliable information on cause of death?

After these questions were presented for further discussion at another time, the meeting was concluded and adjourned by John Glasser.

E. Durry

Analytical Group -- Bill Barlow (GHC); John Mullooly (NWK); Bruce Fireman, Paula Ray (NCK); Peter Christenson, Marlene Lugg (SCK); Suresh Rastogi, Henry Hsu (FDA); Phil Rhodes, John Glasser (CDC)

We spent the morning conversing with Phil in Atlanta via telephone about solutions to problems that he had encountered in screening our 34 outcomes of interest for association with the common childhood vaccines, and most of the afternoon discussing the packaging these results for various audiences, dealing with automated data of variable quality (e.g., whether we should plan on case-cohort analyses or not, and if so, whether or not everyone should extract additional information the next time that they reviewed the 1-2% samples) and complementary analyses that other statisticians could perform (e.g., Poisson regression at NCK with misclassification corrections from NWK).

Phil employed a Cox model stratified on HMO, whether or not outpatient visits were captured and date of birth (within 3 days, but indicated that this could be modified as data accumulated or varied among sites to maintain strata of similar size), with calendar time as the temporal dimension and allowing for multiple entries, exits and events. Whenever events occurred, times since most recent exposure to common childhood vaccines were calculated for every member of the risk set (same values of the stratifying variables) and whether or not each individual was in various risk intervals and windows of particular vaccinations determined.

Our original plan, formulated before Phil joined this project, was to perform cohort analyses if the automated data sufficed for this purpose and case-cohort ones, using augmented records of cases and members of the 1-2% samples, otherwise. Phil's choice was based on computational ease without much loss of efficiency, but won't be as easy to communicate to our primary audience, pediatricians and parents. We decided that Bruce would pursue a modification of the original course, namely use information about misclassification from John Mullooly's assessments of the automated data quality to correct his analytical results.

Phil had advocated reviewing the records of more children who appear to have experienced outcomes of interest, particularly those exposed on the same day as their event (to ensure that exposures preceded these outcomes), but generally because our 1-2% samples contain far less information about rare outcomes than common exposures. In particular, he suggested oversampling such children in the age ranges when they are likely to have been recently exposed. The value of learning more about outcome data quality notwithstanding, it wasn't clear how this would inform Cox analyses. Should we stratify on whether records were reviewed or sample what appeared to be informative strata (i.e., case and risk set discordant in exposure) by virtue of the automated data alone, ...? The neurological case ascertainment provides an opportunity to review the records of children with one-third of our outcomes of interest; should we subject them to the same protocol as we have members of the 1-2% samples?

ARTICLE

Measles-Mumps-Rubella and Other Measles-Containing Vaccines Do Not Increase the Risk for Inflammatory Bowel Disease

ARCHIVES EXPRESS

A Case-Control Study From the Vaccine Safety Datalink Project

Robert L. Davis, MD, MPH; Piotr Kramarz, MD; Kari Bohlke, ScD; Patti Benson, MPH; Robert S. Thompson, MD; John Mullooly, PhD; Steve Black, MD; Henry Shinefield, MD; Edwin Lewis, MPH; Joel Ward, MD; S. Michael Marcy, MD; Eileen Eriksen, MPH; Frank Destefano, MD, MPH; Robert Chen, MD; for the Vaccine Safety Datalink Team

Context: A link between measles virus–containing vaccines and inflammatory bowel disease (IBD) has been suggested by recent studies.

Objective: To address whether receipt or timing of measles-containing vaccine (MCV) increases risk for IBD.

Design: A case-control study.

Setting: Four large health maintenance organizations (HMOs) that are part of the Centers for Disease Control and Prevention's Vaccine Safety Datalink project.

Patients or Other Participants: A total of 155 persons with codes from *International Classification of Diseases, Ninth Revision* specific for IBD, born between 1958 and 1989 and enrolled from birth to the onset of disease, were identified. Up to 5 controls were matched by sex, HMO, and birth year.

Intervention: None.

Main Outcome Measures: Risk for IBD, Crohn's disease, and ulcerative colitis.

Results: Past vaccination was not associated with an increased risk for Crohn's disease (odds ratio [OR] for measles-mumps-rubella vaccine [MMR], 0.4; 95% confidence interval [CI], 0.08-2.0), ulcerative colitis (OR, 0.8; 95% CI, 0.18-3.56), or IBD (OR, 0.59; 95% CI, 0.21-1.68). Risk for IBD was not increased among children vaccinated who were younger than 12 months (OR for MMR, 0.61; 95% CI, 0.15-2.45) or aged 12 to 18 months (OR, 0.86; 95% CI, 0.28-2.59) relative to unvaccinated children. Children vaccinated with MMR who were older than 18 months were at significantly decreased risk for IBD (OR, 0.16; 95% CI, 0.04-0.68). Neither past vaccination nor age at vaccination with other MCV was associated with increased risk for Crohn's disease, ulcerative colitis, or IBD. Risk for Crohn's disease, ulcerative colitis, or IBD was not elevated in the time immediately following vaccination with either vaccine.

Conclusions: Vaccination with MMR or other MCV, or the timing of vaccination early in life, did not increase the risk for IBD.

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The affiliations of the authors appear in the acknowledgment section at the end of the article. A complete listing of the members of the Vaccine Safety Datalink team appears on page 359.

CONCERN about a possible link between measles virus–containing vaccines and inflammatory bowel disease (IBD) was brought to the forefront in 1995 when a study in the United Kingdom by Thompson et al[1] suggested that measles virus–containing vaccine recipients had an up to 3-fold increased risk for subsequently developing Crohn's disease and ulcerative colitis. This concern was further heightened when Wakefield et al[2] published a case series report of 12 children with nonspecific colitis, ileal-lymphoid nodular hyperplasia, and developmental disorders in whom symptoms were reported to have begun shortly after receipt of measles-containing vaccine (MCV).

While these studies have been questioned on methodological grounds, there has been considerable public interest and media attention focused on the safety of measles-mumps-rubella vaccine (MMR).[3,4] Following these early reports, vaccination coverage rates for MMR dropped in the United Kingdom, raising concern about the potential for future outbreaks of these vaccine-preventable diseases.[5,6]

We studied whether MMR or other MCVs increase the risk for IBD using data from the Vaccine Safety Datalink (VSD) project, a collaborative project coordinated by the Centers for Disease Control and Prevention, Atlanta, Ga. The VSD incorporates data from 4 large health maintenance organizations (HMOs) in the United States and captures approximately

SUBJECTS AND METHODS

STUDY SITES

This study was carried out in the 4 HMOs of the VSD: (1) Group Health Cooperative, Seattle, Wash; (2) Kaiser Permanente of Northern California, Oakland; (3) Kaiser Permanente Northwest, Portland, Ore; and (4) Southern California Kaiser Permanente, Los Angeles. The VSD project was started in 1991, and the computerized medical databases at each HMO include information on vaccinations and hospitalizations. Information on outpatient visit encounters and emergency department visits are available for 3 of the HMOs.

CASE AND CONTROL ASCERTAINMENT

We selected potential cases for medical record review by identifying persons with *International Classification of Diseases, Ninth Revision (ICD-9)* codes specific for Crohn's disease, ulcerative colitis, and idiopathic proctocolitis (*ICD-9* codes 555 and 556) in the computerized databases. At 3 sites, we drew our study sample from the population of HMO members born between 1958 (when membership files were first available) and 1989. At 1 site, case and control selection was limited to people born after 1979 since automated membership data were not available prior to that year. At all 4 HMOs, cases were ascertained from hospital databases covering hospital admissions. Outpatient visits, emergency department visits, and urgent care clinic visits were ascertained from 3 HMOs; the earliest dates of case ascertainment from these respective databases were determined by the year the respective databases (eg, outpatient visits) were created. Because outpatient, emergency department, and urgent care clinic databases were not available at 1 HMO, only hospitalized cases were ascertained at this site.

To be included in our sample, cases and controls had to be enrolled from age 6 months up to the index date (the first date of disease diagnosis or symptoms for cases) or reference date for controls. For both cases and controls, we allowed up to 6 months of continuous disenrollment at any time during life to account for transient lapses in insurance coverage. For each case, we matched up to 5 controls according to sex, HMO, and birth year. The reference date of each control was established as the date that the disease was diagnosed for their matched case.

EXPOSURE ASSESSMENT

To accurately capture information on exposure to first MMR or other MCV, we limited our selection of study subjects, as described in the previous section, to patients enrolled for the entire period between 6 months of age and disease onset (for cases) or reference date (for controls). The entire medical record for cases and controls was abstracted to collect information on vaccination history with all types of MCVs. Information on vaccines administered in all health care settings was collected. A second MMR vaccination is recommended either at age 4 to 6 years or 10 to 12 years, but these vaccinations were not analyzed in the current study.

MEDICAL RECORD ABSTRACTION

Trained medical record abstractors at each HMO reviewed medical records using a standardized instrument. Cases were classified according to type of disease (Crohn's, ulcerative colitis/proctitis, or IBD unspecified) and by certainty of diagnosis. We defined cases of "definite IBD" as persons diagnosed with IBD by a gastroenterologist at one of the HMOs who had at least 1 sign or symptom compatible with IBD (such as bloody stool and/or bloody diarrhea or severe and/or recurrent abdominal pain) recorded and a diagnostic test result (such as biopsy with pathology specimen, colonoscopy, or sigmoidoscopy) consistent with IBD. Cases were defined as having "probable IBD" if the diagnosis of IBD was made by either an HMO nongastroenterologist physician or a gastroenterologist outside the HMO, there was at least 1 sign or symptom compatible with IBD, and there was a diagnostic test result consistent with IBD. Potential subjects with possible or questionable IBD who did not meet these criteria were excluded from further study.

STATISTICAL ANALYSES

We used conditional logistic regression to estimate the strength of association between vaccination and disease, while accounting for the matching and enrollment criteria. In all analyses we further adjusted for race, where race was categorized as white (reference category, including Hispanics and non-Hispanics), African American, and other/unknown.

We excluded cases categorized as "possible" or "questionable" from all analyses. Separate analyses were performed on datasets that were limited to definite and probable cases combined or of definite cases only. Because the results from these analyses did not differ appreciably, we present only the results on the larger dataset of definite and probable cases combined.

Finally, we performed analyses with 2 different onset dates. For the analysis of whether receipt of vaccination was associated with an increased risk for IBD, Crohn's disease, or ulcerative colitis, we used as the onset date the first date a diagnosis was made by a physician. The analysis of whether vaccination was associated with the acute onset of symptoms consistent with IBD, Crohn's disease, or ulcerative colitis was dependent on using the onset date of first symptoms rather than the date of first diagnosis (which might lag symptom onset by months). Therefore, for this part of the analysis, we used the patient's first reported symptoms as the onset date. This lowered our case number by a small amount because not all cases with a known date of first diagnosis had a specified date of symptom onset in the medical record.

2% of all children in the US population younger than age 7 years. Our study focused on a series of questions: Was the age of first vaccination with MMR or other MCV, or receipt of vaccination itself, associated with an increased risk for Crohn's disease or ulcerative colitis later in life? Was receipt of MMR or other MCV associated with the acute onset of disease shortly following vaccination?

Table 1. General Descriptives of Cases and Controls*

Characteristic	Cases (n = 142)	Controls (n = 432)
Disease		
Crohn's disease	75 (53)	
Ulcerative colitis	67 (47)	
Sex		
F	74 (52)	224 (52)
M	68 (48)	208 (48)
Race		
White	95 (67)	256 (59)
African American	12 (8)	24 (6)
Other	10 (7)	20 (5)
Unknown	25 (17)	132 (31)
Age at diagnosis, y†		
0-5	7 (5)	24 (6)
6-10	29 (20)	81 (19)
11-14	40 (28)	120 (28)
15-19	43 (30)	144 (33)
20-24	15 (11)	46 (11)
25+	8 (6)	20 (5)

*All values given as numbers (percentages). Percentages do not always equal 100 due to rounding. Ellipses indicate not applicable.
†For controls, age at the date the disease was diagnosed for their matched case.

RESULTS

DESCRIPTIVE

There was a total of 155 cases of IBD. Of these 155 cases, 152 were either definite or probable cases, while 3 were listed as possible or questionable. After excluding the latter 3 cases, along with 7 that lacked a clearly discernible diagnosis and symptom onset date, 2 cases of IBD unspecified, and 1 case with a late age of vaccination (>10 years), there was a total of 142 cases for the analysis of timing of vaccination and diagnosis of IBD.

Of these 142 cases, there were 75 cases of Crohn's disease and 67 cases of ulcerative colitis (**Table 1**). There was a slight excess of cases classified as white or African American compared with controls. Overall, 52% of both cases and controls, respectively, were female, and 58% of cases were diagnosed between age 11 and 19 years, with few cases being diagnosed either after age 25 years or before age 5 years.

Among all cases (n=142), 94 (66%) had been vaccinated with MMR, 38 (27%) with other MCV, and 10 (7%) had never been vaccinated with either. Among the controls (n=432), 300 (69%) had been vaccinated with MMR, 109 (25%) with other MCV, and 23 (5%) had never been vaccinated with either. There were 13 cases that did not have a clearly demarcated first date of symptoms, leaving a total of 129 cases for the separate analysis of vaccination and acute symptom onset.

VACCINATION AND RISK FOR IBD

There were no differences in the lag between vaccination with MMR or other MCV and the case index date (mean and median time between vaccination and onset of symptoms of 143.4 and 136.3 months, respectively) or the control reference date (mean and median time between vaccination and reference date of 143.0 and 136.7 months, respectively). As given in **Table 2**, cases of Crohn's disease, ulcerative colitis, or of all IBD combined were no more likely than controls to have ever been vaccinated.

Table 2. History of Ever Being Vaccinated and Risk for Inflammatory Bowel Disease*

History	Crohn's Disease	UC	All IBD
Ever vaccinated			
MMR	0.40 (0.08-2.00)	0.80 (0.18-3.56)	0.59 (0.21-1.69)
MCV	1.11 (0.26-4.69)	1.05 (0.20-5.42)	0.97 (0.34-2.79)
Unvaccinated	Reference	Reference	Reference

*All estimates shown are from conditional logistic regression, matched on health maintenance organization, sex, and birth year, and adjusted for race. Values are given as odds ratios (95% confidence intervals), except where indicated. UC indicates ulcerative colitis; IBD, inflammatory bowel disease; MMR, measles-mumps-rubella vaccine; and MCV, measles-containing vaccine.

AGE AT VACCINATION AND RISK FOR IBD

Vaccination with MMR or other MCV was most common for both cases and controls who were 12 to 18 months old (**Table 3**). Cases of Crohn's disease, ulcerative colitis, or all IBD combined were no more likely than controls to have been vaccinated while younger than 12 months with either MMR or other MCV (Table 3). Similarly, cases of IBD, Crohn's disease, or ulcerative colitis were no more likely than controls to have been vaccinated at age 12 to 18 months or after age 18 months. Cases of all IBD combined were less likely to have ever been vaccinated with MMR after age 18 months than controls. This decrease was present but not statistically significant when cases were restricted to Crohn's disease or ulcerative colitis and analyzed separately. A significant decrease was not found for vaccination with other MCV after age 18 months.

VACCINATION AND ACUTE ONSET OF SYMPTOMS

The analysis of vaccination and the acute onset of symptoms of IBD revealed no cases of Crohn's disease or ulcerative colitis who were vaccinated in the 2- or 4-month time period just prior to the first symptoms. One case of Crohn's disease (1.5% of cases with defined onset of symptoms) was vaccinated with MMR within the 6-month time window prior to first symptoms, compared with 2 of the controls (1.0%) (odds ratio [OR], 1.86; 95% confidence interval [CI], 0.09-39.4 for Crohn's disease in the 6 months following vaccination). In the year prior to onset of symptoms, there was 1 case (the same that was exposed within 6 months) of Crohn's disease who was vaccinated with MMR (1.5%) and 3 controls (1.4%) (OR, 0.72; 95% CI, 0.06-8.29 for Crohn's disease in the 12 months following vaccination). Overall, there were no statistically significant elevations in risk for developing symptoms of

Table 3. Age at Vaccination and Risk for Inflammatory Bowel Disease*

Age Vaccinated, mo	Crohn's Disease	UC	All IBD	Cases, No.	Controls, No.
MMR, 12	0.38 (0.05-2.86)	0.96 (0.12-7.57)	0.61 (0.15-2.45)	6	25
MCV, 12	0.43 (0.05-3.54)	1.75 (0.20-15.3)	0.78 (0.18-3.37)	5	18
MMR, 12-15	0.54 (0.10-3.07)	1.14 (0.23-5.59)	0.66 (0.28-2.59)	84	223
MCV, 12-15	1.16 (0.24-5.53)	1.25 (0.23-6.72)	1.07 (0.35-3.26)	22	62
MMR, 16-18	0.18 (0.03-1.21)	0 (0)	0.16 (0.04-0.68)	4	52
MCV, 16-18	1.56 (0.25-9.92)	0.71 (0.09-5.38)	0.88 (0.24-3.28)	11	29
Unvaccinated	Reference	Reference	Reference	10	23

*All estimates shown are from conditional logistic regression, matched on health maintenance organization, sex, and birth year, and adjusted for race. Values are given as odds ratios (95% confidence intervals), except where indicated. UC indicates ulcerative colitis; IBD, inflammatory bowel disease; MMR, measles-mumps-rubella vaccine; and MCV, measles-containing vaccine.

Crohn's disease, ulcerative colitis, or all IBD together in the 2, 4, 6, or 12 months following vaccination with either MMR or other MCV.

COMMENT

In this population-based study of IBD at 4 large HMOs, we found no evidence that vaccination with MMR or other MCV, or that the age of vaccination early in life, was associated with an increased risk for development of IBD. In addition, we did not find evidence that MMR or other MCV acutely triggers the onset of either ulcerative colitis/proctitis or Crohn's disease.

This study was performed to address concerns raised by others regarding whether MMR is associated with an increased risk for either IBD or nonspecific colitis.[1,2] Because MMR coverage in the US pediatric population is currently greater than 90% and vaccination with MMR is generally required for school attendance, a link with a serious chronic condition such as IBD would understandably raise widespread concern and would lead to questions about the safety of the currently recommended vaccination schedule for children. In the first study to suggest a possible association,[1] a cohort of children aged 10 to 24 months were enrolled in a 1964 United Kingdom Medical Research Council vaccine trial of the Schwarz strain (derived from the Enders-Edmonston B strain) and followed through 1994. Children in this cohort were compared with a group of presumably nonvaccinated children in the National Child Development Study, a longitudinal study of children born in a single week in 1958. Among vaccinated children, the rate of reported Crohn's disease was 3-fold higher (relative risk [RR], 3.01; 95% CI, 1.45-6.23), and ulcerative colitis 2.5-fold higher (RR, 2.53; 95% CI, 1.15-5.58), than in the National Child Development Study comparison group.

These findings by Thompson et al[1] were questioned most seriously because the method of disease ascertainment differed considerably between the 2 cohorts.[3-4] The ascertainment of disease among the vaccinated children relied on questions specifically focused on gastrointestinal disease, while the unvaccinated group was asked about long-standing illnesses or disabilities. In addition, follow-up among the vaccinated group was approximately half that of the unvaccinated cohort, raising the possibility for biased response rates related to disease status. As a result, it was not clear whether the observed relationship between measles vaccine and IBD was due to the vaccine itself or to study design limitations.

The study by Wakefield et al[2] did not look specifically at IBD but focused on a group of 12 children with a complex of nonspecific colitis, ileolymphoid hyperplasia, and pervasive developmental disability, in which most but not all reported that symptoms began following vaccination with an MCV. Of these 12 children, 6 had gastrointestinal symptoms, and 11 had abnormal histological findings in ileum and colon biopsy specimens (most commonly of nonspecific colitis and lymphoid hyperplasia). This study was questioned owing to lack of specification of the source population, making it impossible to determine whether vaccination was more common among these cases than among a comparable set of children without disease. Because MMR is given to approximately 600 000 children yearly in the United Kingdom, some cases of disease will likely follow vaccine temporally, although not necessarily as a result of cause and effect.[5] Others questioned whether the gastrointestinal findings were unusual or represented nonspecific findings common in the age group studied.[6]

Several other studies have subsequently addressed the risk for IBD following MCV. A case-control study by Feeney et al[9] from the United Kingdom looked at 140 patients with IBD born after 1968, matched to 280 controls by age, sex, and location. No increased risk was found for either Crohn's disease (OR, 1.08; 95% CI, 0.6-1.9) or ulcerative colitis (OR, 0.84; 95% CI, 0.4-1.6) among children receiving measles vaccine compared with unvaccinated children. Other data by Morris et al[10] on a national longitudinal study of children born in the United Kingdom found no increased risk for Crohn's disease or ulcerative colitis by age 25 to 26 years associated with measles vaccination. Only sparse details were reported, but there were no significantly increased risks (Crohn's disease: RR, 1.21; 95% CI, 0.5-2.9; ulcerative colitis: RR, 1.31; 95% CI, 0.47-3.7; and IBD: RR, 1.25; 95% CI, 0.64-2.43).

Multiple ecological analyses have also shown no apparent increase in IBD following the introduction of, or increased use of, MMR. In one study, Miller and Waight[11] used computerized hospital discharge statistics from 1992 through 1996 to look for evidence of an increase in Crohn's disease subsequent to a 1994 national measles-

...ranged school-aged children. Although the follow-up time was limited to only the first 16 months following vaccination, there was no apparent increase in the rate of hospital admissions for Crohn's disease and hence no suggestion that MMR triggered the onset of symptoms as suggested in the study by Wakefield et al.[2]

In a second study, Pebody et al[12] used Finnish data and contrasted the rate of Crohn's disease with the proportion of the population receiving measles vaccine. Although there was an increase over time in the proportion of the population receiving 1 or more doses of measles virus vaccine, the rate of Crohn's disease remained stable among 2 age groups of children and adolescents aged 0 to 14 years and adolescents and young adults aged 15 to 24 years. Finally, a study by Hermon-Taylor et al[13] contrasted the annual incidence of Crohn's disease at 3 United Kingdom centers (south Wales, Derby, and northeast Scotland) with the introduction of measles vaccine and MMR. In this study there was a marked rise in the rate of Crohn's disease over the study period, but the increased rate of disease predated introduction of the measles vaccine by approximately 20 years.

A number of studies have attempted to find evidence of persistent measles virus genome in pathology specimens obtained from patients with IBD. These investigations were prompted by a report of measles virus nucleocapsid protein found in 13 of 15 patients with Crohn's disease.[14] Most subsequent studies by Afzal et al[15] on 19 patients with IBD, by Chadwick et al[16] on 20 cases, and by Iizuka et al[17] on 21 cases have failed to replicate these findings, arguing that measles virus genome is not present in the gut mucosa of patients with Crohn's disease or ulcerative colitis. However, a recent study by Kawashima et al[18] detected measles genomic RNA in peripheral mononuclear cells in 1 of 8 cases of Crohn's disease and 1 of 3 with ulcerative colitis but no measles RNA in 8 subjects with subacute sclerosing panencephalitis, systemic lupus erythematosus, or HIV (human immunodeficiency virus) infection. This latter study did not examine intestinal pathology specimens.

There are some unique aspects to our study that deserve mention. First, previous studies of the relationship between measles vaccination and IBD have been conducted on populations outside of the United States. This is the first study of MMR and other MCVs and IBD used historically and presently in the United States. Second, that we did not find a relationship between MMR vaccine and IBD argues against the suggestion that concurrent exposure to measles and mumps antigens increases the risk for IBD[19] and against the need to deliver these vaccinations as individual antigens.[20] Third, this study uses information from a population-based group of HMO members and was therefore likely free from the biases that might occur in a study that relied on self-referred patients or patients studied specifically because symptoms might have occurred following vaccination. Finally, our study included only patients enrolled from (or shortly after) birth up to the time of disease or the similar age for controls, and we reviewed each patient's medical record to ascertain vaccination status. Consequently, the completeness and quality of information on the timing and type of vaccine received is likely to be good. Because we were able to ascertain the timing of the first symptoms and date of first diagnosis of disease from the outpatient medical records at each HMO, we were able to calculate an unbiased relationship between receipt of vaccination and disease onset.

There are some limitations to our study. We included only patients with a physician diagnosis (usually a gastroenterologist) of IBD, and we have the inherent limitations of diagnostic accuracy in a retrospective study. We have little information on children or adults who had nonspecific colitis that did not eventually lead to a diagnosis of IBD. Nevertheless, our study provides evidence against the hypothesis that MMR or other MCV leads to IBD. Another limitation to our study concerned power. We were able to effectively rule out associations larger than 2-fold between ever being vaccinated with MMR and developing IBD and associations larger than 3-fold between vaccination with other MCV and IBD. However, we had a limited sample size from which to look at the independent associations between vaccination and either Crohn's disease or ulcerative colitis (Table 2) or at the relationship between timing of vaccination early in life and subsequent risk for Crohn's disease or ulcerative colitis (Table 3).

There has been recent interest in the role of early exposure to measles virus and subsequent risk for development of IBD. A few studies have suggested that intrauterine or early-in-life exposure to infectious agents or measles virus may lead to an increased risk for IBD.[21,22] Although we collected information on intrauterine and early-in-life measles exposure, we did not identify any mothers of case or control subjects who were noted to have first trimester measles infection. In addition, only 1 case of IBD and 2 controls had had measles infection. These small numbers precluded analysis of the relationship between measles infection and subsequent development of IBD; however, if such a risk does exist, the magnitude must be too small to identify accurately with a study of our size.

Finally, it is important to recognize that the apparent protective effect against IBD of primary vaccination with MMR after 18 months of age was not an a priori hypothesis of ours, and a similar finding was not seen among children vaccinated after age 18 months with other MCV. If subsequent studies are conducted on the relationship between IBD and primary vaccination, attention should be paid to the risk among children vaccinated after age 18 months with MMR.

In conclusion, our study of IBD using a population-based sample of cases from 4 large HMOs did not find evidence of an elevated risk for disease following vaccination with MMR or other MCV.

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VACCINE SAFETY (AND DEVELOPMENT)
Highlights 1996

Robert T. Chen, M.D., M.A.

Vaccine Safety (and Development) Highlights 1996

Vaccine schedule:
- **Anticipate 2 major changes based on safety:**
  - **DTaP for infants**
  - **IPV/OPV**
- **Future:**
  - **Many new vaccines**
  - **Many new combination vaccines**
  - **New schedules**
- **Limits in testing of permutations pre-use**

Increasing Awareness of Vaccine Safety
- **Public**
  - **Vocal consumer groups**
  - **VAERS 1-800: 6000 (1992) => 18,000 (1995)**
  - **Internet: anti-vaccine >> pro-vaccine**
- **Policy groups**
  - **National Vaccine Advisory Committee (NVAC)**
  - **Advisory Commission Childhood Vax (ACCV)**
  - **Joint NVAC/ACCV Subcommittee on Vax Safety**
  - **PHS Task Force on Safer Childhood Vaccines**
- **IOM Vaccine Safety Forum**
  - **Polio Policy**
  - **How to Detect & Respond VAEs?**
  - **How to Prevent VAEs?**
  - **Risk Communications**

Vaccine Safety = 4 leg stool
- **Passive Surveillance/Signal Generation (VAERS)**
  - **Detect New VAE (Hep B + Alopecia)**
  - **Detect Change in Known VAE (GBS 93-94 Flu)**
- **Active Surveillance/Validation (LLDB + ad hoc)**
- **Risk Communications**
- **Vaccine Development (Safer Vaccines)**
  - **Impending "embarrassment of riches"?**

LLDB Request For Proposal FY95 (+ FY96)
- Core: Vax safety: age 0-6 years (GHC,NCK,SCK)
- E1: Vax safety adoles age 7-17 years (")
- E2: Vax safety adults age 18+ years (")
- E3: Incidence of VPD
- E4: PII/III safety immunog (PPV2, GHC)
- E5: Cost-benefit

Resources for LLDB
- Only vax safety budget line item for VAERS
- LLDB funded mostly by NIP end-of-year$ ($4-5m)
- New contract does not allow forward funding
- Possible sources of stable funding:
  - Reprogram from other NIP activities
  - Budget initiative
  - Vaccine Injury Compensation Program
    - Excise Tax
    - Trust fund
  - Industry

Personnel Changes
- CDC
  - Gain: F DeStefano, B Kimsey, J Lloyd, B Weniger, S Ashley, Data Management, (Emory: K Sullivan, D Nordenberg).
  - Loss: J Hardy, L Phillips, S Rosenthal, E Durry, J Tuttle, (L Schultz).
- FDA:Gain: M Salive, M Braun, M Niu.
- GHC:Gain: L Jackson

How to Attract/Stabilize Personnel?
- (Historical) Negatives:
  - Risk (and Benefit) of Vaccination
  - Infrastructure for research poor
  - Studies difficult (= few publications)
  - Funding unsure
- Safety (+) vs. Adverse Events (-)
- LLDB addresses many of above negatives

LLDB 1996 Goals:

- **Stabilize Funding Source**
- **Improve Analytical Capabilities**
- **Improved Coordination/Leadership**
  - **Within project**
  - **With outside**
    - **Policy groups**
    - **Industry**
- **Publish, publish, publish**

INDUSTRY INTERFACE

AND

ALTERNATE FUNDING SOURCES

Robert T. Chen., M.D., M.A.

Harry Guess, M.D.

Steve Black, M.D.

Possible Interface With Industry - LLDB

- Vaccine Development Paradigm
  - Pre licensure
    - Phase I, Phase II (NIH VTEV)
    - Phase III
      A. Efficacy (high incident population)
      B. Field effectiveness (1 HMO/LLDB)

- Post Licensure
  - Phase IV (1HMO)
  - Phase V (VAERS + LLDB- multiple HMOs)
    - Manufacturer A vs. B
    - Mix and Match

- Mechanisms
  - Coop Research & Development Agreement (CRADA)
  - CDC Foundation
  - HMO Foundation (existing vs. new)
  - Fee-for-service

- Pro & Cons
  - Additional resources to support project
  - Maximize use of (unique) infrastructure
  - Speed up development of improved/new vaccines, combination vaccines, schedules.
  - ? Contract of interest
  - Control/Coordination

Black -- Varicella Vaccine

Introduction and Methods

The Merck Oka strain varicella vaccine was licensed for use in March, 1995. Beginning in May, 1995, Northern California Kaiser Permanente Vaccine Study Center began a 15 year post-marketing study to evaluate the safety and long term effectiveness of the Merck varicella vaccine. The evaluation includes serial cross-sectional surveys to evaluate the impact of vaccine on varicella disease, 15 year follow-up of a vaccinated cohort for break-through disease, and an assessment of safety through rates of events resulting in clinic, emergency or hospital utilization. These utilization events are ascertained by linkage of the study population data base with existing clinic, ER and hospital data bases. We report here on safety data in recipients through January 23, 1996.

Summary of Individuals and Follow-up Time

Age Group (years)	Number of Individuals	Number of Immunizations
1	15,175	15,175
2-12	27,464	27,464
13-17	930	1,410
≥ 18	800	1,194
TOTAL	44,369	45,243

Follow-up Time[1]

Age Group (years)	Risk Period 0-30 days after vaccine	Control Period 1 91-120 days after vaccine	Control Period 2 31-60 days before vaccine
1	1158.0	725.2	1246.4
2-12	2149.5	1500.9	2255.8
13-17	110.1	41.1	76.4
≥ 18	90.5	34.7	65.7
TOTAL	3508.1	2301.6	3644.3

[1] Displayed follow-up time (person-years) is for the emergency utilization analysis. Exact follow-up time varies by site of care.

Changing Epidemiology of Varicella Baseline Incidence Survey in Children 5-19 Years of Age

Age in Years	*N* in Survey	Incidence Cases per 1000 person years	95% C.I.
5-9	1,122	103.4	85.6, 121.2
10-14	1,085	19.4	11.2, 27.6
15-19	5,879	12.2	9.4, 15.1
All Ages	8,086	25.8	22.4, 29.3

Emergency Room Visits Following Varicella Vaccine
One Year of Age – Immunizations through 01/23/96
0-30 Day Risk Period and 91-120 Days After Control Period

Relative Risk Estimates and 95% Confidence Intervals (Rates per 1000 Person-Years)

Comparison	0-30 days N	0-30 days Rate	91-120 days N	91-120 days Rate	Relative Risk Estimate	95% CI Lower Bound	95% CI Upper Bound	p-Value (Mid-Prob.)
Abscess	0	0.00	1	1.38	0.00	0.00	11.90	0.385
Acute Gastroenteritis	43	37.13	19	26.20	1.42	0.83	2.48	0.204
Allergic incl Angiodema	2	1.73	3	4.14	0.42	0.05	2.81	0.368
Allergic not incl Angiodema	2	1.73	3	4.14	0.42	0.05	2.81	0.368
Anorexia	0	0.00	1	1.38	0.00	0.00	11.90	0.385
Asthma	22	19.00	12	16.55	1.15	0.57	2.40	0.713
Bronchiolitis	7	6.04	1	1.38	4.38	0.68	99.55	0.143
Cellulitis	1	0.86	1	1.38	0.63	0.02	24.43	0.770
Congenital Anomaly	0	0.00	1	1.38	0.00	0.00	11.90	0.385
Conjunctivitis	1	0.86	1	1.38	0.63	0.02	24.43	0.770
Constipation	1	0.86	0	0.00	-	0.03	-	0.615
Croup	14	12.09	9	12.41	0.97	0.42	2.35	0.940
Drug Reaction	1	0.86	0	0.00	-	0.03	-	0.615
Elective Procedure	5	4.32	4	5.52	0.78	0.20	3.28	0.716
Epilepsy	6	5.18	1	1.38	3.76	0.55	87.03	0.212
Epistaxis	1	0.86	0	0.00	-	0.03	-	0.615
Febrile Illness	13	11.23	0	0.00	-	2.42	-	0.002
Hives	4	3.45	0	0.00	-	0.56	-	0.143
Hydrocephalus	0	0.00	1	1.38	0.00	0.00	11.90	0.385
Infection	2	1.73	0	0.00	-	0.18	-	0.378
Irritable Child	2	1.73	0	0.00	-	0.18	-	0.378
Local Swelling	1	0.86	0	0.00	-	0.03	-	0.615
Otitis Media	72	62.18	61	84.11	0.74	0.53	1.04	0.085
Pharyngitis	2	1.73	3	4.14	0.42	0.05	2.81	0.368
Pneumonia	8	6.91	4	5.52	1.25	0.38	4.77	0.739
Poisoning/Ingestion	10	8.64	13	17.92	0.48	0.20	1.11	0.086
Rash	5	4.32	3	4.14	1.04	0.24	5.30	0.976
Seizure, Febrile	21	18.13	17	23.44	0.77	0.41	1.49	0.434
Sinusitis	1	0.86	0	0.00	-	0.03	-	0.615
Thrush	1	0.86	0	0.00	-	0.03	-	0.615
Tonsillitis	1	0.86	1	1.38	0.63	0.02	24.43	0.770
Trauma	166	143.35	84	115.82	1.24	0.95	1.61	0.109
URI	26	22.45	14	19.30	1.16	0.61	2.29	0.660
UTI	1	0.86	1	1.38	0.63	0.02	24.43	0.770
Varicella	1	0.86	0	0.00	-	0.03	-	0.615
Varicella w & w/o Cellulitis	2	1.73	0	0.00	-	0.18	-	0.378
Varicella w/ Cellulitis	1	0.86	0	0.00	-	0.03	-	0.615
Viral Syndrome	46	39.72	30	41.37	0.96	0.61	1.54	0.857
Well Child/Reassurance/FU	8	6.91	5	6.89	1.00	0.32	3.37	0.999
*Total	481	415.36	286	394.35	1.05	0.91	1.22	0.488

* Total may be somewhat less than column total due to multiple diagnoses per visit

Mid-Probability Method for CI and Two-Sided Exact Binomial Test

Emergency Room Visits Following Varicella Vaccine
2 - 12 Years of Age – Immunizations through 01/23/96
0-30 Day Risk Period and 31-60 Days Before Control Period

Relative Risk Estimates and 95% Confidence Intervals (Rates per 1000 Person-Years)

Comparison	0-30 days N	0-30 days Rate	31-60 days before N	31-60 dys before Rate	Relative Risk Estimate	95% CI Lower Bound	95% CI Upper Bound	p-Value (Mid-Prob.)
Abscess	0	0.00	1	0.44	0.00	0.00	19.94	0.512
Acute Gastroenteritis	34	15.82	43	19.06	0.83	0.53	1.30	0.419
Allergic Incl Angiodema	2	0.93	6	2.66	0.35	0.05	1.65	0.202
Allergic not incl Angiodema	1	0.47	6	2.66	0.17	0.01	1.18	0.080
Appendicitis	1	0.47	0	0.00	-	0.06	-	0.488
Asthma	39	18.14	44	19.51	0.93	0.60	1.43	0.744
Bronchiolitis	4	1.86	3	1.33	1.40	0.29	7.50	0.681
Cellulitis	2	0.93	1	0.44	2.10	0.16	61.91	0.598
Cerebral Palsy	0	0.00	1	0.44	0.00	0.00	19.94	0.512
Conjunctivitis	5	2.33	5	2.22	1.05	0.28	3.90	0.941
Constipation	2	0.93	2	0.89	1.05	0.11	10.08	0.964
Croup	19	8.84	6	2.66	3.32	1.37	9.09	0.007
Elective Procedure	13	6.05	13	5.76	1.05	0.48	2.30	0.903
Epilepsy	2	0.93	3	1.33	0.70	0.08	4.70	0.726
Epistaxis	1	0.47	0	0.00	-	0.06	-	0.488
Febrile illness	3	1.40	0	0.00	-	0.61	-	0.116
GI Bleed	1	0.47	0	0.00	-	0.06	-	0.488
Gingivitis	0	0.00	1	0.44	0.00	0.00	19.94	0.512
HS Purpura	1	0.47	0	0.00	-	0.06	-	0.488
Headache	1	0.47	0	0.00	-	0.06	-	0.488
Hemophilia	1	0.47	1	0.44	1.05	0.03	40.93	0.976
Hives	4	1.86	4	1.77	1.05	0.24	4.65	0.947
Hydrocephalus	1	0.47	0	0.00	-	0.06	-	0.488
Hypoglycemia	0	0.00	1	0.44	0.00	0.00	19.94	0.512
Hypoglycemic Seizure	1	0.47	0	0.00	-	0.06	-	0.488
Infection	1	0.47	0	0.00	-	0.06	-	0.488
Kawasaki's Disease	2	0.93	0	0.00	-	0.30	-	0.238
Muscle pain	1	0.47	0	0.00	-	0.06	-	0.488
Musculoskeletal pain	1	0.47	0	0.00	-	0.06	-	0.488
Otitis Media	69	32.10	66	29.26	1.10	0.78	1.54	0.591
Pharyngitis	6	2.79	5	2.22	1.26	0.37	4.48	0.715
Pneumonia	4	1.86	11	4.88	0.38	0.11	1.16	0.093
Poisoning/Ingestion	10	4.65	9	3.99	1.17	0.46	2.97	0.744
Rash	4	1.86	4	1.77	1.05	0.24	4.65	0.947
Seizure, Febrile	7	3.26	9	3.99	0.82	0.29	2.24	0.698
Sickle Cell Disease	2	0.93	0	0.00	-	0.30	-	0.238
Sinusitis	0	0.00	1	0.44	0.00	0.00	19.94	0.512
Skin Infection	0	0.00	2	0.89	0.00	0.00	3.64	0.262
Syncope/LOC	1	0.47	0	0.00	-	0.06	-	0.488
Synovitis	1	0.47	0	0.00	-	0.06	-	0.488
Thrush	1	0.47	0	0.00	-	0.06	-	0.488
Tonsillitis	1	0.47	1	0.44	1.05	0.03	40.93	0.976
Trauma	239	111.19	230	101.96	1.09	0.91	1.31	0.349
URI	20	9.30	24	10.64	0.87	0.48	1.59	0.662
UTI	4	1.86	1	0.44	4.20	0.53	103.88	0.200
Varicella	2	0.93	0	0.00	-	0.30	-	0.238
Varicella w & w/o Cellulitis	2	0.93	0	0.00	-	0.30	-	0.238
Viral Syndrome	40	18.61	47	20.84	0.89	0.58	1.36	0.602
Well Child/Reassurance/FU	15	6.98	4	1.77	3.94	1.37	13.79	0.009
Wheezing/SOB	2	0.93	0	0.00	-	0.30	-	0.238
*Total	568	264.25	547	242.49	1.09	0.97	1.23	0.152

* Total may be somewhat less than column total due to multiple diagnoses per visit
Mid-Probability Method for CI and Two-Sided Exact Binomial Test

Emergency Room Visits Following Varicella Vaccine
2 - 12 Years of Age – Immunizations through 01/23/96
0-30 Day Risk Period and 91-120 Days After Control Perio

Relative Risk Estimates and 95% Confidence Intervals (Rates per 1000 Person-Years)

Comparison	0-30 days N	0-30 days Rate	91-120 days N	91-120 days Rate	Relative Risk Estimate	95% CI Lower Bound	95% CI Upper Bound	p-Value (Mid-Prob.)
Acute Gastroenteritis	34	15.82	21	13.99	1.13	0.66	1.98	0.666
Allergic incl Angiodema	2	0.93	3	2.00	0.47	0.06	3.13	0.433
Allergic not incl Angiodema	1	0.47	3	2.00	0.23	0.01	2.18	0.221
Anal fissure	0	0.00	1	0.67	0.00	0.00	13.27	0.411
Appendicitis	1	0.47	0	0.00	-	0.04	-	0.589
Asthma	39	18.14	25	16.66	1.09	0.66	1.82	0.746
Bronchiolitis	4	1.86	6	4.00	0.47	0.12	1.70	0.249
Cellulitis	2	0.93	0	0.00	-	0.20	-	0.347
Cerebral Palsy	0	0.00	1	0.67	0.00	0.00	13.27	0.411
Conjunctivitis	5	2.33	1	0.67	3.49	0.48	83.08	0.258
Constipation	2	0.93	0	0.00	-	0.20	-	0.347
Croup	19	8.84	12	8.00	1.11	0.54	2.35	0.797
Elective Procedure	13	6.05	14	9.33	0.65	0.30	1.40	0.267
Epilepsy	2	0.93	3	2.00	0.47	0.06	3.13	0.433
Epistaxis	1	0.47	1	0.67	0.70	0.02	27.23	0.822
Febrile Illness	3	1.40	0	0.00	-	0.41	-	0.204
GI Bleed	1	0.47	0	0.00	-	0.04	-	0.589
HS Purpura	1	0.47	0	0.00	-	0.04	-	0.589
Headache	1	0.47	0	0.00	-	0.04	-	0.589
Hemophilia	1	0.47	1	0.67	0.70	0.02	27.23	0.822
ves	4	1.86	1	0.67	2.79	0.35	69.12	0.389
drocephalus	1	0.47	0	0.00	-	0.04	-	0.589
Hypoglycemic Seizure	1	0.47	0	0.00	-	0.04	-	0.589
Infection	1	0.47	0	0.00	-	0.04	-	0.589
Kawasaki's Disease	2	0.93	0	0.00	-	0.20	-	0.347
Migraine	0	0.00	1	0.67	0.00	0.00	13.27	0.411
Muscle Pain	1	0.47	0	0.00	-	0.04	-	0.589
Musculoskeletal Pain	1	0.47	0	0.00	-	0.04	-	0.589
Otitis Media	69	32.10	46	30.65	1.05	0.72	1.53	0.813
Pharyngitis	6	2.79	4	2.67	1.05	0.29	4.21	0.960
Pneumonia	4	1.86	6	4.00	0.47	0.12	1.70	0.249
Poisoning/Ingestion	10	4.65	6	4.00	1.16	0.42	3.45	0.787
Rash	4	1.86	1	0.67	2.79	0.35	69.12	0.389
Seizure, Afebrile	0	0.00	1	0.67	0.00	0.00	13.27	0.411
Seizure, Febrile	7	3.26	10	6.66	0.49	0.18	1.30	0.152
Sickle Cell Disease	2	0.93	0	0.00	-	0.20	-	0.347
Sinusitis	0	0.00	1	0.67	0.00	0.00	13.27	0.411
Syncope/LOC	1	0.47	1	0.67	0.70	0.02	27.23	0.822
Synovitis	1	0.47	1	0.67	0.70	0.02	27.23	0.822
Thrush	1	0.47	0	0.00	-	0.04	-	0.589
Tonsillitis	1	0.47	4	2.67	0.17	0.01	1.39	0.108
Trauma	239	111.19	141	93.94	1.18	0.96	1.46	0.111
URI	20	9.30	17	11.33	0.82	0.43	1.59	0.552
UTI	4	1.86	2	1.33	1.40	0.25	10.90	0.737
Varicella	2	0.93	0	0.00	-	0.20	-	0.347
Varicella w & w/o Cellulitis	2	0.93	0	0.00	-	0.20	-	0.347
al Syndrome	40	18.61	22	14.66	1.27	0.76	2.17	0.372
ell Child/Reassurance/FU	15	6.98	0	0.00	-	3.16	-	<0.001
Wheezing/SOB	2	0.93	0	0.00	-	0.20	-	0.347
*Total	568	264.25	352	234.52	1.13	0.99	1.29	0.078

* Total may be somewhat less than column total due to multiple diagnoses per visit
Mid-Probability Method for CI and Two-Sided Exact Binomial Test

Emergency Room Visits Following Varicella Vaccine
13 - 17 Years of Age -- Immunizations through 01/23/96
0-30 Day Risk Period and 91-120 Days After Control Period

Relative Risk Estimates and 95% Confidence Intervals (Rates per 1000 Person-Years)

Comparison	0-30 days N	0-30 days Rate	91-120 days N	91-120 days Rate	Relative Risk Estimate	95% CI Lower Bound	95% CI Upper Bound	p-Value (Mid-Prob.)
Abscess	0	0.00	1	24.33	0.00	0.00	7.09	0.272
Acute Gastroenteritis	1	9.08	0	0.00	-	0.02	-	0.728
Asthma	0	0.00	1	24.33	0.00	0.00	7.09	0.272
Elective Procedure	0	0.00	1	24.33	0.00	0.00	7.09	0.272
Migraine	1	9.08	0	0.00	-	0.02	-	0.728
Otitis Media	0	0.00	2	48.66	0.00	0.00	1.30	0.074
Pleuritis	1	9.08	0	0.00	-	0.02	-	0.728
Trauma	19	172.57	8	194.66	0.89	0.39	2.15	0.758
* Total	22	199.81	13	316.32	0.63	0.32	1.29	0.198

* Total may be somewhat less than column total due to multiple diagnoses per visit
Mid-Probability Method for CI and Two-Sided Exact Binomial Test

Emergency Room Visits Following Varicella Vaccine
13 - 17 Years of Age -- Immunizations through 01/23/96
0-30 Day Risk Period and 31-60 Days Before Control Period

Relative Risk Estimates and 95% Confidence Intervals (Rates per 1000 Person-Years)

Comparison	0-30 days N	0-30 days Rate	31-60 days before N	31-60 dys before Rate	Relative Risk Estimate	95% CI Lower Bound	95% CI Upper Bound	p-Value (Mid-Prob.)
Abscess	0	0.00	1	13.09	0.00	0.00	13.18	0.410
Acute Gastroenteritis	1	9.08	2	26.18	0.35	0.01	4.56	0.435
Allergic inc Angiodema	0	0.00	1	13.09	0.00	0.00	13.18	0.410
Allergic not incl Angiodema	0	0.00	1	13.09	0.00	0.00	13.18	0.410
Asthma	0	0.00	1	13.09	0.00	0.00	13.18	0.410
Congenital Anomaly	0	0.00	1	13.09	0.00	0.00	13.18	0.410
Epilepsy	0	0.00	1	13.09	0.00	0.00	13.18	0.410
Migraine	1	9.08	0	0.00	-	0.04	-	0.590
Pleuritis	1	9.08	0	0.00	-	0.04	-	0.590
Trauma	19	172.57	14	183.28	0.94	0.47	1.92	0.859
UTI	0	0.00	1	13.09	0.00	0.00	13.18	0.410
* Total	22	199.81	22	288.01	0.69	0.38	1.26	0.229

Total may be somewhat less than column total due to multiple diagnoses per visit
Mid-Probability Method for CI and Two-Sided Exact Binomial Test

Emergency Room Visits Following Varicella Vaccine
18+ Years of Age -- Immunizations through 01/23/96
0-30 Day Risk Period and 91-120 Days After Control Period

Relative Risk Estimates and 95% Confidence Intervals (Rates per 1000 Person-Years)

Comparison	0-30 days N	0-30 days Rate	91-120 days N	91-120 days Rate	Relative Risk Estimate	95% CI Lower Bound	95% CI Upper Bound	p-Value (Mid-Prob.)
Acute Gastroenteritis	1	11.05	0	0.00	-	0.02	-	0.723
Bronchiolitis	1	11.05	1	28.86	0.38	0.01	14.94	0.554
Drug Reaction	2	22.10	0	0.00	-	0.11	-	0.523
Headache	2	22.10	0	0.00	-	0.11	-	0.523
Ingrown Toenail	1	11.05	0	0.00	-	0.02	-	0.723
Otitis Media	1	11.05	0	0.00	-	0.02	-	0.723
Pharyngitis	0	0.00	1	28.86	0.00	0.00	7.28	0.277
Rash	0	0.00	1	28.86	0.00	0.00	7.28	0.277
Syncope/LOC	1	11.05	0	0.00	-	0.02	-	0.723
Trauma	6	66.31	2	57.71	1.15	0.24	8.27	0.914
URI	0	0.00	1	28.86	0.00	0.00	7.28	0.277
UTI	0	0.00	1	28.86	0.00	0.00	7.28	0.277
* Total	15	165.78	7	201.99	0.82	0.34	2.15	0.655

* Total may be somewhat less than column total due to multiple diagnoses per visit
Mid-Probability Method for CI and Two-Sided Exact Binomial Test

Emergency Room Visits Following Varicella Vaccine
18+ Years of Age -- Immunizations through 01/23/96
0-30 Day Risk Period and 31-60 Days Before Control Period

Relative Risk Estimates and 95% Confidence Intervals (Rates per 1000 Person-Years)

Comparison	0-30 days N	0-30 days Rate	31-60 days before N	31-60 dys before Rate	Relative Risk Estimate	95% CI Lower Bound	95% CI Upper Bound	p-Value (Mid-Prob.)
Acute Gastroenteritis	1	11.05	2	30.44	0.36	0.01	4.77	0.456
Bronchiolitis	1	11.05	0	0.00	-	0.04	-	0.579
Drug Reaction	2	22.10	0	0.00	-	0.21	-	0.336
Elective Procedure	0	0.00	1	15.22	0.00	0.00	13.80	0.421
Headache	2	22.10	0	0.00	-	0.21	-	0.336
Hemophilia	0	0.00	1	15.22	0.00	0.00	13.80	0.421
Ingrown Toenail	1	11.05	0	0.00	-	0.04	-	0.579
Otitis Media	1	11.05	0	0.00	-	0.04	-	0.579
Syncope/LOC	1	11.05	0	0.00	-	0.04	-	0.579
Trauma	6	66.31	5	76.09	0.87	0.25	3.10	0.818
URI	0	0.00	1	15.22	0.00	0.00	13.80	0.421
Viral Syndrome	0	0.00	1	15.22	0.00	0.00	13.80	0.421
Well Child/Reassurance/FU	0	0.00	1	15.22	0.00	0.00	13.80	0.421
* Total	15	165.78	12	182.63	0.91	0.42	1.99	0.800

* Total may be somewhat less than column total due to multiple diagnoses per visit
Mid-Probability Method for CI and Two-Sided Exact Binomial Test

Hospitalizations Following Varicella Vaccine
One Year of Age -- Immunizations through 01/23/96
0-60 Day Risk Period and 31-90 Days Before Control Period

Relative Risk Estimates and 95% Confidence Intervals (Rates per 1000 Person-Years)

Comparison	0-60 days N	0-60 days Rate	31-90 days before N	31-90 dys before Rate	Relative Risk Estimate	95% CI Lower Bound	95% CI Upper Bound	p-Value (Mid-Prob.)
Acute Gastroenteritis	22	9.99	9	3.61	2.77	1.29	6.32	0.008
Agranulocytosis	0	0.00	1	0.40	0.00	0.00	21.50	0.531
Anemia	2	0.91	0	0.00	-	0.33	-	0.220
Aspiration	0	0.00	1	0.40	0.00	0.00	21.50	0.531
Asthma	12	5.45	21	8.42	0.65	0.31	1.31	0.231
Ataxia	0	0.00	1	0.40	0.00	0.00	21.50	0.531
Bronchiolitis	3	1.36	0	0.00	-	0.66	-	0.103
Cardiac Disease	1	0.45	0	0.00	-	0.06	-	0.469
Cellulitis	2	0.91	2	0.80	1.13	0.12	10.87	0.907
Cerebral Palsy	0	0.00	2	0.80	0.00	0.00	3.93	0.282
Chronic Sinusitis	1	0.45	0	0.00	-	0.06	-	0.469
Congenital Anomaly	15	6.81	17	6.82	1.00	0.49	2.02	0.999
Congenital Heart Disease	0	0.00	1	0.40	0.00	0.00	21.50	0.531
Constipation	0	0.00	1	0.40	0.00	0.00	21.50	0.531
Croup	7	3.18	8	3.21	0.99	0.34	2.81	0.989
E Coli Septicemia	1	0.45	0	0.00	-	0.06	-	0.469
Elective Procedure	50	22.70	69	27.68	0.82	0.57	1.18	0.287
Epiglottis	1	0.45	0	0.00	-	0.06	-	0.469
Epilepsy	5	2.27	2	0.80	2.83	0.56	21.06	0.224
Erythema Multiforme	0	0.00	1	0.40	0.00	0.00	21.50	0.531
FUO	2	0.91	0	0.00	-	0.33	-	0.220
Failure to Thrive	0	0.00	2	0.80	0.00	0.00	3.93	0.282
GI Bleed	2	0.91	0	0.00	-	0.33	-	0.220
Hemophilia	0	0.00	1	0.40	0.00	0.00	21.50	0.531
Hydrocephalus	1	0.45	0	0.00	-	0.06	-	0.469
Hypovolemia	0	0.00	8	3.21	0.00	0.00	0.51	0.006
Infection	2	0.91	0	0.00	-	0.33	-	0.220
Kawasaki's Disease	1	0.45	1	0.40	1.13	0.03	44.14	0.938
Mastoiditis	1	0.45	0	0.00	-	0.06	-	0.469
Otitis Media	29	13.17	46	18.45	0.71	0.44	1.13	0.154
Pharyngitis	0	0.00	1	0.40	0.00	0.00	21.50	0.531
Pneumonia	15	6.81	8	3.21	2.12	0.91	5.28	0.084
Poisoning/Ingestion	1	0.45	1	0.40	1.13	0.03	44.14	0.938
Seizure, Febrile	7	3.18	5	2.01	1.58	0.49	5.46	0.446
Sickle Cell Disease	0	0.00	1	0.40	0.00	0.00	21.50	0.531
Sleep Apnea	0	0.00	2	0.80	0.00	0.00	3.93	0.282
Trauma	8	3.63	15	6.02	0.60	0.24	1.41	0.253
URI	2	0.91	0	0.00	-	0.33	-	0.220
UTI	1	0.45	3	1.20	0.38	0.01	3.54	0.440
Viral Syndrome	2	0.91	6	2.41	0.38	0.05	1.78	0.240
*Total	191	86.71	231	92.67	0.94	0.77	1.13	0.498

*Total may be somewhat less than column total due to multiple diagnoses per visit

Mid-Probability Method for CI and Two-Sided Exact Binomial Test

Hospitalizations Following Varicella Vaccine
2 - 12 Years of Age -- Immunizations through 01/23/96
0-60 Day Risk Period and 91-150 Days After Control Period

Relative Risk Estimates and 95% Confidence Intervals (Rates per 1000 Person-Years)

Comparison	0-60 days N	0-60 days Rate	91-150 days N	91-150 days Rate	Relative Risk Estimate	95% CI Lower Bound	95% CI Upper Bound	p-Value (Mid-Prob.)
Acute Gastroenteritis	14	3.37	6	2.25	1.50	0.59	4.24	0.420
Adenitis	1	0.24	0	0.00	-	0.03	-	0.609
Appendicitis	1	0.24	0	0.00	-	0.03	-	0.609
Asthma	14	3.37	14	5.24	0.64	0.30	1.37	0.248
Cancer, R/O Cancer	2	0.48	1	0.37	1.28	0.10	37.89	0.886
Cellulitis	3	0.72	2	0.75	0.96	0.14	8.10	0.950
Cerebral Palsy	1	0.24	1	0.37	0.64	0.02	25.05	0.782
Congenital Anomaly	11	2.65	4	1.50	1.77	0.58	6.41	0.341
Constipation	1	0.24	2	0.75	0.32	0.01	4.22	0.399
Croup	2	0.48	1	0.37	1.28	0.10	37.89	0.886
Developmental Delay	2	0.48	0	0.00	-	0.19	-	0.371
Diabetes	1	0.24	1	0.37	0.64	0.02	25.05	0.782
Elective Procedure	67	16.12	59	22.10	0.73	0.51	1.04	0.079
Epilepsy	3	0.72	5	1.87	0.39	0.08	1.67	0.205
GE Reflux	1	0.24	0	0.00	-	0.03	-	0.609
GI Bleed	1	0.24	0	0.00	-	0.03	-	0.609
Hemolytic Anemia	2	0.48	2	0.75	0.64	0.07	6.17	0.679
Histiocytosis	2	0.48	0	0.00	-	0.19	-	0.371
Hydrocephalus	2	0.48	0	0.00	-	0.19	-	0.371
Hypoglycemia	1	0.24	0	0.00	-	0.03	-	0.609
Hypoglycemic Seizure	1	0.24	0	0.00	-	0.03	-	0.609
Hypovolemia	0	0.00	1	0.37	0.00	0.00	12.20	0.391
Infection	2	0.48	1	0.37	1.28	0.10	37.89	0.886
Kawasaki's Disease	1	0.24	0	0.00	-	0.03	-	0.609
Osteomyelitis	0	0.00	2	0.75	0.00	0.00	2.23	0.153
Otitis Media	38	9.14	14	5.24	1.74	0.96	3.32	0.070
Pituitary Insufficiency	1	0.24	0	0.00	-	0.03	-	0.609
Pneumonia	8	1.92	8	3.00	0.64	0.23	1.77	0.385
Poisoning/Ingestion	3	0.72	2	0.75	0.96	0.14	8.10	0.950
Psychiatric	1	0.24	0	0.00	-	0.03	-	0.609
Seizure, Afebrile	0	0.00	1	0.37	0.00	0.00	12.20	0.391
Seizure, Febrile	2	0.48	1	0.37	1.28	0.10	37.89	0.886
Sickle Cell Disease	3	0.72	3	1.12	0.64	0.11	3.74	0.604
Sleep Apnea	1	0.24	0	0.00	-	0.03	-	0.609
Small Bowel Obstruction	1	0.24	0	0.00	-	0.03	-	0.609
Syncope/LOC	0	0.00	1	0.37	0.00	0.00	12.20	0.391
T&A	1	0.24	0	0.00	-	0.03	-	0.609
Thalassemia	1	0.24	0	0.00	-	0.03	-	0.609
Trauma	25	6.01	13	4.87	1.24	0.64	2.49	0.547
URI	3	0.72	0	0.00	-	0.37	-	0.226
UTI	1	0.24	1	0.37	0.64	0.02	25.05	0.782
Viral Syndrome	3	0.72	3	1.12	0.64	0.11	3.74	0.604
Well Child/Reassurance/FU	1	0.24	0	0.00	-	0.03	-	0.609
R/O Sepsis	1	0.24	0	0.00	-	0.03	-	0.609
Total	229	55.09	144	53.93	1.02	0.83	1.26	0.845

* Total may be somewhat less than column total due to multiple diagnoses per visit

Mid-Probability Method for CI and Two-Sided Exact Binomial Test

Hospitalizations Following Varicella Vaccine
13 - 17 Years of Age -- Immunizations through 01/23/96
0-60 Day Risk Period and 91-150 Days After Control Period

Relative Risk Estimates and 95% Confidence Intervals (Rates per 1000 Person-Years)

Comparison	0-60 days N	0-60 days Rate	91-150 days N	91-150 days Rate	Relative Risk Estimate	95% CI Lower Bound	95% CI Upper Bound	p-Value (Mid-Prob.)
Elective Procedure	1	5.38	1	14.57	0.37	0.01	14.40	0.539
Seizure, Type Unk.	1	5.38	0	0.00	-	0.02	-	0.730
Trauma	4	21.52	0	0.00	-	0.33	-	0.285
* Total	6	32.28	1	14.57	2.21	0.33	51.30	0.508

* Total may be somewhat less than column total due to multiple diagnoses per visit
Mid-Probability Method for CI and Two-Sided Exact Binomial Test

Hospitalizations Following Varicella Vaccine
18+ Years of Age -- Immunizations through 01/23/96
0-60 Day Risk Period and 31-90 Days Before Control Period

Relative Risk Estimates and 95% Confidence Intervals (Rates per 1000 Person-Years)

Comparison	0-60 days N	0-60 days Rate	31-90 days before N	31-90 dys before Rate	Relative Risk Estimate	95% CI Lower Bound	95% CI Upper Bound	p-Value (Mid-Prob.)
Abortion	0	0.00	1	7.61	0.00	0.00	16.25	0.461
Aseptic Meningitis	0	0.00	1	7.61	0.00	0.00	16.25	0.461
Cancer, R/O Cancer	1	6.51	2	15.22	0.43	0.01	5.62	0.540
Cholelithiasis	1	6.51	0	0.00	-	0.05	-	0.539
Elective Procedure	2	13.02	5	38.05	0.34	0.05	1.73	0.208
Pneumonia	1	6.51	0	0.00	-	0.05	-	0.539
Pregnancy	1	6.51	8	60.88	0.11	0.00	0.67	0.012
Psychiatric	1	6.51	0	0.00	-	0.05	-	0.539
Sepsis	0	0.00	1	7.61	0.00	0.00	16.25	0.461
Trauma	1	6.51	0	0.00	-	0.05	-	0.539
* Total	8	52.07	18	136.97	0.38	0.16	0.86	0.020

* Total may be somewhat less than column total due to multiple diagnoses per visit
Mid-Probability Method for CI and Two-Sided Exact Binomial Test

Conclusions

- **In this cohort of 44,369 children and adults, the Merck Varicella vaccine appeared safe and free of local and systemic reactions resulting in hospital, emergency or clinic utilization.**

- **Baseline age specific rates of varicella in this population have been established to allow long term evaluation of the impact on varicella vaccination on this population.**

- **A cohort of 7,000 recipients of vaccine are being followed for fifteen years with semi-annual telephone interviews to evaluate breakthrough rates and vaccine efficacy.**

Varicella Vaccine

Post Marketing Surveillance

Objectives

- **10-Year persistence of antibody in children and adults**
- **Short-term (60 days) safety in 25,000 vaccinees**
- **Varicella and herpes zoster incidence over 15 years**
- **Changing epidemiology of varicella with vaccine use**
- **Case-control studies of long-term vaccine effectiveness**
- **Assess pregnancy exposures and outcomes**

Kaiser Short-Term Safety Study

Objective: Rare adverse events following vaccination

Setting: Kaiser Permanente Northern California

Subjects: At least 25,000 children 12-23 months of age vaccinated in ordinary well-child care

Outcomes: Adverse events resulting in:
(1) Clinic visits or ER visits within 30 days after vaccination, or
(2) Hospitalizations or death within 60 days after vaccination

Event ascertainment by Kaiser computer database, with chart review where diagnosis suggests possible vaccine effect

Design: Observational study: Rates of any events where Kaiser, Merck, or CBER consider a vaccine relationship appears possible will be compared with rates in:

(1) Same cohort in 30 [or 60] day period ending 1 month prior to vaccination

(2) Same cohort in 30 [or 60] day period starting 3 months after vaccination

(3) Age-matched non-vaccinated controls over 30 [or 60] days one year prior to vaccine introduction.

Changing Epidemiology of Varicella

Kaiser Studies

Objectives: Effect of vaccine on age-specific incidence of varicella in 5-19 year-olds

Estimate vaccine effectiveness as a function of age and time since vaccination using case-control studies

Design: Telephone surveys of age-stratified random sample of Kaiser population at baseline (pre-vaccine) and 6, 9, 12, and 15 years after licensure

Case-control studies of vaccine effectiveness, using the telephone surveys at 6, 9, 12, and 15 years to identify cases and controls

15-Year Follow-up Study

Objective: Long-term clinical effectiveness of vaccine

Setting: Kaiser Permanente Northern California

Subjects: 7,000 children from the short-term study

Outcomes: Rate and severity of breakthrough varicella and herpes zoster and breakthrough rates from household exposures

Design: Event ascertainment by telephone follow-up, with phone calls every 6 months for 15 yrs

Chart review of any cases with doctor visit

Annual disenrollment rate is 3%-6%, but will attempt to follow-up even after disenrollment

Hypotheses: (1) No increase in varicella rate or severity
(2) Zoster incidence not elevated over that in unvaccinated children of same age, following natural chickenpox

Power: Varicella: ≥ 90% power to determine if rate over any 2 consecutive years is 2X baseline rate, assuming baseline rate ≥ 1%/year

Zoster: 90% power to detect 5X increase in observed number of cases over the number expected with background rate of 8/10,000/yr

Duke Day Care Study

Objective: Changing varicella epidemiology in day-care

Setting: 10 Day Care centers in North Carolina
Followed by Duke University Pediatrics

Subjects: Approximately 1,200 children under 5 years of age enrolled in these day care centers at any time

Outcomes: (1) Rates of vaccination

(2) Rate and severity of varicella in vaccinated and unvaccinated children within each day care center, to determine vaccine effectiveness in day care setting

(3) Comparison of severity in primary and secondary cases within each day care center in vaccinated and unvaccinated children

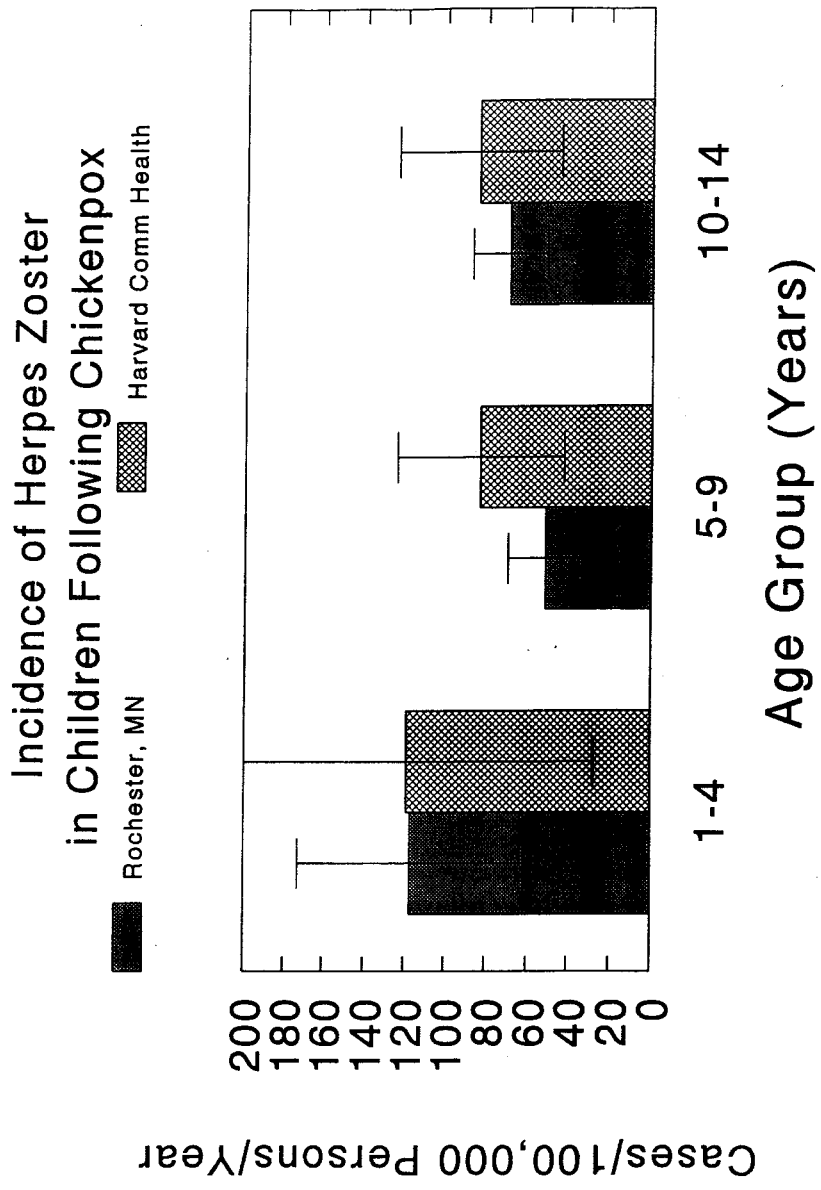
(4) Rates and severity of zoster

Design: Observational open cohort study of five years duration

Announcement: VARIVAX® Pregnancy Registry

VARIVAX®, a live attenuated virus vaccine for prevention of chickenpox, has recently been licensed for individuals 12 months of age and older. Use of VARIVAX® during pregnancy is contraindicated, and it is recommended in the package insert that pregnancy be avoided for at least 3 months following vaccination. There are no data on the potential risks of VARIVAX® in pregnancy, however natural varicella, the wild-type virus, has sometimes been associated with a pattern of birth defects called congenital varicella syndrome. Given that women of reproductive age may receive VARIVAX® and that vaccination may inadvertently occur during pregnancy, a registry is being established by Merck & Co., Inc., in collaboration with the Centers for Disease Control & Prevention, to follow the outcomes of pregnancies when vaccination with VARIVAX® has occurred within three months prior to pregnancy or at any time during pregnancy. The purpose of this registry is to obtain information on pregnancy outcomes that may be of use to health care providers and to women who are vaccinated during this interval.

We encourage patients and health care providers to report any vaccinations with VARIVAX® that occur three months prior to pregnancy or at any time during pregnancy. Telephone calls can be directed to the VARIVAX® Pregnancy Registry at 1-800-986-8999. Written reports can be sent to Merck Research Labs., Worldwide Product Safety & Epidemiology, BLA-31, West Point, PA 19486.


Incidence of Herpes Zoster
in Children Following Chickenpox
Rochester, MN
Harvard Comm Health
Cases/100,000 Persons/Year
200
180
160
140
120
100
80
60
40
20
0
1-4
5-9
10-14
Age Group (Years)

Herpes Zoster Surveillance

Because breakthrough varicella in vaccinees is expected to be about 30 times more common than zoster, and because the two can be misdiagnosed, there is a high potential for creating an artifactual increase in the reported incidence of zoster among vaccinees

Per 10,000 vaccinees per year expect about 240 cases of breakthrough varicella and 8 cases of zoster.

If each case is equally likely to be misclassified as the other and the rates are as above, the reported incidences would be as follows:

Misclassification Rate	Reported Zoster cases per 10,000 vaccinees	Reported Breakthrough Varicella cases per 10,000 vaccinees
20%	54 (6.8-fold increase)	208 (13% decrease)
10%	31 (3.9-fold increase)	217 (10% decrease)
5%	20 (2.5-fold increase)	228 (5% decrease)
1%	10	238
None	8	240

Table 5. Aggregate Protective Efficacy of Polyvalent Pneumococcal Vaccine against Serotypes in the Vaccine in Immunocompetent Patients, According to Age Group and Time since Vaccination

Age (Yr.)	No. of Case - Control Pairs	Time since Vaccination*		
		<3 yr	**3-5 yr**	**>5yr**
<55	125	93 (82 to 97)	89 (74 to 96)	85 (62 to 94)
55-64	149	88 (70 to 95)	82 (57 TO 93)	75 (38 to 90)
65-74	213	80 (51 to 92)	71 (30 to 88)	58 (-2 to 83)
75-84	188	67 (20 to 87)	53 (-15 to 81)	32 (-67 to 72)
≥85	133	46 (-31 to 78)	22 (-90 to 68)	-13 (-174 to 54)

*The effect was estimated by conditional logistic regression, with control for race, residence in a chronic care facility, and source of primary medical care (private physician vs. clinic)

Shapiro et al. Efficacy of polyvalent pneumococcal polysaccharide vaccine. NEJM 1991; 325:1453-1460.

VACCINE DEVELOPMENT AND ECONOMIC STUDIES

Bruce Weniger, M.D., M.P.H.

Image 1. New Vax list

Since 1980, four diseases -- hepatitis A and B, H. flu B, and varicella -- have become newly-vaccine preventable and two more -- rotavirus and lyme disease -- are expected. Improvements on existing vaccines are here or coming soon, while exciting new vaccine technologies hold much promise for the future.

These are all welcome fruits of the biotechnology revolution. However, they pose daunting challenges for the public health and medical communities. The U.S. immunization schedule is already highly complex, requiring multiple clinic visits during the first 2 years of life. Children, parents, and providers will likely not tolerate ever-increasing numbers of injections on a single visit. Recommending additional visits would incur higher costs and probably decreased compliance, and thus decreased coverage, and, perhaps, increased disease.

Image 2. Combo Lists

The short-term solution to the dilemma of increasing numbers of vaccine-preventable diseases has been to combine multiple antigens into single vials, assuming problems of chemical incompatibility and immunological interference can be overcome, as has been done for years with **DTP**, **MMR**, and trivalent polio vaccines.

The current menu of available products (*point*) involves little overlap of antigens. But as you can see from the list of new and expected combination products (*point*), before long there will likely be much overlap among these products. This list even leaves off antigens like hepatitis A that may be joined into combinations, as well as the polyvalent pneumococcal and meningococcal combinations in development.

Some antigens potentially will appear in several possible combinations. **Hib**, for example, may come in combination with **DTaP**, and also separately with **HepB**, with or without **IPV**. In at least one case, an antigen for which competition in the industry is expected -- varicella -- may be combined with a current single-source product -- **MMR**.

Image 3. Issues/Challenges

I would like to briefly define some of the issues and challenges that the new combination vaccines will pose. "**Polypharmacy**" refers to the stocking in the distribution system and in provider refrigerators of several or all possible vaccine products, with some antigens appearing in more than one product -- both single-antigen and in combinations -- even though not all such products would be needed to fully immunize any one patient.

If polypharmacy is avoided by stocking only a limited selection of products, then "**overimmunization**" may occur when separate antigens in a combination product require doses at different ages. A booster shot for one antigen may include an unnecessary dose at that time for another disease against which the patient is already fully immunized. This may waste money and possibly increase unnecessary side effects. For example, if the clinic only stocks a **DTP-Hib** combination vaccine (with the HIb of the PRP-OMP conjugate type), a shot of this at 2, 4, and 6 months of age would be needed to fully immunize for diphtheria, tetanus, and pertussis, but the **Hib**-(PRP-OMP) dose at 6 months would represent unnecessary "overimmunization" for Hemophilus influenzae at that age.

"**Mixing and Matching**" is the phrase coined to refer to the use in a single child of different

vaccine products from separate manufacturers in order to complete a primary and booster series for a given disease. The effectiveness of such practice has been validated for **Hib** and **HepB** vaccines from different companies. But for the new acellular pertussis vaccines with their diverse antigen components, it will be a challenge to determine the efficacy of "mixing and matching" them in children who move between clinics during their immunization series.

With many new combinations available, it will be difficult to maintain a single, understandable schedule which could apply to all permutations of vaccines that might be available. To respond to this challenge, we may need flexibility to adjust the schedule. For that flexibility, we will need more data on the efficacy or immunogenicity of both existing and new products at ages other than the current schedule of 2, 4, and 6 months, for example. Will the vaccines work at ages 0, 2, and 4 months? Or 1, 3, and 5 months? Would two doses at ages 2 and 4 months, or 2 and 6 months, work as well? Such additional information is going to be very helpful.

Finally, do we need an industrial policy? We are now down to four major vaccine suppliers in the U.S. How will we maintain a secure vaccine supply, and a healthy, competitive vaccine industry, with incentives for continued innovation for new products, when the public sector seeks the simplest vaccine delivery system at the lowest overall cost to taxpayers?

Image 4. Economic Model

Various different mechanisms have been proposed from various quarters for modifying the vaccine procurement system in the U.S. to meet the challenge of the new combination vaccines. We don't have the time to describe all of these, but a couple of them would require making difficult choices to buy only a subset for the public sector among all available vaccines. Managed care organizations would face this same choice, as it is likely they would want to stock only the minimal number of products to immunize their patients and avoid polypharmacy. How might this be done in a fashion that would get the "best value" for our public funds and also stimulate investment, innovation, and competition in the vaccine industry?

One idea would use economic data to consider <u>all</u> the costs of disease prevention through immunization, and not just vaccine purchase prices, in choosing vaccine products. This would require policy decisions on which features of vaccines are important to recognize and to value in the selection model. This algorithm is not considered an official proposal or preference of CDC. It is put forward solely as an example of one method by which we might face the difficult choices when multiple new vaccines and combination products appear.

In this table, such "product-related variables" are shown in the left-hand column. The price of the vaccine is the only factor currently used to make purchase decisions. Other features which influence the overall cost of immunization are:

- the number of doses required,
- the route of administration (injection vs. oral),
- how much time it takes the clinic staff to mix and prepare a dose for administration,
- the earliest age at which full immunity could be achieved,

- the degree of efficacy of the vaccine,
- the nature and frequency of the vaccine's adverse effects,
- the refrigeration and transport requirements,
- and the shelf life of the product.

Relevant cost-data for each of these variables is shown in the adjacent right-hand column, and would have to be collected from studies and research. It might include determining:

- the average cost of a visit to a provider,
- the cost of injections versus oral administration,
- the costs of staff time to prepare vaccines,
- the cost of caring for patients who develop the disease because full immunity cannot be achieved at birth or because vaccines do not have 100% efficacy,
- the cost of caring for adverse effects,
- and the costs of cold chain, spoilage, and wastage.

These costs, as they become available and are added to the model, are summed to determine the total cost to protect against a specific disease with a specific antigen in a specific product. The next steps involves using standard economic linear programming to pick the best mix of specific vaccine products which would function together to minimize the overall costs of disease prevention through immunization.

Image 5. Needed Health Economic Data

This film summarizes the kind of cost data that would be needed for a vaccine selection algorithm. The starred items represent those features of vaccines which we want to encourage and for which the related cost data would permit us to value in a procurement selection algorithm. We would like to "brainstorm" today how the larged linked database (LLDB) network of health maintenance organizations represented here might be able to contribute to the process of generating this kind of economic data related to vaccines and immunizations. We ought to consider for what kinds of data the Vaccine Safety Datalink (VSD) institutions would have a comparative advantage over other potential sources of this information. The National Vaccine Program Office has awarded funds for economic research relevant to vaccine schedules and procurement, and we hope to use part of these monies to fund suitable electives within the framework of the LLDB/VSD project.

First, it would be important to know what are the costs of a visit to an immunization provider. In this way we can give value to those vaccines requiring fewer doses. Costs of an immunization visit itself might be broken into item I-a, Staff Labor, Training, and Fringe Benefits. We would want to know from time and motion studies (item I-b) how much time it takes to prepare and administer specific vaccine formulations from different manufacturers. By combining labor cost data from I-a and minutes it takes per dose from I-b, we could show the economic advantage of more convenient and efficient dosage formats.

Knowing the costs of needles, syringes, and jet injectors (item I-c) would allow a vaccine selection system to recognize the potential cost advantages of vaccine administration via oral route or via needleless-injection over hypodermic needles. Shipping and storing heat-sensitive vaccines so

that they remain refrigerated or frozen is a major but often hidden cost in immunizations. Knowing the total costs per dose of this cold chain for refrigeration and the wastage which occurs when the hain is broken, would permit demonstrating the cost advantages of more heat-stable vaccines.

In order to give credit to desired vaccine products which might be able to completely immunize at an earlier age, or immunize with increased protective efficacy, or immunize with fewer doses and thus avoid coverage falloff, we would want to know the costs of caring for each of the associated vaccine-preventable diseases (item II). As an alternative to valuing such improvements in vaccines, we could measure the "willingness to pay" among consumers to avoid such diseases.

To give weight in the selection algorithm to improved vaccines with fewer adverse effects, we would want to know the frequency of such events for different vaccine products (item III) and also the costs of caring for these symptoms and illnesses caused by the vaccine. How much does it cost to prevent or treat vaccine-induced fevers with acetaminophen? Or to consult a physician, or to visit an emergency room, or to be admitted to hospital for rare sequelae?

Knowing the frequency and costs of wastage (item IV) when vaccines expire before they can be used would permit valuing in the selection process those products which can offer longer shelf lives. Finally, how many separate injections on a single clinic visit are tolerable by patients, parents, and/or providers? When more than this number of antigens is recommended at a certain age, which vaccines will be "deferred" -- perhaps never to be given? Knowing these "constraints" will permit better design of immunization schedules and permit proper weighting to combination vaccines that might avoid such deferrals.

We look forward to the ideas and reactions of the managed care organizations participating in the VSD project to this model to use economic data to find some answers to the challenge of recommending a workable immunization schedule and method of procuring vaccines. We hope to learn how this may be relevant to the needs of these organizations, and how their systems may contribute to the economic research needs that have been presented.

NEWLY VACCINE-PREVENTABLE DISEASES SINCE 1980

	Licensed
☐ Hepatitis B	1981 (plasma-derived)
☐ Haemophilus influenzae b	1988 (toddlers)
	1990 (infants)
☐ Varicella	1995
☐ Hepatitis A	1995
☐ Rotavirus	199?
☐ Lyme Disease	199?

RECENT AND EXPECTED VACCINE IMPROVEMENTS

☐ Hepatitis B	1986 (recombinant)
☐ Acellular Pertussis	1992 (4th & 5th doses)
	199? (all doses)
☐ Pneumococcal Conjugate	199? (for infants)
☐ Meningococcal Conjugate	199?

FUTURE VACCINE TECHNOLOGIES

☐ Nucleic acid vaccines	20??
☐ Recombinant plant vaccines	20??
☐ New Adjuvants	20??
☐ Microencapsulation	20??

ISSUES AND CHALLENGES OF COMBINATION VACCINES

◯ **"Polypharmacy"**	**Stocking multiple vaccine products in which some antigens appear in more than one product**
◯ **"Overimmunization"**	**Use of a combination vaccine in which the antigens contained require different numbers of doses**
◯ **"Mixing & Matching"**	**Use of vaccines from different manufacturers in a single child to complete a primary and booster series for a given disease.**
◯ **Uniform Schedule**	**To develop a single, understandable immunization schedule applicable to all permutations for using combination vaccines**
◯ **Industrial Policy?**	**- Secure vaccine supply** **- Healthy, competitive industry** **- Incentives for innovation** **- Simplest vaccine delivery system** **- Lowest overall cost**

NEEDED COST DATA FOR VACCINE SELECTION ALGORITHM

Immunization Visit to a Provider (labor, equipment, supplies, building)
★ *Fewer vaccine doses required*

I-a **Staff Labor, Training, and Fringe Benefits** attributable to preparing and administering vaccines (calculated per minute)
★ *More convenient and efficient dosage formats*

I-b **Time and Motion Studies** for preparing and administering specific product brands and dosage forms -- prefilled-syringe, single-dos vial, multidose vial, oral vaccine, jet injector
★ *More convenient and efficient dosage formats*
★ *More convenient routes (oral > needleless injection > needle*

I-c **Supplies and Equipment** (needles, syringes, jet injectors)
★ *More convenient routes (oral > needleless injection > needle*

I-d **Cold Chain** (shipping, refrigeration vs. freezing, storage, wastage)
★ *More heat-stable vaccines*

Cases of Vaccine-preventable Diseases (direct: medical care; indirect: time/life): DTP, Hib, HepB, HepA, V, P, MMR, PC, MC, rota, lyme
★ *Earlier age of vaccines administration (incomplete immunity)*
★ *Increased efficacy of vaccines (less than 100% VE)*
★ *Fewer vaccine doses required (coverage falloff)*

Adverse Effects of vaccines (direct: drugs, medical care; indirect: time lost);
Frequency of Adverse Effects by specific vaccine types and brands
★ *Safer, less reactogenic vaccines*

Wastage Due to Product Expiration, frequency
★ *Longer "shelf lives" for vaccines*

Tolerable Number of Separate Injections on a single visit
★ *Improving the "constraints" of the selection algorithm*

Minutes of the Annual Vaccine Safety Datalink (VSD) Meeting
Oakland, California
January 25-27, 1995

Present: In addition to participants from four research sites and three Federal Agencies were three external advisors and one special guest.

Group Health Cooperative (GHC): William Barlow, Virginia Immanuel, Thomas Knauss, Robert Thompson, Bob Davis

Harbor-UCLA with Southern California Kaiser (SCK): Marlene Lugg, S. Michael Marcy, Constance Vadheim, Patricia Osborne, Joel Ward, Diane Petitti, Mike Wulfsohn

Northern California Kaiser (NCK): Steven Black, Henry Shinefield, Bruce Fireman, Jean Hayward, Ned Lewis, Paula Ray

Northwest Kaiser (NWK): John Mullooly, Lois Drew, John Pearson, William Shields

CDC: Robert Chen, Stephen Hadler, John Glasser, Steve Rosenthal, Janet Hardy, Jessica Tuttle, Emmett Swint, Phil Rhodes

FDA: Suresh Rastogi, Robert Wise, Peter Patriarca, Peter Lachenbruch

HRSA (Vaccine Injury Compensation Program): Vito Caserta

External Advisors: Marie Griffin, Alexander Walker, Harold Guess

Special Guest: Ed Marcuse (National Vaccine Advisory Committee)

PRELIMINARIES, JAN 25, AM:

Steve Black welcomed us to NCK's new research facility and described logistics and social events planned for the evenings.

Bob Chen reviewed portentous events in vaccine safety and development since we last met, among them integration of these issues on reorganization of the NIP. Notable elsewhere were the 10-year follow-up of children with chronic encephalopathy in the UK's NCES. The risk within 7 days of DTP was 5.5 times background (95% CI 1.6-23.7), and such children have poor long-term prognoses. The ACIP's recommendation, Vaccine Injury Table and Package Inserts are being revised to match the conclusion of

the 1991 and 1994 IOM Reports on Vaccine Adverse Events.

Three IOM workshops are planned to follow "Research Strategies for Assessing Vaccine Adverse Events," with topics under current discussion. FDA's VRBPAC, the NVP's NVAC, VICP's ACCV and CDC's ACIP all endorsed the active surveillance of which large-linked databases (LLDB) are now and vaccine registries eventually will be capable. The VAERS contract was renewed for another 5 years with such improvements as better follow-up of deaths and other serious reports, ability to report by telephone and facsimile, and request vaccine safety literature searches.

The government was conspicuous at the 1994 meeting of the ISPE with 10 abstracts and separate oral and poster sessions. Other countries emphasizing vaccine safety include Sweden and the UK, with UNICEF also concerned about ways to ameliorate problems largely caused by inadequate sterilization of needles.

Steve Hadler reviewed considerations that affect priorities and our ability to address them via LLDBs. He reviewed our current procedures. These include routine validation of neurological outcomes via chart review and ad hoc verification of outcomes plausibly associated with vaccination on screening. This permits a second level of screening using only validated cases and actual onset versus visit dates. Vaccine-associated outcomes that withstand such scrutiny may then be scheduled for nested, chart-based studies.

Steve reviewed plans for the remainder of this FY. This includes submission of another tape (including files not yet submitted as well as more enrollments), exposures and outcomes (see data manager's report), digestion of second screening results, completion of the nested seizure study, and chart reviews of other neurological and selected non-neurological outcomes. With regard to the seizure study, he expressed interest in distinguishing febrile and afebrile seizures, if not the finer categories discussed (e.g., simple and complex febrile), and considering new onset seizure disorders as well as exacerbation of chronic conditions. With regard to exposures, he indicated interest in old and new vaccines per se and in the combinations in which they typically are administered.

Power to detect associations with other neurological conditions likely is low, but effort required to review these charts is minimal, provided that protocols have been developed. Similarly for deaths, power likely is low, but once protocols have been developed for linking enrollment files to death certificates, minimal effort is required to identify and review records.

Other possible priorities arising from IOM reviews and recent literature include thrombocytopenia and MMR, GBS and both T-containing vaccines and OPV, seizure disorders and M-containing

vaccines, age-at-vaccination dependent risk of, or protection against, diabetes mellitus, Crohn's disease and M-containing vaccines, neither of which may be testable, and alopecia and hepatitis B vaccine, which may not be captured in automatic codes. Parent consumer groups are concerned about the risk of serious events following simultaneous vaccination, new vaccines and combinations.

Then Steve enquired about means of including our most recent screening results; should we consider any statistical association, only serious outcomes, and if so, how should seriousness be judged (e.g., via absolute or relative numbers hospitalized)? Finally, he proposed a straw man based on outdated power calculations that included studies not related to particular exposure-outcome associations, discussed resource needs and proposed a plan of action for later discussion.

Emmett Swint summarized the contents of files included in each HMO's second tape. He diagrammed general edits that were conducted prior to performing the screening analyses and computing exposure and outcome rates. Tape collection periods at each HMO indicate that between 12 and 31 months were reported. Birth cohort data indicate that GHC and NWK enroll approximately 6,000 children per year; NCK, approximately 33,000 and SCK, 40,000 children.

Emmett enumerated children with vaccination records and vaccination dates, and doses administered overall and within enrollment intervals by vaccine. Availability of manufacturer and lot number were indicated too. He also enumerated children with diagnoses, medical care dates, and diagnoses assigned, outcomes within enrollment intervals and LLDB outcomes of interest by setting. Finally, Emmett illustrated how he had created the exposure and outcome rate files, neurology review samples and screening analysis files via flow diagrams.

RESULTS, JAN 25, AM AND PM

John Glasser described the denominators for Emmett's rate calculations, antigen-specific vaccination rates, average numbers of doses administered and vaccine coverage. Then he illustrated the rates at which children presented with seizures by site and setting and argued that separate models of the age-specific rates within these strata provided most of the information needed about each outcome; conditional likelihood ratios complete the picture. He also tabulated the outcome rates and provided a graph whereby our ability to reject false null hypotheses could be guesstimated given real risks while he completed the exposure and outcome rates, projected the numbers of exposed and unexposed cases and estimated power more precisely.

Phil Rhodes described his second tome, which is similar to the first in containing outcome-specific results, but also includes a summary section. Various permutations of events and visits by site, setting, age, gender, item, exposure status and narrative summaries constitute his descriptions of each outcome. He provided site- and setting-specific analyses of possible associations with common childhood vaccines for common outcomes, three individual vaccine effects on seizures also were estimated by controlling for simultaneous exposure to the others, with rarer outcomes being represented only by site-specific analyses. His summary section enumerates common vaccine combinations by site, as did the first volume, but also compares the numbers of events and visits by site, setting and tape, and the timing of common exposures among children with each outcome by site. This masterful presentation of screening results should once again provide ample grist for review during the coming months.

Steve Black and Steve Rosenthal presented results of several ongoing ad hoc studies. Steve Black described studies of arthropathy among adult females following rubella vaccination, which had been presented at ICAAC, and comparison of events for which children presented at ERs or were hospitalized within 30 days of TD vaccination in two age groups, one corresponding to the currently-recommended age, 14-16 years, and one to the age that the ACIP is considering, 10-12 years. No significant difference was found. Then Steve Rosenthal described studies of seizures following DTP doses during the first and second years of life, which had been presented at an EIS conference, and following receipt of DTP and DTaP, which was being prepared for the next ACIP meeting.

MINUTES FUTURES (OR FUTURE ACTIVITIES), JAN 26, AM

Priorities

Discussions on priorities were held on day 1 (general overview), day 2 (discussion) and day 3 (specific assignments). There was consensus that "nothing focuses the mind like writing a paper" and the highest priority for the project was in publishing the results of the studies - thereby garnering visibility and hopefully continued support and funding. A six month target date was set for several paper topics and the primary sites responsible (see separate attachment).

Written status updates will be requested of each site prior to subsequent conference calls. A similar list of priorities will be developed by the statisticians and the data managers to track their progress.

Role of External Advisory Committees

The three external advisors attending this meeting, Drs. Griffin, Guess (representing PHARMA), and Walker, fortuitously were the same advisors that CDC sought advice from prior to the initiation of the LLDB project in 1990. At that time, they had offered a "yellow light" for this endeavor, i.e. proceed with caution, making sure to harmonize protocols among sites as much as possible. The advisors were intimate participants throughout the meeting, asking many questions and offering much valuable advice. There was consensus that similar advisors will be invaluable in future LLDB meetings. Joel Ward offered a comprehensive overview of the potential roles of such an advisory committee - one of which is to assure "buy-in" by interested parties. Drs. Griffin, Guess, and Marcuse have provided insightful suggestions and recommendations in writing subsequently (see separate attachments).

Vaccine Development and the LLDB (Handout)

Bob Chen outlined the new developments in biotechnology which as revolutionalized the new vaccines potentially available in the future. Due to the additional benefits of reduced number of visits needed to complete immunization, combination vaccines have been the focus of much recent work. For such combination vaccines, questions of safety (?sum>parts) are more difficult to answer than questions of immunogenicity (?sum<parts) as they require larger sample sizes. If vaccine development can be divided into Phases I, II, IIIa (clinical efficacy), IIIb (field effectiveness), IV (immediate post-licensure), and V (general post-licensure), LLDBs due to their large sample size, may potentially have important roles to play in phases III-V. Analogous to the prioritization process worked out for testing of acellular pertussis vaccine in Sweden, a similar process may be useful for the limited resource represented by LLDB's. Discussion focused on multiple topics, including 1) feasibility of LLDB charging "user fees" to vaccine manufacturers to minimize CDC resource needs to sustain the project, 2) feasibility of the HMO's organizing themselves into an independent consortium.

Vaccine Safety Bibliography (Handout)

Bob Chen discussed the need for an easily accessible repository of information on vaccine safety - somewhat analogous to what has been developed for hotlines on toxic substances. He noted that a variety of information are currently available (e.g. adverse event sections for respective vaccines in ACIP/AAP recs and textbooks), but these refs have not collated. The recent Institute of Medicine reviews of VAEs provide the most complete recent compilation of vaccine safety literature. The new VAERS contract calls for the contractor to maintain and update the IOM bibliography in an electronic format. In addition to the MESH

headings, the articles will be coded in both COSTART and ICD-9. Ultimately, electronic imaged articles may also be available. When VAERS shifts to the Windows NT architecture, this bibliography will become accessible to outside researchers on vaccine safety.

DEATH CAPTURE STUDIES UPDATE, JAN 26, AM

Bob Wise led a discussion on the progress made in capturing deaths that do not occur in medical facilities, or occur at facilities whose records are not automated.

The discussions were relatively brief as work is not fully underway on these studies. Status reports were given by each of the sites followed by Dr. Wise's comments and suggested questions the mortality data may help to answer in the future. Please refer to Dr. Wise's handout material for further details.

Status of the sites:

1) Similar to all sites, NCK and SCK are currently working on methodology and feasibility issues for collecting death record information for California. NCK has indicated that only 5 counties will contribute death record data (* NCK - please verify this statement). As noted in a later document, SCK has summarized their preliminary efforts and has provided a short protocol and timeline for completing the study over the next few months.

2) NWK has compared Oregon state information to death rates from their ER and hospital databases. The results of the comparison were somewhat poor and highlighted the need to directly access the death records. NWK also recognized the need to modify the LLDB method for subject capture so that information on infants who died before 1 month of age could be retrieved. They anticipate less than 50 deaths per year in the age range being studied.

3) R. Thompson summarized GHC's current status and discussed some expected difficulties in starting the death capture study. As with NWK, GHC anticipates capturing relatively few deaths per year. Please refer to their handout material for more detail.

Several programming options exist for matching death records to children registered in the study. Options being considered include the algorithm that J. Mullooly and his colleagues have developed at NWK as well M. Griffin's linkage program developed at Vanderbilt University.

IMPLEMENTATION, JAN 26, PM

OUTCOME DEFINITIONS:
In an all-afternoon session with J. Hardy, investigators from each of the sites discussed the outcome definitions in detail. Contributions were also made by Drs. Walker and Guess, consultants on the project. The document relevant to this review was J. Hardy's spreadsheet entitled: "Vaccine Safety Datalink: Automated Outcome Ascertainment" and indirectly to J. Glasser's document entitled "Vaccine Safety Datalink Tape II: Screening & Other Analytical Issues." The key decisions made were:

1) To rename the 3 columns pertaining to the need for chart review:
"Review not required" was changed to "Automated Data Sufficient for Screening Analyses"
"Review" was changed to "Chart Review Required"
"Review not warranted" was changed to "Do not include in Analyses"

2) To subdivide the outcome Encephalitis/opathy was into the following analytic groups:
Idiopathic disease
Disease due to vaccine preventable disease or vaccination
Other

3) To move some of the ICD9 codes in the outcome Ataxia to the "do not include in analyses" category. One of the codes in particular, ICD9 781.3 (lack of coordination), accounts for 80% of the cases of ataxia as presented in the tape 2 screening analyses.

4) The outcome Guillain-Barre Syndrome should now routinely contain all of the codes from the outcome Transverse Myelitis.

5) The outcome Polio and Acute Paralytic Syndromes should now routinely contain all of the codes from the outcomes GBS and Transverse Myelitis.

6) The outcome Allergic Reactions was subdivided into the following analytic groups:
Systemic Allergic Reactions, including anaphylaxis
Dermatologic Reactions, including all else but ICD9 code 999.5 (Other serum reaction)

7) Create a new subcategory entitled "Unspec. Adverse Events" which will contain all cases encoded 999.5 (other serum reaction). This code was previously analyzed under the outcome subcategory Allergic Reactions.

8) The outcome Thrombocytopenia was subdivided into the following analytic groups:
Thrombocytopenia
Purpura condition
Transient neonatal thrombocytopenia (* need to view counts of children sorted according to < or = 1 mth of age, versus > 1 mth of age prior to further decisions)

9) With the exception of a few ICD9 codes from each outcome, all of the codes in the outcome Arthropathy/Arthritis will be included in the outcome Autoimmune/Immune Complex Diseases and vice versa.

10) The outcome Non-bacterial Pneumonia has been renamed"Bacterial and Non-bacterial Pneumonia"

11) ICD9 code 775.6 (neonatal hypoglycemia) should be analyzed apart from the rest of the codes in the Hypoglycemia outcome.

12) The counts of children for the outcomes Breath Holding and Apnea need to be sorted according to < or = 1 mth of age, versus > 1 mth of age prior to further decisions.

13) The outcome SIDS should be restricted to children < or = to 1 year of age.

Other changes were made to each outcome at the item level & are documented in the enclosed updated spreadsheet.

NEUROLOGISTS SESSION - PROTOCOL UPDATE, JAN 26, PM

Participants: John Pearson, Tom Knauss, Jean Hayward, Paula Ray, Bob Davis, Vito Caserta, Connie Vadheim, Steve Rosenthal

There was general agreement among the group that good progress has been made in the development of the neurological outcome forms. The neurologists felt that the forms were developing nicely. A few of the lessons learned from the seizure abstraction experience were discussed. Much of the clinical and laboratory data questions presently on the forms was not particularly useful; it was decided that the other outcome forms could omit these questions. The case definition of encephalopathy was discussed and compared with the newly published definition by DVIC, and a final version will be distributed among the group.

Abstraction forms and instructions for the other neurologic outcomes will be finished within the next 2 months by the assigned centers. These will be distributed to the other sites and piloted.

DATA MANAGERS SESSION, JAN 26, PM AND JAN 27, AM

Participants: Emmett Swint, CDC; Virginia Immanuel, GHC; Ned Lewis, NCK; Loie Drew, NWK; and Patricia Osborne, SCK.

Data managers met the afternoon of 1/26/1995 and morning of 1/27/1995 to discuss LLDB data management activities.

LLDB Automated Tapes

Data managers reviewed automated files that are currently being submitted to CDC and projected when data may be available for other systems.

GHC Current: CONSTANT, ENROLL, VACCINE, OUTCOME (all components), HOSPDXHX, LAB, PHARMACY, PROCED, ADDRESS and GEOCODE
Future: None (all components currently are submitted)
Not Avail: None (all components currently are submitted)

NCK Current: CONSTANT, ENROLL, VACCINE, OUTCOME (hospital, ER and 3 clinics), HOSPDXHX, PROCED (excluding neurology referrals), ADDRESS and GEOCODE
Future: (1) Some LAB data from their old lab files will be submitted in mid-June for tape 3. Results from a new lab system will be submitted for tape 4. (2) Outpatient data for all clinics may be available for tape 4 from a new outpatient clinic system that was implemented in January, 1995.
Not avail: (1) Pharmacy file; (2) neurology referrals in the procedure file.

NWK Current: CONSTANT, ENROLL, VACCINE, OUTCOME (hospital and ER visits), HOSPDXHX, PROCED, ADDRESS, and GEOCODE files.
Future: (1) LAB file will be available in next six months
Not avail: (1) Clinic visits in the OUTCOME file. A system is under long-term development.

SCK Current: CONSTANT, ENROLL, VACCINE, OUTCOME (hospitalizations), ADDRESS and GEOCODE
Future: (1) OUTCOME (ER visits); (2) HOSPDXHX in summer, 1995; (3) LAB in June, 1995; (4) PHARMACY in fall, 1995; and (5) PROCED in Summer, 1995;
Not avail: (1) OUTCOME (clinic visits)

Files Involving Chart Reviews

SAMPLE file. Emmett indicated that Phil Rhodes would like to begin reviewing the first SAMPLE file results. SCK has submitted

their SAMPLE file to CDC. NCK and NWK indicated their files are available. GHC's file would not be available until after the third tape.

Neurology review files. CDC has received the seizure review file from NWK. In order for Bill Barlow to do additional analyses at GHC, he will send Emmett a list of studyid numbers. Emmett will return the file with enrollment, vaccine and any other automated variables.

Loie Drew indicated that NWK used ancillary information to identify additional children with seizures. Children appearing in the PHARMACY and PROCEDURE files were identified as prospects for any neurology outcome. Their medical charts were reviewed and all ICD-9 codes within a given time period of each ancillary reference date were identified. Children having any seizure ICD-9 code in this list were added to the seizure sample. The chart review was performed and all children were classified as either a seizure case or non-seizure case.

There was general discussion about the neurology review protocols. Data managers preferred that the formats have a common uniform component followed by questions that might be specific to a given disorder.

Files Involving Matching

The geocode and birthref files are used to match with census files and state birth certificate files. Emmett indicated that CDC will not perform these functions until additional contract FTEE can be obtained. The death file will be a new file that will require HMOs to match children with the state death certificate files and other local sources for deaths.

Data managers discussed the structure needed to report deaths. It was agreed that a separate DEATH file should be created but it should be consistent with existing LLDB files. It was agreed that the same death matching file could not easily be used at all HMOs. Emmett agreed to review previous documents that were written and to describe the methods that each HMO are using to identify deaths. Ned indicated that NCK deaths occurring outside the HMO were reported in the CONSTANT file. The target date for death files would after the tape 3 submission date.

LLDB Edits

Data managers reviewed some of the edits that were used with LLDB tape 2. It was requested that data managers apply these edits locally and resolve records that do not pass edits prior to submitting tape 3.

Corrections were identified and the following edits are to be added to the list:

(1) Vaccine file -- vaccines reported in tape 2 should appear in tape 3 unless the child has been dropped for ineligibility reasons or the vaccine record was corrected after tape 2.

(2) Outcome file -- diagnoses reported in tape 2 should appear in tape 3 unless the child has been dropped for ineligibility reasons or the vaccine record was corrected after tape 2.

Data Dictionary Modifications

The data structure of all LLDB automated files was reviewed to determine if changes were needed. Emmett will incorporate the corrections and republish the data dictionary. HMOs should proceed with tape 3 based on these changes.

Emmett indicated that the enrollment start and stop dates provided by the HMOs in the ENROLL file would be the ones used without additional adjustments. Ned agreed to describe the adjustments that each HMO uses, e.g., collapsing enrollments that are within 90 days of each other. There was discussion about whether shots and vaccines outside the enrollment intervals should be submitted as part of the VACCINE and OUTCOME files since analyses excluded these shots. Data managers preferred not to submit exposures and events outside these intervals.

NCK will be submitting adolescent data. Ned wanted to know how much historical hospital data should be included in the HOSPDXHX file. The files could become very large and local hospital discharge files may not be as accurate and complete for adolescents ready to age-out.

Transport Files

Emmett indicated that some form of SAS transport file would be needed for HMOs with non-UNIX operating systems to submit files to CDC. A routine was distributed describing how to prepare and read transport files. Ned Lewis indicated that some systems could not handle block sizes of 32000 or higher and recommended that "blksize=31920" be used when creating the transport dataset.

ANALYTICAL ISSUES, JAN 26, PM, AND JAN 27, AM

The statisticians met twice to discuss analytical issues, beginning with technical questions (i.e., why Phil had screened exactly as he had), some of which had been discussed before Michael joined SCK, but were worth reconsidering (e.g., matching more finely on calendar time than age accounts for different

probabilities of recent exposure on weekends and week days). Other issues concerned refinements of subsequent analyses.

Causing conditions is more interesting substantively than exacerbating them, which however might be more challenging statistically. With regard to the nested seizure study, someone suggested that first events and ones following febrile and afebrile first events be analyzed separately. Given that their records are complete, though not necessarily automated, children born into these HMOs and continuously enrolled might be analyzed separately to overcome the arbitrary nature of first events among those born before or elsewhere. This led to discussion of chronic conditions, which screening of first events, all events and ones remaining after application of our rule for distinguishing acute and follow-up care is meant to address crudely. Ideally, one would condition on prior occurrences such that comparison groups differ only in most recent exposure. The high risks associated with Flu and DT vaccines probably would disappear if otherwise similar children were being compared.

On another topic, the external advisors recommended reviewing the charts of exposed cases and sampling the others whenever associations were found; one could target children whose automated records indicated were behind, which likely are incomplete, as is being done routinely at NWK; the nested seizure study is being done differently, but it might be possible to remedy this at the larger sites where substantial fractions of charts remain to be reviewed. One goal of any such reviews might be discovering which associated codes (and ancillary information) are most predictive of validated cases; Janet Hardy is formulating just such a study.

Suggested analytical priorities were: (a) first event analyses of recurrent outcomes, (b) children born into study and continuously enrolled, (c) stratification to elucidate effect modification by age, (d) simultaneous administration (individual or synergistic effects?), (e) stratification for effect modification by gender. Further analyses were recommended only of exposure-outcome pairs that seem to be associated in screening. Advisors recommended that we not be paralyzed by multiple comparisons because outcomes are different, and that the VAERS be used for hypothesis generation and the VSD for evaluation.

Phil promised to make his programs more friendly and provide them to other statisticians as a means whereby they might become more comfortable with what he had done and possibly assume some of the responsibility. Which analyses others might perform were not specified, but some are interested to general issues (e.g., Michael in confounding, Bruce in Poisson regression, John in misclassification) and others in specific outcomes (e.g., Bill in seizures). This discussion should continue during analytical conference calls, whose participants also might consider a

proposed new rule for distinguishing acute and follow-up care, based on recent revision of the original periods beyond which follow-up didn't usually extend and provision of usual durations of acute care, and its empirical evaluation, the strange age-distributions of NCK and SCK, summary document entitled "Screening and Other Issues," particularly the questions and their analytical implications (e.g., windows of risk post-vaccination)

DRAFT

FDA CBER SUGGESTIONS FOR JAN. '95 LLDB MEETING AGENDA

1. Lot-Specific Signals

Can the LLDB help with lot-specific signals? Do annual tapes and/or cumulative local HMO data show sufficient utilization of particular vaccine lots to allow evaluation of at least broad indices of safety, such as total hospitalizations in 2 or 6 (or other window) weeks after vaccination vs. pre or vs. same windows post for recent or other comparator lots? How rapidly could we discover whether one or more data systems have enough uses of a given lot? If not currently possible to rapidly check whether LLDB has data on a lot, can we develop a procedure to allow for such inquiries in the near future?

2. DTP vs. DTAP

If some sites still don't use DTAP, can we get a status report on this comparison, probably stratified by age and with attention to possible confounders? Are patients or sites using DTP of lower socioeconomic status, for example?

3. DTP + HIBV vs. DTPH

As above for DTP vs. DTAP, if LLDB data are heterogeneous with respect to DTPH, we would appreciate a status or feasibility report on evaluating DTPH safety vis a vis simultaneous DTP + HIBV. Note that DTP + HIBV, in turn, may be two separate injections or a single one with mixture into one syringe immediately before administration. As above, we would expect to stratify on age and to consider possible confounders.

4. Safety of Other Vaccine Combinations

In addition to the specific question of DTP + HIBV vs. DTPH, can LLDB data shed light on other combinations? DTP with vs. without HIBV? Does addition of HEP to the routine vaccines add risks of post-vaccinal hospitalization, neurologic visit, seizure, or death?

5. Mortality

A status report on both methods and results would be helpful. Is the ancillary ascertainment through vital records "up and running" at least at some sites? Do we have enough data yet to demonstrate freedom of the more recent infant vaccines (HIBV, DTAP, DTPH, HEP) from association with SIDS? (Empirical demonstration of such safety has only been conducted for DTP, and those data are several years old now.) Can we show that neonatal HEP is free from association with mortality and other serious adverse effects?

6. Pre-Existing Conditions as Risk Factors for Post-Vaccinal Death

VAERS receives occasional reports of babies with congenital heart disease who died after vaccinations. Unlike the principal LLDB outcomes of interest, congenital heart disease and prematurity are at least two potential risk factors for post-vaccinal mortality. The conventional medical view would probably be that patients with these conditions would be most vulnerable to the target diseases, and therefore should clearly be vaccinated. Do LLDB data support this perspective? Is it possible that we should be deferring routine vaccinations until they are somewhat older or stronger?

7. Manufacturer-Specific Issues

Does LLDB data contain sufficient heterogeneity in brands to allow comparisons of general safety (risks of post-vaccinal hospitalization, neurologic visit, seizure, or death) between manufacturers for neonatal and later infant HEP and for other products with multiple sources?

8. Status Report on ER visits after FLU, this year vs. last

At the October conference call I mentioned a signal of a few reports of possible anaphylaxis associated with influenza vaccination. They were from a commercial firm which was giving thousands of flu shots to Walgreen's customers nationwide. At least one LLDB site has data on adult immunizations, even though not covered by LLDB. After another month or so, ER visits following this year's FLU vs. last year's might be available. Although LLDB does not currently cover patients beyond age 7, perhaps it would be useful to invite a status report. The topic has obvious public health importance. But it could also help us to demonstrate the value in extending LLDB methods to older ages.

c:\dbe94\lldb195 Bob Wise HFM-225 12/14/94

Children's
Hospital & Medical Center

EXHIBIT
12

February 9, 1995

Robert Chen, MD
Steve Hadler, MD
National Immunization Program (E-61)
Centers for Disease Control and Prevention
Rm 4218.01
12 Corporate Square Blvd.
Atlanta, Georgia 30333

Dear Bob and Steve:

In a letter sent to you today under separate cover, I've outlined my view of the importance of the Vaccine Datalink system and offered some critical comments which I hope will prove helpful.

I sincerely believe the project is of enormous importance to our national immunization enterprise. If you believe I could assist in some substantive way, I would be interested in exploring such an opportunity with you. However, I regret I cannot realistically consider playing an ongoing role unless a portion of my salary was reimbursed to the University of Washington or Children's Hospital and Medical Center. My discretionary time is over-committed meeting my responsibilities to NVAC and related activities.

By this brief note I wanted to make clear to you both my interest and my constraint.

Sincerely,

Edgar K. Marcuse, MD, MPH
Chairman, National Vaccine Advisory Committee
Professor of Pediatrics, University of Washington

EKM:nc

ekm\corres\Datalink2

Children's
Hospital & Medical Center

February 9, 1995

Robert Chen, MD
John Glasser, PhD
Stephen Hadler, MD
National Immunization Program (E-61)
Centers for Disease Control and Prevention
Rm 4218.01
12 Corporate Square Blvd.
Atlanta, Georgia 30333

Dear Bob, John, and Steve:

Thank you for the opportunity to attend the Vaccine Safety Datalink meeting January 26 in Oakland, and for inviting me to share some observations by this letter.

I believe the Large Linked Database project (LLDB) is five years old. Although I have listened to Bob's informative periodic updates at the National Vaccine Advisory Committee (NVAC) and reviewed all of the helpful background materials furnished me by John, I recognize I do not have a complete or detailed understanding of the project. Please keep that in mind as you weigh my comments.

I want to outline what I see as the significance of this project. Last fall, the NVAC identified the four highest priority activities which that committee believed were the keys to realizing the full potential of modern vaccines to prevent costly disease and improve the public health. The four were: increase coverage of childhood vaccines; enhance vaccine safety; facilitate vaccine development; and expand adult immunization. Vaccine safety warrants such a very high priority for several reasons:

> Public confidence in vaccine safety is very tenuous. The average parent is perplexed by periodic media reports of serious adverse events associated with vaccines. The pictures of damaged children, the anguish of their parents as shown on TV are very real images, whereas the threat of vaccine-preventable disease is remote. Relative risks are very hard to fathom.
>
> There is very little public awareness of many government and industry activities that ensure vaccine safety and efficacy. Most of these activities are invisible and largely incomprehensible. They come to public attention only when immunization is "on the defensive", responding to a report of an adverse event. Concepts of good manufacturing practice (GMP), Phase I-V testing are arcane, not only to the public but to most health care providers. There is an unfounded but understandable, seldom-voiced suspicion of

collusion between government, industry, and doctors, to which the media sometimes plays.

Parents have been overwhelmed by the addition of seven more "routine" shots before age two, for diseases they never heard of, and therefore do not generally perceive as threats to their children. Common sense prompts any parent to question "Are you *sure* it's safe?" when a provider recommends a 4-month-old brought in for a cold receive Hib, DTP, Hepatitis B, and OPV.

At this time, recommendations in government documents for providers and parents contain contradictory statements. While there are reasons for this conflict which are understandable to the "*cognoscenti*", the general public and many providers ask simply "Do 'they' really know what they're doing?"

Viewed against this background, the enormous value and potential importance of LLDB is readily apparent. It is either the only or the best way to ascertain the safety and efficacy of various combinations of childhood vaccines, the wisdom of administering at a single visit all vaccines for which a child is eligible, and confirming or refuting reports of alleged associations between adverse events in vaccines stemming from the medical literature or the Vaccine Adverse Event Reporting System (VAERS).

I think that confirming the appropriateness of the immunization practices recommended in the standards is perhaps of overriding importance. There is precious little data corroborating the safety and efficacy of these practices. Weekly, concerned mainstream parents ask: How do you *know* it is safe?

At this time, the potential for immunization chaos due to safety concerns is considerable: witness the public concern generated last year by the program NOW with Tom Brokaw and Katie Couric. Indeed, most parents and providers still believe there are "hot lots" of DTP. Public concern about vaccine safety could rapidly escalate and disrupt public health programs nationwide.

I believe the Vaccine Safety Datalink project represents a very wise and strategic investment in a scientifically credible system to monitor and assess vaccine safety. An enormous amount of work has gone into building a foundation for future cooperative studies to ensure the data from the four sites is comparable. Unfortunately, like the foundation of a modern skyscraper, much of this work is not visible from afar. Today, few who administer or receive vaccines are aware of the Vaccine Datalink Study. Because of the increasing number of vaccines, the plethora of possible combinations, and the relative rarity of associated adverse events, the task of the LLDB is technically very difficult and requires very large numbers of patients. Nonetheless, most simply put, the LLDB is the keystone in the arch supporting the entire structure that makes up the U.S. vaccine safety system. This system must be made visible to bolster and sustain public confidence in modern vaccines. The disparate vaccine safety enterprise, including the Vaccine Datalink Study, must be systematically "marketed" to providers and to the public. A predictable, regular

series of scientific and public reports and informational releases is needed to develop and sustain support for the project. All reports from the Vaccine Datalink Study must be easily identified and of unassailable quality. Publications should be generated for providers and the public as well as the scientific community.

Each of the four participating sites boast an impressive group of investigators, sophisticated data systems, and a very large number of cooperating clinicians and patients. Staff who are expert on the methodology of vaccine safety should be encouraged to interact with clinicians and public health workers in public discussions to increase awareness of vaccine safety activities and an understanding of its complexities. Consider presenting a variety of workshops at clinical, public health, and academic meetings. Safety issues need to be widely discussed to generate some consensus on the appropriate investment in vaccine safety research. In other words, how great must be a risk before we devote resources to investigate it? This issue should be discussed broadly at the ACIP, Red Book, NVAC, ACCV, and elsewhere. The public policy implications of the work of the Vaccine Datalink Study are profound. The project leaders and principal investigators have a special responsibility to educate the project's "potential customers", which include clinical and public health providers, the scientific community, vaccine manufacturers, and "resource allocators" within HHS.

Overall, the vaccine safety effort in the U.S. is comprised of a variety of loosely coordinated government and industry activities, of which the Vaccine Datalink is a circumscribed, potentially very powerful component. You who instigated the project along with the principal investigators and scientific staff recognize better than I the potential of the system you've created to answer important questions about vaccine safety. Is this valuable system being fully exploited at this time? If not, why not?

Discussions at the recent meeting suggested that limited or unpredictable resources are part of the problem. Limited numbers of staff available to do sophisticated statistical analysis, at least in some instances, has become the rate-limiting step in producing data. My observation of the meeting suggests that coordinating the four sites is no easy task. Vaccine safety is not the principal business of the sites, nor necessarily of the principal investigators or their staff. An improved system for setting priorities, developing timelines, and ensuring timely production of deliverables may be required to demonstrate the potential utility of the system and thereby ensure its continued support. How this may be achieved through the mechanism of a CDC contract overseen by worthy, but changing staff of contract officers coordinating the efforts of PI's at four sites is not obvious to me. What is needed is coordinated leadership of the project to support sites and hold them accountable, agree on priorities, market the project, support the sites, and obtain reliable resources. At this time, it might be productive to consider if there are structures other than a CDC contract that would better exploit the full potential of the project.

For example: Could vaccine safety be regarded as a "business opportunity" which could be best developed by a public service corporation set up as a partnership between the four sites? Such a corporation could contract with CDC, other government agencies, and vaccine manufacturers to

produce specific deliverables. Responsibility for project coordination and administration would shift from CDC to the corporation which presumably would also allocate resources provided by the contractors to the sites. I recognize in this form this is a simplistic idea, but consideration of such a model may make clearer some of the problems in the present structure, and suggest creative solutions.

I believe an external advisory committee can assist project leaders and PI's by helping to build support for the project, participating in priority setting, providing a broad perspective, and offering criticism and validation, but outside advisors cannot provide leadership, which requires day-to-day participation and the authority to hold participants accountable.

Thank you again for the opportunity of attending the meeting, and inviting these comments.

Sincerely,

Edgar K. Marcuse, MD, MPH
Chairman, National Vaccine Advisory Committee
Professor of Pediatrics, University of Washington

EKM:nc

ekm/corres/datlink

Rob.

-----Original Message-----
From: Pless, Robert
Sent: Friday, July 02, 1999 9:33 AM
To: Schwartz, Ben (NIP); Allen, Curtis; Nowak, Glen; Broom, William L.
Cc: 'chenr@who.int'
Subject: RE: thimerosal Q&A's

Ben,

Beyond the basic questions, there will be others we can think of in response to the wording of any statement that comes out, unless they can be anticipated and written into the statement.
For example, the current draft Talking Points mentions the Dec 98 request by FDA for manufacturers to provide info on the thimerosal (ethylmercury) content of vaccines... YOU MEAN FDA DOES NOT ALREADY KNOW! HOW COULD THEY APPROVE A PRODUCT WITHOUT KNOWING HOW MUCH MERCURY IT CONTAINS? WHAT ELSE IS LURKING THAT NOBODY KNOWS ABOUT?

I think history leads us well here: there has been no vaccine safety issue to date that I can recall that was "well received" and generated a rational public response. There is also a recent history of rebuttals to every statement made by the authorities. When Bob and Frank wrote their editorial criticizing Wakefield's paper, CDC was attacked for trying to discredit independent research. When the epi study of SV40 was released suggesting no increase in cancer incidence, the same people felt free to attack it as biased since it was written by "government scientists". Can't win!

If we think along those lines, is it wise to even try to maintain the status quo with the vaccine schedule? I don't think we can say on the one hand, we are moving towards mercury free products, while on the other hand suggesting that any mercury is at safe levels so don't worry about your child. It is also no longer going to wash that "there is no data to suggest a risk". Opponents of vaccination don't need data to support allegations of a risk, and this frustrates us. Continuing to vaccinate until the new products arrive may be difficult...

If we consider that vaccination programs around the world may take a hit, perhaps we need to rethink the communications strategy. I cannot think beyond a "lose lose" situation. Is there a role to get some expert risk communicators together to problem-solve through the various scenarios - and come up with strategies without starting out with the premise that we must maintain the current immunization schedule and mandatory immunization laws. Even going so far as to "allow" for differals? In situations where it is not viable to defer or use single doses, such as WHO's concerns, we have to point out the risk of contamination (with specific examples?) that thimerosal is meant to mitigate, and for which there is no replacement at the moment.

As I figure, and have mumbled earlier, this is similar to BSE/CJD/nvCJD and blood and beef. It's "easy" to ban beef from the UK on theoretical grounds, and ignore the plight of the beef industry. Easy to recall blood products - and ignore the next trauma victim who arrives just as the last batches of blood or plasma are being wheeled out by regulators... At the level of the individual, theoretical population outbreaks of disease if coverage drops may not generate any concerns, but an outbreak in progress might lead to acceptance of

vaccination with a thimerosal-containing product. Just like if there was nothing else to eat but beef, and you are starving.

The public even then is not totally rational: David Salisbury once pointed out that at the height of the beef scare, nobody was buying British beef - until it went on sale!

Just some musings.

Rob

-----Original Message-----
From: Schwartz, Ben (NIP)
Sent: Thursday, July 01, 1999 6:37 PM
To: Pless, Robert
Subject: FW: thimerosal Q&A's

Ben Schwartz
404-639-8953 (tel)
404-639-8616 (fax)
bxs1@cdc.gov

-----Original Message-----
From: Nowak, Glen
Sent: Thursday, July 01, 1999 6:31 PM
To: Reynolds, Barbara S.
Cc: Thompson, Charlis J.; Allen, Curtis; Schwartz, Ben (NIP)
Subject: RE: thimerosal Q&A's

Thanks for the update. Could you forward the draft Q and A's for thimerosal? We're also developing additional Q and A's. In addition, here's the Q and A's developed by AAP's media office:

1. When was it determined that high levels of thimerosal content in vaccines is a potential problem? Why wasn't it detected earlier? Who's at fault? What made FDA begin to study the issue?

2. How do physicians review the contents of vaccines?

3. What should parents do (vaccinate or not vaccinate with thimerosal-containing vaccines)?

4. What proof do parents have that vaccinating their children is safe? What scientific information do you have to backup your recommendation to vaccinate?

5. What should pediatricians tell worried parents?

6. Can all vaccines be made thimerosal-free, or within accepted guidelines? If so, how quickly?

7. Are children who've been given vaccines with thimerosal at risk for adverse side effects? How can we know for sure? What are the possible side effects? What kind of treatment can a child receive?

8. How many children in the U.S. have been given more than the recommended amount of thimerosal through vaccines?

9. In light of this information, would you vaccinate your own children right now with thimerosal-containing vaccines?

From: Pless, Robert
Sent: Friday, July 02, 1999 9:33 AM
To: Schwartz, Ben (NIP); Allen, Curtis; Nowak, Glen; Broom, William L.
Cc: 'chenr@who.int'
Subject: RE: thimerosal Q&A's

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DRAFT – MAY CONTAIN ERROR OF FACT OR OMISSION

Risk of neurologic and renal impairment associated with thimerosal-containing vaccines.

Thomas Verstraeten, Robert Davis, Frank DeStefano, and the VSD team

Abstract

Background: Thimerosal is a mercury-based preservative in vaccines. Theoretical concerns have been raised that, through vaccinations, infants were being exposed to mercury levels exceeding Environmental Protection Agency guidelines. We used automated data from two health maintenance organizations, prospectively collected for vaccine safety studies, to assess the risk of neurologic and renal impairment associated with exposure to thimerosal-containing vaccines.

Methods: Cumulative exposure to mercury from thimerosal was evaluated at 1, 2, 3 and 6 months of age for 213,185 infants born between 1992 and 1997. Using proportional hazards models, we compared the risk of 16 neurologic disorders and 1 renal disorder to the cumulative exposure levels.

Results: We identified 3517 children with neurologic disorders, and 106 with renal disorders. We found a statistically significant positive correlation between the following measures of exposure and outcomes:

- the cumulative exposure at 2 months of age and unspecified developmental delay
- the cumulative exposure at 3 months of age and tics
- the cumulative exposure at 6 months of age and attention deficit disorder
- the cumulative exposure at 1, 3 and 6 months of age and language and speech delay
- the cumulative exposure at 1, 3 and 6 months of age and neurodevelopmental delays in general.

Conclusion: This analysis suggests that in our study population, the risks of tics, ADD, language and speech delays, and developmental delays in general may be increased by exposures to mercury from thimerosal containing vaccines during the first six months of life. Confirmation of these findings in a different population and further quantification of the dose response effect are needed.

Brockner Ryan, Beth

From: Patriarca, Peter
Sent: Tuesday, June 29, 1999 12:39 PM
To: 'rhb2@cdc.gov'; 'jfc1@cdc.gov'
Subject: FW: "vaccine preservative WG"

Roger/Jose: have not yet received Roger's "position paper" by e-mail, but wanted to get some comments to you quickly. Draft we heard on the call is really excellent. However, (1) would add some of the elements of my "pros and cons" listing below (especially related to the BENEFITS of having thimerosal in the first place); and (2) try to avoid suggesting that the "interim plan" would be effective "immediately". The fact of the matter is that an "interim plan" (for potential removal of thimerosal) has ALREADY been in place for MANY YEARS ... we just need to "speed up" the EXISTING plan ... not create a "new" interim plan". We are proactive ... not reactive. Thanks. Peter P.

----Original Message----
From: Patriarca, Peter
Sent: Tuesday, June 29, 1999 9:42 AM
To: 'Myers, Martin G.'; 'sja2@cdc.gov'; 'ezg0@cdc.gov'
Subject: RE: "vaccine preservative WG"

PLEASE GIVE TO MARTY MYERS ASAP.

Marty: I have developed a "quick-and-dirty" pros and cons analysis for the AAP policy statement:

The AAP should release its policy statement in more-or-less current form:

PROS

Will demonstrate that the AAP reacted urgently to recently uncovered information, and to disclose this information to practitioners and consumers.

Will demonstrate that the AAP adopts the most conservative position possible when it comes to protecting American children.

Will force manufacturers to develop "crash" programs for removal of all thimerosal from all vaccines.

CONS

Will raise questions about FDA being "asleep at the switch" for decades, by allowing a potentially hazardous compound to remain in many childhood vaccines, and not forcing manufacturers to exclude it from new products. Will also raise questions about various advisory bodies about aggressive recommendations for use. [We must keep in mind that the dose of ethyl mercury was not generated by "rocket science": conversion of the % thimerosal to actual ug of mercury involves 9th grade algebra. What took the FDA so long to do the calculations? Why didn't CDC and the advisory bodies do these clacutations while rapidly expanding the childhood immunization schedule?]

Will precipitate a vaccine shortage, leaving many children unimmunized. Removal of thimerosal could delay the availability of sufficient supplies of vaccines for at least 2 years, pending proper studies.

Thimerosal has benefits: it is there for a reason. Precipitous removal may generate problems in vaccine stability (affecting efficacy), and component inactivation (affecting safety). Proper studies must be done before it can be removed from products without a thimerosal-free presentation.

Will precipitate a worldwide crisis in confidence in vaccines. This is especially true for whole-cell DTP vaccines, which are still being used throughout much of the world. Thimerosal is used in these vaccines as an inactivating agent for pertussis cells.

ALTERNATE APPROACH: LOW KEY, SYSTEMATIC, DELIBERATE PRIVATE-PUBLIC APPROACH

PROS

Already going on for quite some time.

Shows careful consideration to all benefits and risks (as enumerated above) with rational and deliberate plan of action.

Consistent with European position.

CONS

MERCK
Research Laboratories

CONFIDENTIAL

NOT FOR DISTRIBUTION

MEMO

TO: Please See List DATE: June 9, 2000

FROM: Dr. H. A. Guess

SUBJECT: Scientific Review of Vaccine Safety
Datalink Information

For your information.

H. A. G. - 2422

Attachment

TO:

John Boslego	UNC -141
Isabelle Claxton	WP97-B346
Edward Sargent	WS2F-45
Alan Shaw	WP16-100
Robert Sharrar	BLB-30
Robert Trinkle	WP53C-310
Henrietta Ukwu	UN-B121
Thomas Vernon	WP97-A337

Scientific Review of Vaccine Safety Datalink Information
June 7-8, 2000
Simpsonwood Retreat Center

Agenda

Day One – North Georgia Room
Wednesday, June 7th

10:00	Welcome	Walter Orenstein
10:05	Introductions	All
10:15	Chronology of Events & Charge to the Consultants	Roger Bernier
10:30	Summary of Thimerosal Workshop in August 1999	Martin Myers
10:45	Introduction to Vaccine Safety Datalink Study	Frank DeStefano
11:00	Presentation of Vaccine Safety Datalink Information	Tom Verstraeten
11:30	Discussion	
12:30	***LUNCH***	
2:00	Results from Chart Reviews	Bob Davis
2:15	Discussion	
2:30	Presentation of an Independent Review of the Data	Phil Rhodes
2:45	Discussion	
3:00	Comments on Biologic Plausibility and Consistency	Loren Koller
3:30	Discussion	
3:45	*** BREAK***	
4:15	Open Discussion	All
6:00	Adjourn	

Scientific Review of Vaccine Safety Datalink Information
June 7-8, 2000
Simpsonwood Retreat Center

Agenda

Day Two - Watson Room
Thursday, June 8th

8:00	Open Discussion Continued	All
9:00	Individual Consultant Opinions on the Data (Round I)	Consultants
10:00	***BREAK***	
10:30	Presentation of Potential Next Steps for Research	Frank DeStefano/ Bob Davis
11:00	Individual Consultant Opinions on Research Needs (Round II)	Consultants
12:00	Rapporteur's Summary	Paul Stehr-Green
12:30	Adjourn	

Risk of neurologic and renal impairment associated with thimerosal-containing vaccines.

Thomas Verstraeten, Robert Davis, Frank DeStefano, and the VSD team

Abstract

Background: Thimerosal is a mercury-based preservative in vaccines. Theoretical concerns have been raised that, through vaccinations, infants were being exposed to mercury levels exceeding Environmental Protection Agency guidelines. We used automated data from two health maintenance organizations, prospectively collected for vaccine safety studies, to assess the risk of neurologic and renal impairment associated with exposure to thimerosal-containing vaccines.

Methods: Cumulative exposure to mercury from thimerosal was evaluated at 1, 2, 3 and 6 months of age for 213,185 infants born between 1992 and 1997. Using proportional hazards models, we compared the risk of 16 neurologic disorders and 1 renal disorder to the cumulative exposure levels.

Results: We identified 3517 children with neurologic disorders, and 106 with renal disorders. We found a statistically significant positive correlation between the following measures of exposure and outcomes:

- the cumulative exposure at 2 months of age and unspecified developmental delay
- the cumulative exposure at 3 months of age and tics
- the cumulative exposure at 6 months of age and attention deficit disorder
- the cumulative exposure at 1, 3 and 6 months of age and language and speech delay
- the cumulative exposure at 1, 3 and 6 months of age and neurodevelopmental delays in general.

Conclusion: This analysis suggests that in our study population, the risks of tics, ADD, language and speech delays, and developmental delays in general may be increased by exposures to mercury from thimerosal containing vaccines during the first six months of life. Confirmation of these findings in a different population and further quantification of the dose response effect are needed.

Introduction

Thimerosal has been used as an additive to biologics and vaccines since the 1930's for preventing bacterial contamination, particularly in opened multi-dose containers. Some but not all of the vaccines recommended routinely for children in the United States contain thimerosal. Thimerosal consists by weight of 49% mercury in the form of ethylmercury.

Mercury exists in metallic, inorganic or organic form. Ethylmercury belongs to the organic group, which includes methylmercury, a better known compound mostly found in fish. As little is known on the pharmacokinetics and toxicology of ethylmercury, and although some argue that ethylmercury behaves more like an inorganic, it is probably most conservative to assume that ethylmercury behaves like methylmercury.

Mercury is known to target mostly the neurologic and renal systems. The effects range over a wide variety of conditions, depending on mode of exposure and form of mercury. All research so far has focused on exposure either through inhalation or oral ingestion. Any knowledge on the effects of injection of mercury compounds in humans comes from anecdotal case reports.

Two prospective cohort studies, undertaken to assess the impact of prenatal exposure to methylmercury from fish consumption on the neurophysiological and neuropsychological development in children, have resulted in conflicting findings. In the Faroe Islands, Grandjean et al found an association with cognitive development at 7 years of age, whereas Davidson et al found no association in the Seychelles.
The current study is to our knowledge the first epidemiologic study to study the effect of thimerosal in vaccines on long-term neurologic and renal outcomes.

Methods and materials

Study participants

We selected a cohort of infants from the Vaccine Safety Datalink (VSD) database. VSD was created in 1991 by the National Immunization Program of the Centers for Disease Control and Prevention (CDC). The project links medical event information, vaccine history, and selected demographic information from the computerized clinical databases of four staff model health maintenance organizations (HMO)s: Group Health

Cooperative of Puget Sound (GHC) in Seattle, Washington; Kaiser Permanente Northwest (NWK) in Portland, Oregon; Kaiser Permanente Medical Care Program of Northern California (NCK) in Oakland, California; and Southern California Kaiser Permanente (SCK) in Los Angeles, California. HMO members have unique HMO identification numbers that can be used to link data on their medical services within the HMO. Vaccination data are derived from computerized immunization tracking systems that are maintained by each of the HMOs. Quality control comparisons of the computerized immunization data with information recorded in paper medical records have shown high levels of agreement. For medical encounters, each of the HMOs maintains computerized databases on all hospital discharges and emergency room visits; diagnoses from outpatient clinic encounters are available from some of the HMOs for certain years.

We have restricted our cohort to children born between 1992 and 1997 into one of the two HMOs with the most complete automated outpatient data set (GHC and NCK). For these two HMOs we have follow-up data to the end of 1998. Children in the cohort thus have a follow-up time of 1 to 7 years.

To ensure capture of all vaccinations in the first year of life within the HMO, we restricted the cohort to children that were born into the HMO, continuously enrolled for the first year of life and that received at least 2 polio vaccines within the HMO by the age of 1 year. We excluded infants with ICD9 codes indicative of congenital disorders, severe perinatal disorders, recipients of HepB immunoglobulins, and gestational age less than 38 completed weeks. For this last group we performed separate analyses.

Exposure assessment

We calculated the cumulative exposure to ethylmercury from individual automated vaccination records, assuming each vaccine to contain the mean dose reported by manufacturers to the FDA. We assessed this cumulative exposure at the end of the first, second, third and sixth months of life. The Thimerosal content of childhood vaccines used in the two HMOs is as follows:

Hepatitis B: 25 µg (12.5 µg ethylmercury)

Haemophilus Influezae: 50 µg (25 µg ethylmercury)

Diphtheria Tetanus Pertussis (whle cell or acellular): 50 µg (25 µg ethylmercury)

Polio, Measles, Mumps, Rubella, Varicella and Pneumococcal: 0 µg

Outcome assessment

A case was defined as any child that was assigned one of the ICD9 codes, listed below. No distinction was made on whether a code was assigned after a clinic visit or hospital stay.

1. Degenerative disorders:

Code	Description
330.x	Cerebral degenerations usually manifest in childhood
331.x	Other cerebral degenerative disease
333.x	Other extrapyramidal disease and abnormal movement disorders
334.x	Spinocerebellar disease
335.x	Anterior horn cell disease

2. Developmental disabilities:

Code	Description
299.0	Autism
299.8	Other childhood psychosis
299.9	Other unspecified childhood psychosis
307.0	Stammering
307.2	Tics
307.3	Repetitive movements
307.4	Sleep disorders
307.5	Eating disorders
307.6	Enuresis
313	Disturbance of emotions specific to childhood and adolescence
314.0	Attention deficit disorder
315.x	Specific delays in development
317-319	Mental retardation

3. Other neurologic conditions:

Code	Description
343.x	Infantile cerebral palsy
345	Epilepsy
346	Migraine
348.x	Other conditions of brain (cysts, encephalopathy, compression, edema)
349.82	Toxic encephalopathy
349.9	Unspecified disorders of nervous system
356.4, 356.8, 356.9	Idiopathic progressive and unspecified polyneuropathy
357.8, 357.9	Other and unspecified polyneuropathies

358.2, 358.8, 358.9	Toxic and other myoneural disorders
359.4, 359.8, 359.9	Toxic and other myopathies

4. Renal conditions

Code	Description
580 (exc. 580.81)	Acute glomerulonephritis
581 (exc. 581.81)	Nephrotic Syndrome
582 (exc 582.81)	Chronic glomerulonephritis
583 (exc. 583.81)	Not specified as acute or chronic nephritis and nephropathy
584, 585	Acute and chronic renal failure
586	Unspecified renal failure
593.9	Unspecified disease of kidney and ureter

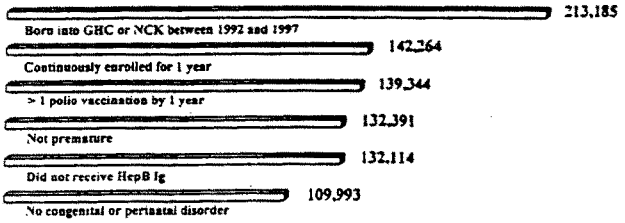
Statistical analyses

We used a Cox proportional hazard model to compare risk of developing any of the outcomes among different levels of exposure. By stratifying on HMO, year and month of birth, we compared children born within the same month at the same HMO. We adjusted the models for gender only. By using age of the child as the time variable in the PH model we also ensured comparison of children of equal age. As endpoint we used whichever of the following occurred first: the date of first diagnosis, the date of first disenrollment from the HMO or the last day of the follow-up period, December 31, 1998. To obtain 80% power in identifying a minimal relative risk of 2, we estimated the minimal number of cases for any outcome to be 50. We subsequently evaluated the impact of increased mercury exposure on the risk of any individual outcome for which we identified at least 50 cases. Because of different coding practices between HMOs and uncertainty on the specific neurologic and renal outcomes related to mercury exposure, we also assessed the risk for the entire categories of neurologic degenerative, neurodevelopmental and renal disorders, respectively. The category of other neurologic disorders was felt to be too heterogeneous for a similar approach. For the disorders of which we identified at least 50 cases among premature infants, we performed separate analyses for premature infants.

Results

The following table illustrates the number of children included in the cohort and the effect of the different eligibility criteria:

Table1. Number of children included:



The final number of children thus included in our cohort was 109,993.

The following graph shows the distribution of the cumulative mercury exposure at 1,2,3 and 6 months of age

Graph 1. Distribution of the cumulative mercury exposure at 1,2,3 and 6 months of age

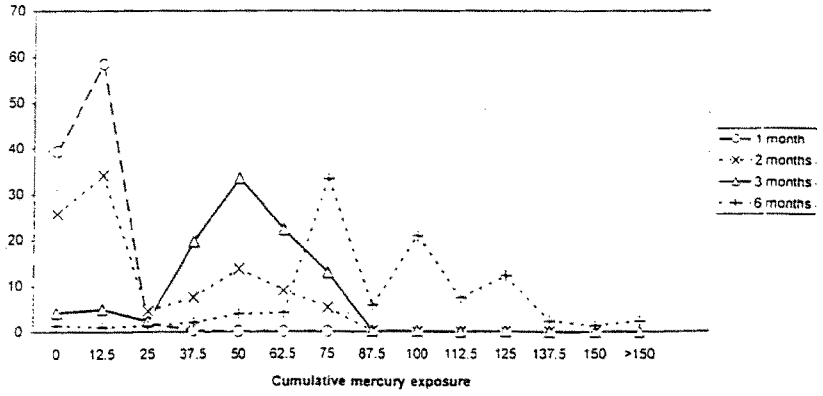


Table 2 shows the number of cases encountered for each disorder, the mean age at first diagnosis, the distribution over the two HMOs and the percentage males among cases.

Table 2. Number of children identified per disorder and some characteristics

				Site (%)		Male (%)
Code	Description	Total	Age *	GHC	NCK	
ALL kids		109,993		14	86	51
Neurologic degenerative disorders:		112	28	27	73	68
330.x	Cerebral degenerations usually	4	25	25	75	50
331.x	Other cerebral degenerative disease	35	19	17	83	69
333.x	Other extrapyramidal disease and	63	33	35	65	70
334.x	Spinocerebellar disease	9	27	11	89	44
335.x	Anterior horn cell disease	9	21	25	75	50
Neurologic developmental disabilities:		3114	32	36	64	69
299.0	Autism	127	42	14	86	83
299.8	Other childhood psychosis	51	49	22	78	92
299.9	Other unspecified psychosis	31	45	100	0	84
307.0	Stammering & stuttering	105	40	51	49	71
307.2	Tics	104	44	36	64	67
307.3	Repetitive movements	2	20	100	0	50
307.4	Sleep disorders	150	27	42	58	57
307.5	Eating disorders	78	21	9	91	53
307.6	Enuresis	20	59	10	90	70
313	Disturbance of emotions specific to	28	35	54	46	66
314.0	Attention deficit Sy	374	49	20	80	80
31531	Developmental language delay	351	34	4	96	74
31539	Developmental speech delay	1533	33	38	62	71
3159	Unspecified developmental delay	555	25	50	50	65
317-319	Mental retardation	17	48	12	88	63
Other neurologic conditions:		442	28	15	85	54
343.x	Infantile cerebral palsy	98	22	17	83	56
345	Epilepsy	236	26	9	91	56
346	Migraine	50	48	22	78	50
348.x	Other conditions of brain	30	23	30	70	51
349.82	Toxic encephalopathy	0				
349.9	Unspecified disorders of nervous	49	29	14	86	53
356.x	Idiopathic polyneuropathy	3	32	0	100	100
357.x	Other polyneuropathies	0				
358.x	Toxic and other myoneural	6	26	67	33	67
359.x	Toxic and other myopathies	8	25	13	87	63
Renal conditions:		151	23	17	87	50
580	Acute glomerulonephritis	3	57	67	33	67

581	Nephrotic Sy	17	31	6	94	71
582	Chronic glomerulonephritis	8	21	75	25	88
583	Not specified as d nephropathy	43	21	16	84	51
584	Acute renal failure	10	24	10	90	50
585	Chronic renal failure	7	44	14	86	57
586	Unspecified renal failure	11	31	45	55	73
593.9	Unspecified disease of kidney	95	25	13	87	54

* at first diagnosis, in months

Results for risk estimates are given first for the cumulative mercury exposure as a continuous variable assessed at 1,2, 3 and 6 months of age. Table 3 shows the number of cases occurring any time after the point at which the exposure is assessed, the relative risk estimate, and its 95% confidence intervals, associated with an increase of 1 microgram of cumulative mercury exposure at 1, 2 ,3 or 6 months of age.

For illustrative purposes we also show the relative risks for categories of increasing mercury exposure at three months of age. These are given in graphs 1 – 20 with their 95% confidence intervals and interconnected to illustrate potential trends. Note that the Y axis can be on a linear or logarithmic scale, depending on the magnitude of the CIs. For most of these analyses the reference category is the group with less then 37.5 µg of ethylmercury cumulative exposure at three months. For the most frequent disorders, the reference category is the 0 exposure group.

For completeness we also add the results of analyses of the cumulative exposure at 1 and 3 months of age compared to EPA guidelines in table 4.

Table 5 gives these results for premature infants, not excluding those with congenital or perinatal disorders, and restricted to neurodevelopmental disorders, speech and unspecified delay, for sample size purposes.

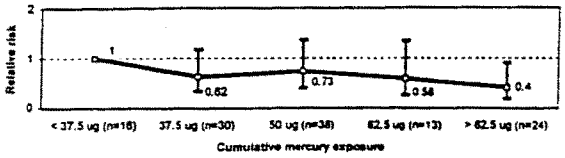
In the following tables, statistically significant results (not adjusting for multiple comparisons) are bolded.

Table 3 Relative Risk associated with an increase at 1, 2 ,3 or 6 months of age of 1 microgram of cumulative mercury exposure and its 95% confidence intervals.

Code	Description	Cases*	RR + 95% CI			
			1 month	2 months	3 months	6 months
Neurologic Degenerative Disorders		121	0.991 (0.964, 1.020)	0.994 (0.986, 1.010)	**0.987 (0.976, 0.999)**	0.994 (0.986, 1.001)
333	Extrapyradianal disease	63	1.003 (0.966, 1.042)	1.004 (0.993, 1.014)	1.003 (0.985, 1.022)	1.000 (0.990, 1.011)
Neurologic Developmental Disorders		3179	**1.007 (1.002, 1.012)**	1.001 (1.000, 1.002)	**1.007 (1.004, 1.010)**	**1.003 (1.001, 1.004)**
299.0	Autism	127	1.008 (0.983, 1.034)	1.003 (0.996, 1.011)	1.005 (0.991, 1.019)	0.999 (0.992, 1.007)
2998	Childhood psychosis	51	0.987 (0.946, 1.030)	1.000 (0.988, 1.012)	1.002 (0.980, 1.022)	1.001 (0.989, 1.013)
307.0	Stammering	105	0.983 (0.951, 1.017)	1.004 (0.996, 1.012)	1.007 (0.989, 1.025)	1.005 (0.997, 1.013)
307.2	Tics	104	1.05 (0.986, 1.045)	1.006 (0.998, 1.014)	**1.021 (1.004, 1.039)**	1.008 (1.000, 1.015)
307.4	Sleep disorders	151	1.003 (0.977, 1.028)	1.002 (0.995, 1.008)	1.004 (0.991, 1.018)	1.000 (0.994, 1.007)
307.5	Eating disorders	78	0.994 (0.961, 1.027)	0.997 (0.986, 1.007)	1.004 (0.986, 1.022)	1.000 (0.991, 1.060)
313.1	Misery disorder	158	1.016 (0.990, 1.044)	1.003 (0.995, 1.008)	1.005 (0.989, 1.021)	0.997 (0.989, 1.006)
313.8	Mixed emotional	156	0.991 (0.916, 1.016)	0.996 (0.989, 1.002)	1.000 (0.988, 1.012)	1.002 (0.996, 1.009)
314.0	Attention deficit Sy	377	1.006 (0.990, 1.021)	1.000 (0.996, 1.005)	1.008 (1.000, 1.016)	**1.006 (1.001, 1.010)**
315.31	Language delay	351	**1.019 (1.004, 1.034)**	1.003 (0.999, 1.008)	**1.021 (1.012, 1.030)**	**1.006 (1.002, 1.011)**
315.39	Speech delay	1533	**1.011 (1.004, 1.019)**	1.001 (0.999, 1.003)	**1.008 (1.004, 1.013)**	**1.002 (1.000, 1.004)**
315.9	Unspecified delays	555	1.005 (0.992, 1.019)	**1.005 (1.001, 1.008)**	**1.007 (1.000, 1.014)**	1.001 (0.997, 1.005)
Other neurologic conditions:						
343.x	Infantile cerebral palsy	98	0.976 (0.945, 1.008)	0.995 (0.985, 1.002)	0.993 (0.979, 1.007)	1.000 (0.992, 1.009)
345	Epilepsy	240	1.011 (0.993, 1.030)	1.002 (0.997, 1.008)	1.004 (0.994, 1.014)	1.000 (0.994, 1.005)
346	Migraine	50	0.981 (0.945, 1.028)	1.001 (0.990, 1.012)	1.018 (0.995, 1.042)	0.994 (0.983, 1.005)
Renal conditions:		164	0.992 (0.969, 1.016)	1.000 (0.994, 1.007)	0.994 (0.983, 1.006)	1.000 (0.993, 1.006)
593.9	Unspecified	106	1.003 (0.975, 1.032)	1.004 (0.995, 1.013)	1.003 (0.987, 1.019)	1.003 (0.994, 1.012)

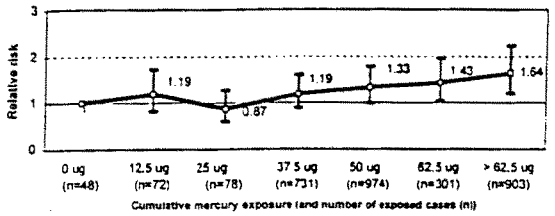
* occurring after 1 month of age

Graph 1: Relative risk + 95 % *CI* of Degenerative neurologic disorders after different exposure levels of thimerosal at 3 months of age, NCK &GHC, Cycle 7



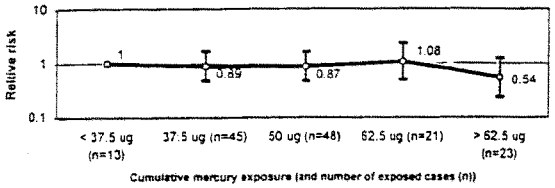
Trend:
0.987/ug
p = 0.03

Graph 2: Relative risk + 95 % *CI* of Developmental neurologic disorders after different exposure levels of thimerosal at 3 months of age, NCK &GHC, Cycle 7



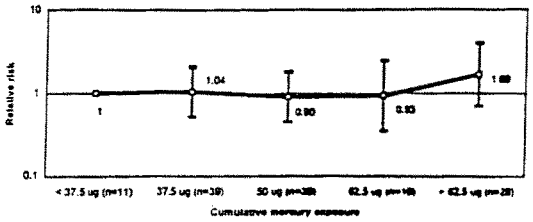
Trend:
1.007/ug
p < 0.01

Graph 3: Relative risk + 95 % *CI* of Renal disorders after different exposure levels of thimerosal at 3 months of age, NCK &GHC, Cycle 7



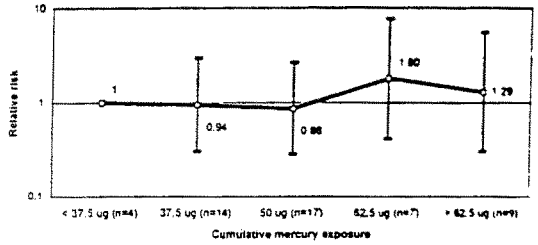
Trend:
0.994/ug
p = 0.71

Graph 4: Relative risk + 95 % *CI* of Autism after different exposure levels of thimerosal at 3 months of age, NCK &GHC, cycle 7



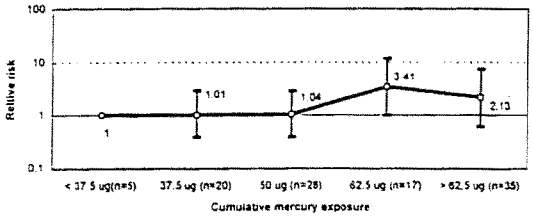
Trend:
1.005/ug
p = 0.48

Graph 5: Relative risk + 95 % *CI* of Childhood psychosis after different exposure levels of thimerosal at 3 months of age, NCK &GHC, cycle 7



Trend:
1.002/ug
p=0.94

Graph 6: Relative risk + 95 % *CI* of Stammering after different exposure levels of thimerosal at 3 months of age, NCK &GHC, cycle 7



Trend:
1.007/ug
p = 0.45

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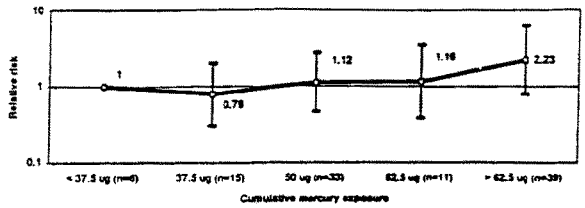
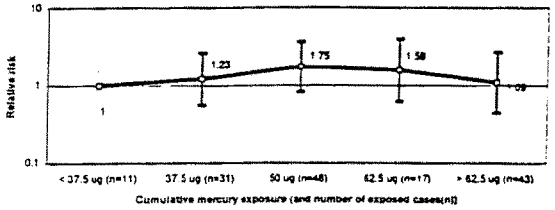
Graph 7: Relative risk + 95 % *CI* of Tics after different exposure levels of thimerosal at 3 months of age, NCK &GHC, cycle 7



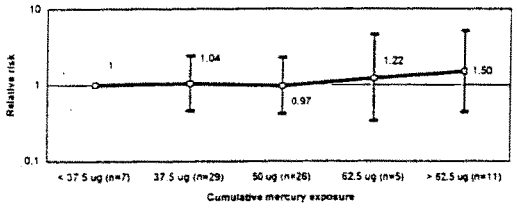
Trend:
1.021/ug
p = 0.02

Graph 8: Relative risk + 95 % *CI* of Sleep disorders after different exposure levels of thimerosal at 3 months of age, NCK &GHC, cycle 7



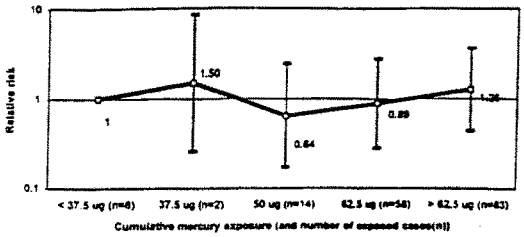
Trend:
1.004/ug
p = 0.51

Graph 9: Relative risk + 95 % *CI* of Eating disorders after different exposure levels of thimerosal at 3 months of age, NCK &GHC, cycle 7



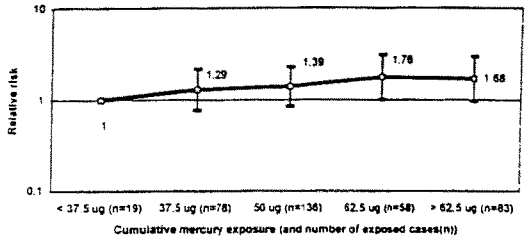
Trend
1.004/ug
p = 0.66

Graph 10: Relative risk + 95 % *CI* of Misery and Unhappiness Disorder after different exposure levels of thimerosal at 3 months of age, NCK &GHC, cycle 7



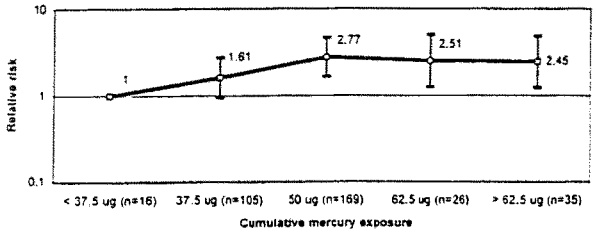
Trend
1.005/ug
p = 0.54

Graph 11: Relative risk + 95 % *CI* of Attention Deficit Disorder after different exposure levels of thimerosal at 3 months of age, NCK &GHC, cycle 7



Trend
1.008/ug
p = 0.06

Graph 12: Relative risk + 95 % *CI* of Developmental language disorder after different exposure levels of thimerosal at 3 months of age, NCK &GHC, cycle 7



Trend
1.021
p < 0.01

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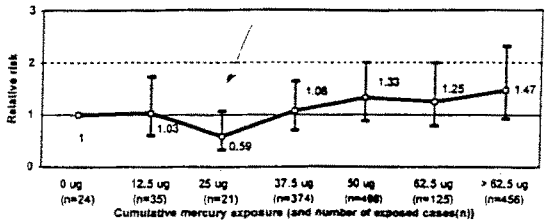
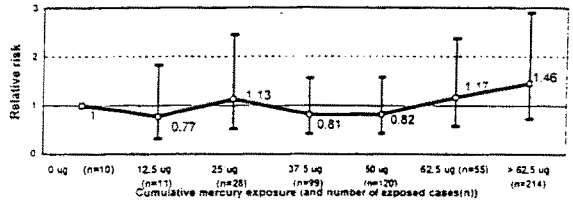
Graph 13: Relative risk + 95 % CI of Developmental speech disorder after different exposure levels of thimerosal at 3 months of age, NCK &GHC, cycle 7



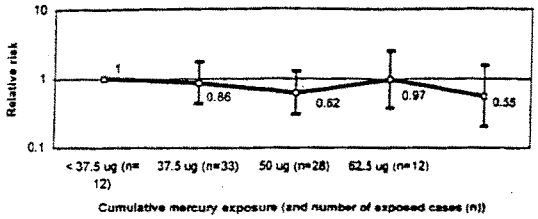
Trend
1.008/ug
p < 0.01

Graph 14: Relative risk + 95 % CI of Unspecified delay in development after different exposure levels of thimerosal at 3 months of age, NCK &GHC, cycle 7



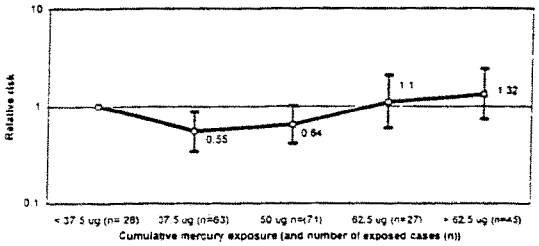
Trend
1.007/ug
p = 0.07

Graph 15: Relative risk + 95 % *CI* of Infantile cerbral palsy after different exposure levels of thimerosal at 3 months of age, NCK &GHC



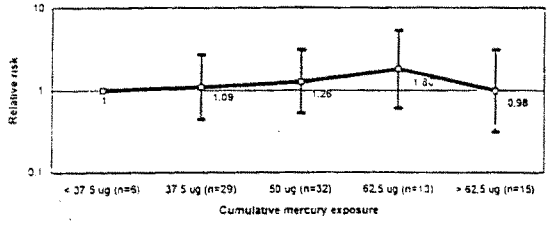
Trend
0.993/ug
p = 0.30

Graph 16: Relative risk + 95 % *CI* of Epilepsy after different exposure levels of thimerosal at 3 months of age, NCK &GHC



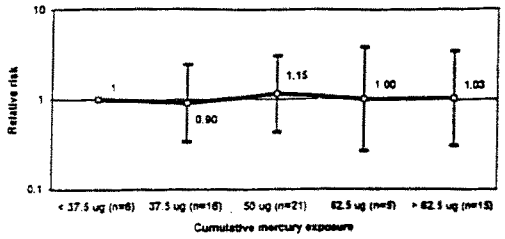
Trend
1.004/ug
p = 0.45

Graph 17: Relative risk + 95 % *CI* of Unspecified kidney or ureter disorder after different exposure levels of thimerosal at 3 months of age, NCK &GHC



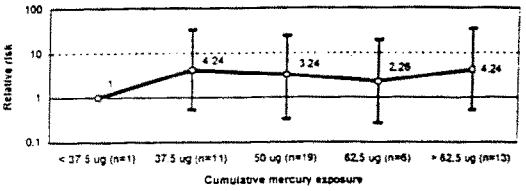
Trend
1.003/ug
p = 0.71

Graph 18: Relative risk + 95 % *CI* of Extrapyramidal disorders after different exposure levels of thimerosal at 3 months of age, GHC & NCK, Cycle7



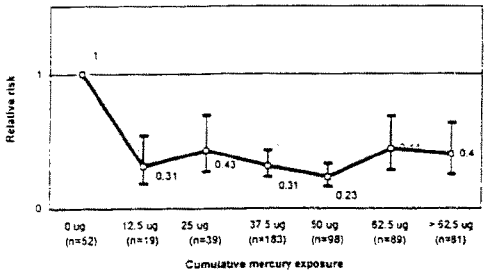
Trend
1.003/ug
p = 0.75

Graph 19: Relative risk + 95 % *CI* of Migraine after different exposure levels of thimerosal at 3 months of age, GHC & NCK, Cycle 7



Trend
1.018/ug
p = 0.13

Graph20: Relative risk + 95 % *CI* of Developmental neurologic disorders among prematures after different exposure levels of thimerosal at 3 months of age



Trend
0.985/ug
p < 0.01

Table 4. Relative risk + 95 % confidence intervals for exposure assessed as exceeding or not the EPA guideline at 1 and 3 months of age (reference category not exceeding guideline)

Code	Description	Cases	RR – 95% CI	
			1 month	3 months
Neurologic Degenerative Diorders		121	0.92 (0.62, 1.35)	0.92 (0.59, 1.43)
333	Extrapyramidal disorders	63	1.12 (0.65, 1.94)	1.22 (0.66, 2.24)
Neurologic Developmental Disorders		3179	**1.14 (1.05, 1.24)**	**1.19 (1.08, 1.30)**
299.0	Autism	127	1.01 (0.71, 1.48)	0.94 (0.62, 1.42)
299.8	Childhood psychosis	51	0.85 (0.47, 1.56)	0.99 (0.50, 1.95)
307.0	Stammering	105	0.87 (0.55, 1.37)	1.14 (0.65, 2.01)
307.2	Tics	104	1.28 (0.82, 2.01)	1.46 (0.85, 2.58)
307.4	Sleep disorders	151	1.03 (0.71, 1.48)	1.43 (0.93, 2.19)
307.5	Eating disorders	78	0.87 (0.55, 1.39)	0.99 (0.60, 1.62)
313.1	Misery disorder	158	**1.96 (1.09, 3.52)**	0.98 (0.58, 2.55)
313.8	Mixed emotional	156	0.88 (0.62, 1.25)	0.76 (0.50, 1.14)
314.0	Attention deficit Sy	377	1.04 (0.83, 1.30)	1.20 (0.91, 1.57)
315.31	Language delay	351	**1.44 (1.16, 1.78)**	**1.85 (1.46, 2.33)**
315.39	Speech delay	1533	**1.21 (1.08, 1.35)**	**1.30 (1.14, 1.48)**
315.9	Unspecified delays	555	1.17 (0.91, 1.36)	1.09 (0.86, 1.39)
Other neurologic conditions:				
343.x	Infantile cerebral palsy	98	0.75 (0.48, 1.16)	0.72 (0.44, 1.16)
345	Epilepsy	240	1.20 (0.92, 1.57)	1.13 (0.84, 1.52)
346	Migraine	50	0.84 (0.44, 1.61)	1.05 (0.48, 2.29)
Renal conditions:		164	0.93 (0.66, 1.29)	0.84 (0.58, 1.22)
593.9	Unspecified	106	1.11 (0.73, 1.70)	1.18 (0.74, 1.90)

Table 5. Relative Risk associated with an increase at 1, 2 ,3 or 6 months of age of 1 microgram of cumulative mercury exposure and its 95% confidence intervals among premature infants.

Code	Description	Cases	RR – 95% CI	
			1 month	2 months
NDD		582	**0.968 (0.955, 0.983)**	**0.994 (0.990, 0.998)**
315.39	speech delay	155	0.995 (0.971, 1.019)	0.994 (0.986, 1.002)
315.9	Unspecified delays	300	**0.951 (0.930, 0.974)**	**0.994 (0.988, 0.999)**

Code	Description	Cases	RR + 95% CI	
			3 months	6 months
NDD			**0.985 (0.980, 0.991)**	0.998 (0.995, 1.02)
315.39	speech delay		0.994 (0.982, 1.005)	0.999 (0.992, 1.007)
315.9	Unspecified delays		**0.980 (0.973, 0.987)**	0.997 (0.991, 1.002)

Code	Description	Cases	RR + 95% CI	
			EPA at 1 month	EPA at 3 months
NDD			**0.58 (0.47, 0.71)**	**0.69 (0.56, 0.85)**
315.39	speech delay		0.89 (0.62, 1.27)	0.95 (0.65, 1.40)
315.9	Unspecified delays		**0.44 (0.31, 0.60)**	**0.65 (0.48, 0.88)**

Discussion

Limitations

- Some misclassification errors may have occurred in the assessment of the inclusion/exclusion criteria: some HepB Ig administrations may be missed, some premature children may not be classified as such. In case of a true effect of thimerosal, this error is likely to cause a bias towards the null hypothesis.

- A lack of specificity in the ICD9 codes for congenital or perinatal disorders may have caused exclusion of children that were not at higher risk for developmental disorders and/or lower risk for vaccination. This error is likely to have decreased the power. Including all children regardless of these disorders results in moderate changes in results towards the null.

- Some misclassification error may have occurred in the exposure assessment: some vaccinations, particularly the neonatal HepB dose may not have been reported. We estimated that approximately 4 and 18 % of these are missed at NCK and GHC respectively. In case of a true effect of thimerosal, this error is likely to cause a bias towards the null hypothesis.

- We were not able to differentiate, using the available automated data, between single dose thimerosal free Hib vaccines and multi-dose thimerosal containing Hib vaccines. The analyses were done assuming all vaccines to come from multi-dose vials. An

analysis assuming all Hib vaccines to come from single dose-vials did not substantially alter the results. An ongoing FDA effort to resolve this question based upon the lot numbers has revealed that about 1 % of the Hib vaccines may be Thimerosal free. In case of a true effect of thimerosal, this error would cause a bias towards the null hypothesis.

- We did not assess the exposure by bodyweight. The birthweight is available only for a subset of 10% of the cohort. We shall present analyses including birthweight at the June 7-8 meeting.

- Some misclassification error may have occurred in the outcome assessment: we used ICD9 codes from automated data that lack specificity for certain disorders and are prone to errors by the person (often administrative) coding and at data entry level. This error is likely to cause an error in the findings for some specific ICD9 codes that may not have an obvious clinical correlate such as 31539 (other developmental speech or language disorder) or 3159 (unspecified delay in development). There is no reason to think that this error would occur differentially among the exposure categories and it is therefore unlikely to affect the estimates.

- We had no information on potential predisposing factors, such as maternal smoking, lead exposure or fish consumption. It is not clear, however, how these factors would be related to the exposure measure and are felt to be unlikely to cause any bias.

- In the analyses using the cumulative mercury exposure, we could not differentiate between the difference in effect from the preservative or other component in the vaccines. Exposure to thimerosal from vaccines is invariably linked to the likelihood of being vaccinated with Hepatitis B, DTP or Hib. An analysis of DTP & Hib in combination vs separate suggests a thimerosal effect for at least a few disorders, particularly among prematures.

- We have limited our analyses to a list of potential outcomes based on prior knowledge of adverse conditions found in infants exposed to high doses of methylmercury. We cannot rule out other disorders potentially related to exposure to ethylmercury.

- We were able to evaluate only relatively severe conditions that come to medical attention, and not possibly more subtle effects. Such an evaluation would require neuropsychological testing.
- The study was underpowered for some conditions, particularly the renal outcomes.
- Additional analyses addressing these limitations will be presented at the June 7-8 meeting.

Methylmercury

Neurotoxic Symptoms

- Tremors (initially hands)
- Emotional lability (irritable, shy)
- Insomnia
- Memory loss
- Neuromuscular (weakness, twitching, atrophy)
- Headaches
- Polyneuropathy
  - Parathesias
  - Stocking glove sensory loss
  - Hyperactive tendon reflexes
  - slowed sensory
  - motor nerve conduction velocities
- Performance deficits (cognitive & motor function tests)
- Hearing & visual loss hallucinations
- Photophobia (children)

Methylmercury

Typical Daily Consumption

- Infants (6-11mm) 0.49µg/day
- Children (2 yr.) 1.30 µg/day
- Females (25-30 yrs.) 2.90 µg/day
- Males (25-30 yrs.) 3.9 µg/day

Per Body weight basis, intake for all age groups

- ~ 0.05 µg/Kg/day (except 2 yr old)

120,000 Health Professions

- Females 8.2 µg/day (0.37-203) = 0.126 µg/Kg/day
- Males 8.6 µg/day (0.22-165) = 0.123 µg/Kg/day

Canadian

- Toddlers (3-4 yrs) 3.3 µg/day
- 5-11 yrs old 5.6 µg/day
- Teens 6.7 µg/day
- Adults 9.4 µg/day

FDA estimates average intake of total mercury is 50-100 µg/Kg/day.

Methylmercury

Seychellosis Child Development Study

- 700 mother-infant pairs tested from parturition through 66 months of age.
- Mercury levels 10-20 times US
- Seychelles pristine environment
- Population highly literate
- Healthy population, low alcohol/tabacco use
- Developing fetuses exposed in utero
- Neonates exposed via breast feeding
- 6.8 ppm (0.5-26.7) mean maternal hair during pregnancy
- 6.5 ppm (0.9-25.8) mean child hair at 66 month age
- Six Neurobehavioral Tests conducted

"None of the tests indicated an adverse effect of methylmercury exposure".

"Four of the six measures showed better scores in the highest methylmercury-exposed groups.

Methylmercury

Seychellois Neurobehavioral Tests

- (1) General; Cognitive Index (GCI) of the McCarthy Scales of Children's Abilities (to estimate cognitive ability);
- (2) the Preschool Language Scale (PLS) total score (to measure both expressive and receptive language ability);
- (3) the Letter and Word Recognition and
- (4) Applied Problems subtests of the Woodcock-Johnson (W-J) Tests of Achievement (to measure reading and arithmetic achievement);
- (5) the Bender Gestalt test (to measure visual-spatial ability); and
- (6) the total T score from the Child Behavior Checklist (CBCL) (to measure the child's social and adaptive behavior).

Methylmercury

Faroe Islands

- 917 children 7 years of age tested
- The neuropsychological testing indicated mercury-related dysfunction of language, attention-memory, and visuospatial and motor function remained after the children and women with maternal hair mercury above 10 ppm were excluded.

Amazon River Basin

- 91 Adults (15-31 yrs) with hair mercury <50ppm
- Clinical examinations normal
- Displayed disorganized movements (alternating movement task)
- Highest mercury levels-some restricted visual fields

Mancora Peru

- 131 infant-mother pairs
- Maternal hair 8.3 ppm (1.2-30)
- No neurodevelopment abnormalities in children

Methylmercury

Hair: Blood Ratios

- 250 (140-416)
- One-half life methylmercury blood ~ 50 days
  - ✓4 week lag in hair
- Seychellosis
  - 15.3 ppm hair (parturition) (12-26.7)
  - ✓0.061 mg/L blood (ppm)
  - ✓0.075 mg/day daily intake equal to blood
  - ✓0.0013 mg/Kg.day

  - 6.8 ppm hair
  - ✓0.027 mg/l blood (ppm)
  - ✓0.034 mg/day
  - ✓0.0006 mg/Kg/day

- Thimerosal (12.5 –25 μg/day ethylmercury)
  - ✓Seychellosis = 27 μg/l
  - ✓Daily intake .50 – 1.3 μg/day (0.05 μg/Kg/day)

Mercury

Stajich et al (2000) (term)

	Blood Mercury	
	Newborn pre-vac	48-72 hr post-vac.
	0.09 ug/l	2.24 ug/l

Ethyl/mercury

12.5 ug	≠ 2.25 ug/l	Cumulative?
25.10 ug	≠ 5.5 ug/l	
50 ug	≠ 11.0 ug/l	

Seychellosis (Continuous Exposure - In Utero, Neonate (breastfed))

Mothers	Daily Intake	Blood (calculated)
6.8 ppm hair (mean)	34 ug/day	27 ug/l
15 ppm hair (high grp)	75 ug/day	61 ug/l
children		
6.5 ppm hair (mean)		~25 ug/l

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Assessment of neurologic and renal impairment associated with Thimerosal-containing vaccines.

Thomas Verstraeten
National Immunization Program

CDC

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Study phases & objectives

- Phase I: Screen automated data for signals
- Phase II: Hypothesis testing through:
  - case-control involving chart reviews
  - cohort study involving neuropsychological testing
  - alternative data bases

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Study design Phase I

- Cohort study of automated VSD data
- Exposure: mercury from thimerosal-containing childhood vaccines at different ages
- Outcomes: range of plausible neurologic and renal disorders

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Study population

- Born between 1992 and 1997
- Born into one of two HMOs of VSD:
  - Northern California Kaiser
  - Group Health Cooperative
- Continuously enrolled first year
- Received at least 2 polio vaccinations by 1 year of age *

*: added to original protocol

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Study population: excluded infants

- Premature (separate analyses)
- Recipients of HepB immunoglobulins *
- Congenital or severe perinatal disorders *

*: added to original protocol

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Exposure assessment

- Cumulative mercury exposure calculated from individual automated vaccination records
- Assessed at 1,2,3,and 6 months of age
- Categorized by levels of 12.5 ug mercury
- Assumption: all conjugate Hib vaccine thimerosal containing

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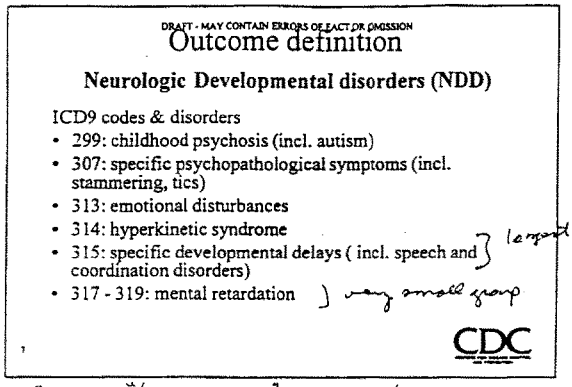

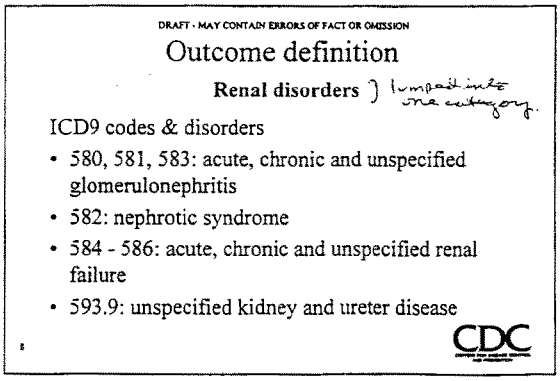

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Statistical analyses

- Proportional hazards models
- Stratified on HMO, year and month* of birth
- Adjusted for gender – (the only adjustment factor)
- Separate analysis for each disorder with n >=50

*: added to original protocol

compare cases & controls in same HMO & same birth month

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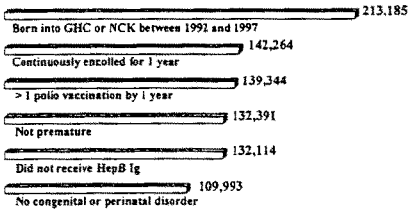
Results: eligible children



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Vaccines contributing to mercury distribution at three months

Category	Frequency	Combinations
0 ug	2493 (2.3%)	No vaccines
12.5 ug	3039 (2.8%)	1 HepB only
25 ug	3863 (3.5%)	2 HepB, 0 DTP, 0 Hib (25%) 0 HepB, 1 DTP-Hib (75%)
37.5 ug	33839 (30.8%)	1 HepB, 1 DTP-Hib
50 ug	35951 (32.7%)	2 HepB, 1 DTP-Hib (75%) 0 HepB, 1 DTP, 1 Hib (25%)
62.5 ug	11635 (10.6%)	1 HepB, 1 DTP, 1 Hib
75 ug	18855 (17.1%)	2 HepB, 1 DTP, 1 Hib
> 75 ug	299 (0.3%)	> 1 DTP, > 1 Hib, + flu

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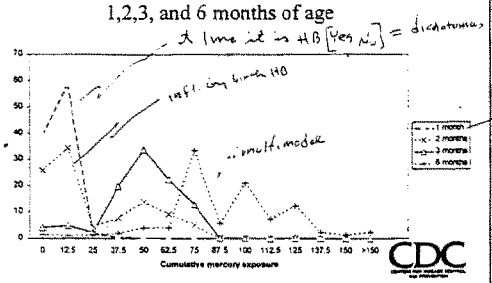
Cumulative ethylmercury exposure from thimerosal-containing vaccines: 1,2,3, and 6 months of age



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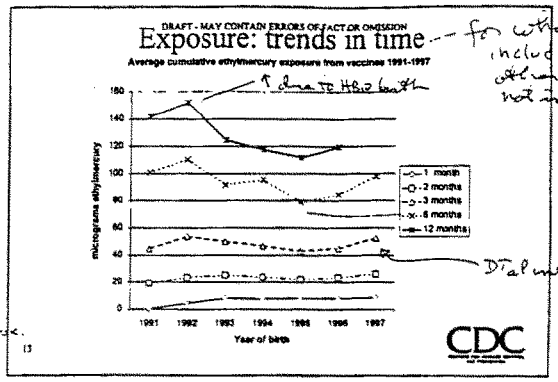

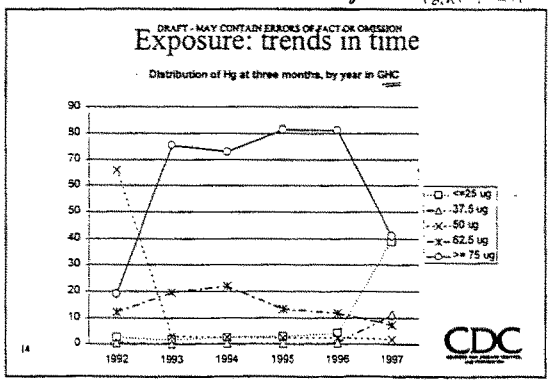

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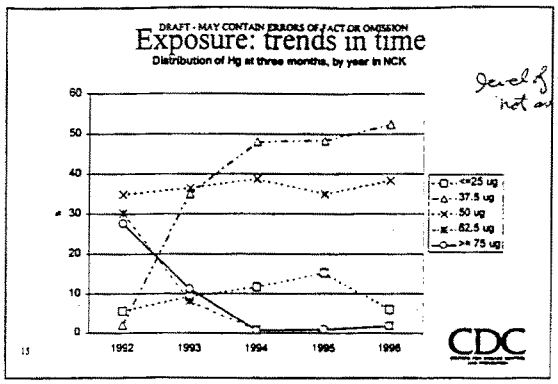

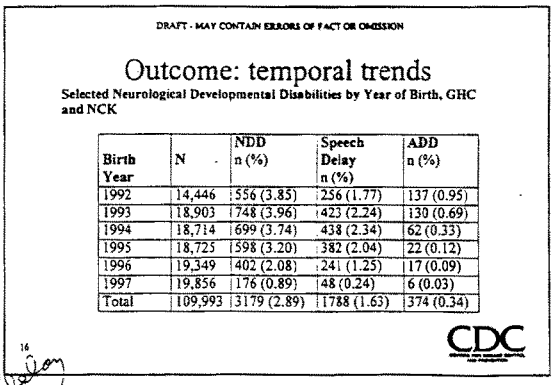

Birth Year	N	NDD n (%)	Speech Delay n (%)	ADD n (%)
1992	14,446	556 (3.85)	256 (1.77)	137 (0.95)
1993	18,903	748 (3.96)	423 (2.24)	130 (0.69)
1994	18,714	699 (3.74)	438 (2.34)	62 (0.33)
1995	18,725	598 (3.20)	382 (2.04)	22 (0.12)
1996	19,349	402 (2.08)	241 (1.25)	17 (0.09)
1997	19,856	176 (0.89)	48 (0.24)	6 (0.03)
Total	109,993	3179 (2.89)	1788 (1.63)	374 (0.34)

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Outcome vs exposure: crude incidence rates

Selected Neurological Developmental Disabilities by Cumulative Hg Exposure at 3 months, GHC and NCK

Cumulative Hg exposure	N	NDD n (rate*)	Speech Delay n (rate*)	ADD n (rate*)
0	2,493	49 (7.5)	26 (4.0)	
12.5	3,035	73 (8.6)	40 (4.4)	19 (1.0)
25	3,864	84 (8.6)	25 (2.4)	
37.5	33,832	734 (7.9)	453 (4.8)	78 (0.8
50	35,940	983 (9.9)	611 (6.0)	136 (1.4)
62.5	11,631	310 (11.5)	149 (5.4)	58 (2.1)
>75	19,148	946 (19.0)	484 (9.4)	83 (1.6)

* per 1,000 person-year

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Outcome vs exposure: crude incidence rates by HMO

Incidence Rates of Neurological Developmental Disabilities and Speech Delay by Cumulative Mercury Exposure at 3 Months

Cumulative Hg exposure	Speech Delay (rate per 1,000 child-years)		ADD (rate per 1,000 child-years)	
	NCK	GHC	NCK	GHC
0	4.7	13.0	0.7	4.1
12.5	5.4	13.8	1.1	1.7
25	2.8	8.3	0.5	0.8
37.5	6.4	5.0	0.8	0.0
50	7.0	14.7	1.3	2.5
62.5	4.5	14.9	2.7	0.8
>75	4.6	19.0	1.9	1.5
Total	6.1	17.2	1.2	1.6

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801292

cells sparse.

Speech therapy is not covered services in NCK so dx'd less often in GHC – they now are

incidence rates differ by HMO for speech delay

temporal trends also differ by HMO

Trivia comment)

"clearly under-ascertain of all"

Bob Davis these are "real world" Ped or FamPract dx

Not a specialist dx.

Alex-Walker the dx could represent a "bringing forward in time" something that would have been dx'd later

9

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Summary of Descriptive Analyses

- Exposure varies by HMO and time
- Outcomes vary by HMO and time
- Difficult to interpret crude results
- Need to account for temporal trends and differences by HMO in analysis

19

CDC

So 2x2 tables would have lots of potential confounding

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Results: risk calculations

- Compared in total 17 individual (out of 38 "plausible") and 3 grouped outcomes to 7 measures of exposure
- Statistically significant relationships:
  - exposure at 2 months of age and unspecified developmental delay
  - exposure at 3 months of age and tics
  - exposure at 6 months of age and attention deficit disorder
  - exposure at 1, 3 and 6 months of age and language and speech delay
  - exposure at 1, 3 and 6 months of age and neurodevelopmental delays in general.

20

CDC

those with ≥ 50 cases

cont @ 1, 3, 6

categor @ 3 mo

dichot 1 mo, 3 mo using EPA cut off to define Hi/Low

B01293

confidential

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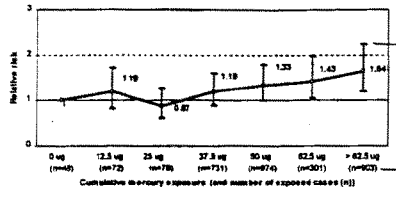
Relative risk associated with exposure at 3 months of age: neurologic developmental disorders (NDD)



Trend: 1.007 (1.004, 1.010), p < 0.01

21

CDC

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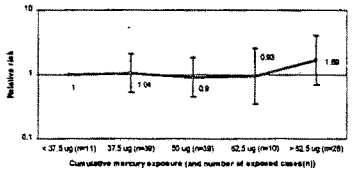
Relative risk associated with exposure at 3 months of age (NDD): Autism (ICD9 2990)



Trend:1.005 (0.991, 1.019), p = 0.48

22

CDC

B01294

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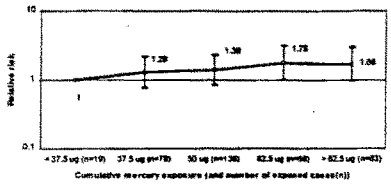
Relative risk associated with exposure at 3 months of age (NDD): attention deficit disorder (ICD9 3140)



Trend: 1.008 (1.000, 1.016), p = 0.06

23

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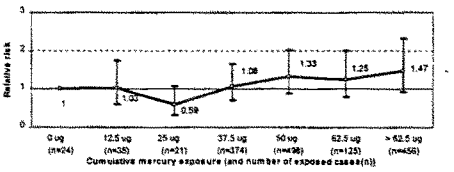
Relative risk associated with exposure at 3 months of age (NDD): speech delays (ICD9 31539)



Trend: 1.008 (1.004, 1.013), p = 0.0004

24

B01295

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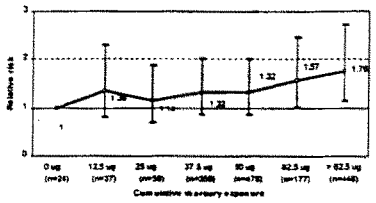
Relative risk associated with exposure at 3 months of age (NDD): All excluding speech delay



Trend:1.005 (1.001, 1.009)

25

this is NDD minus the speech delay one

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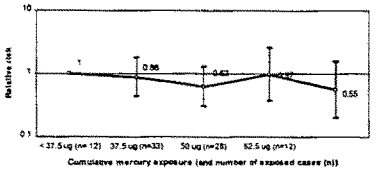
Relative risk associated with exposure at 3 months of age :Cerebral palsy(ICD9 343)



Trend:0.993 (0.979, 1.007), p = 0.30

26

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13

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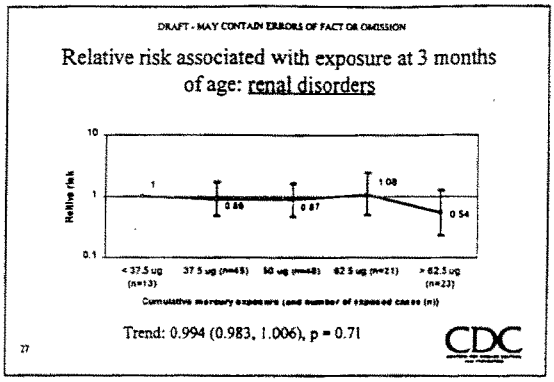

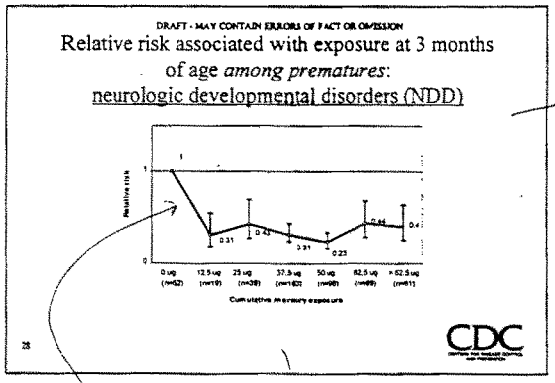

test for trent is 55 negative driven by the 0µg vs > 0µg

his conclusion — those @ high risk are not getting vaccinated.

B01297

14

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Exposure: by birthweight

- Based on linkage to state birth files
- Only at Group health Cooperative
- Only for approx 10,000 children

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CDC

DRAFT - MAY CONTAIN ERRORS OF FACT OR OMISSION

Exposure: by birthweight

Selected Neurological Developmental Disabilities by Cumulative Hg Exposure at 3 months / Birthweight GHC

Cumulative Hg / birthweight exposure	N (%)	NDD n (%)	Speech Delay n (%)	ADD n (%)
0-14 ug/kg	1651 (17)	148 (9.0)	90 (5.5)	17 (1.0)
15-17 ug/kg	1807 (19)	131 (7.3)	80 (4.3)	6 (0.4)
18-20 ug/kg	2707 (28)	256 (9.5)	159 (5.9)	17 (0.6)
21-23 ug/kg	2088 (22)	148 (7.1)	82 (3.9)	13 (0.6)
>23 ug/kg	1376 (14)	140 (10.3)	57 (4.1)	9 (0.7)

approximating birth weight quintiles

30

CDC

B01298

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Exposure: by birthweight

ICD9	Exposure	Sub-analysis	RR + 95% CI
3140	Birthweight in kilos		0.86 (0.53, 1.37)
(ADD)	Cumulative at 3 months	Stratified on BW (categories of 250g)	1.006 (0.982, 1.030)
	Cumulative/Birthweight		1.025 (0.872, 1.081)
31539	Birthweight in kilos		1.20 (1.06, 1.36)
(speech)	Cumulative at 3 months	Stratified on BW (categories of 250g)	1.006 (0.998, 1.015)
	Cumulative/Birthweight		0.987 (0.968, 1.006)
NDD	Birthweight in kilos		0.92 (0.81, 1.05)
	Cumulative at 3 months	Stratified on BW (categories of 250g)	1.007 (1.001, 1.014)
	Cumulative/Birthweight		1.025 (1.010, 1.040)

31

CDC

expected

unexpected heavier babies more speech delayed

strat. on Bw ↓ not affected — by Bw – it does affect results

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Limitations

- Misclassification exposure
  - HepB birthdose
  - Thimerosal free Hib
  - Limited (birth) weight information
- Misclassification outcome: ICD9 codes
- Unknown: medical care utilization factors
- Only conditions that come to medical attention
- Insufficient power for some conditions

32

CDC

more thing have lots of Hib

FDA has said that ↓ 1% of Hib was thimerosal free

the speaker said

This is a central concern of mine & of theirs

FDA person Alec Walton also asked this

The more parents who bring children for vaccination may be more likely to have developmental strat – SAME can be said for providers differing in some way

B01299

6/6/00

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Discussion

- Inconsistency:
  - No association among premature infants
- Exclusion congenital & perinatal disorders
- Variation in exposure
- Effect thimerosal vs other (aluminum, number antigens ...)

33

CDC

thus the association could be argued to be not due to Hg but due to number of antigens given

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Discussion

- This screening analysis suggests a possible association between certain neurologic developmental disorders (i.e. tics, ADD, speech and language disorders) and exposure to mercury from thimerosal containing vaccines before the age of 6 months
- No association was found for renal disorders

34

CDC

B01300

these are visits

	Well Child <3m	Well child <12	<3	<12
1	0.7	2.6	1.6	8.0
2	1.3	41		
		35	2.6	11.8
			31	11.7
3	1.3	4.0	2.7	
4	1.4	35	2.4	10.5
5				
6		32	30	9.5
7	1.6	36	36	10.5
				11.5

~~visits~~ ~~visits~~

these are diagnostic codes; not visits

Bob Davis
2 wk
2 mo
4 6
9 mo
12
than 2 URI's
.. get 12 [illegible]

he put this in model & did not affect

Paul Stehr Green – this won't control [illegible] bec [illegible]
try siblings; answer could do in database

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Thimerosal - VSD study

Additional analyses

CDC

Areas of concern

- Exposure ascertainment
- Outcome ascertainment
- Cohort selection
- Confounders - Biases

CDC

Exposure - HepB birthdose

Assumed missing if:

- only 2 doses of Hep B by the age of 2 yrs, but all 4 DTP and Hib and 3 polio

3.8% and 16.5% missed at NCK and GHC

- only 1 dose of HepB by 6 months, but 2 DTP, Hib and Polio

4.2 % and 17.9% missed at NCK and GHC

CDC

Exposure - HepB birthdose

3 months results: stratification by HepB birth dose:

	HepB birth = 1	HepB birth = 0	Stratified
ADD	1.014 (0.998, 1.031)	1.007 (0.995, 1.019)	1.010 (1.000, 1.020)
Speech delay	1.004 (0.997, 1.012)	1.006 (0.999, 1.014)	1.005 (1.000, 1.011)
Unspecified delay	1.011 (0.998, 1.023)	1.002 (0.991, 1.014)	1.006 (0.998, 1.015)

CDC

Exposure - Thimerosal content Hib:
sensitivity analysis for 3m results

	Hibtiter Thimerosal containing	Hibtiter Thimerosal free
ADD	1.008 (1.000, 1.016)	1.009 (1.001, 1.018)
Speech delay	1.008 (1.004, 1.011)	1.007 (1.003, 1.011)
Unspecified delay	1.007 (1.000, 1.014)	1.008 (1.000, 1.015)

CDC

Exposure - influence high categories at 3 months

Code	Descripcion	RR + 95% CI (Ref. = 0 ug)	
		Hg <= 50 ug	
		n	RR
Neurologic developmental disabilities		1903	1.006 (1.002, 1.011)
299.0	Autism	89	0.997 (0.979, 1.014)
307.0	Stammering & stuttering	33	1.005 (0.976, 1.030)
307.4	Sleep disorders	90	1.018 (0.997, 1.039)
313	Disturbance of emotions specific to	132	0.994 (0.980, 1.009)
313.1	Misery and unhappiness disorder	24	Not estimated
313.8	Mixed emotional disturbances	102	0.994 (0.978, 1.009)
314.0	Attention deficit Sy	233	1.006 (0.994, 1.019)
315	Specific delays in development	1369	1.008 (1.003, 1.013)
315.39	Developmental speech delay	952	1.010 (1.004, 1.017)
315.9	Unspecified delays o development	268	0.997 (0.986, 1.007)
Other neurologic conditions			
343.x	Infantile cerebral palsy	73	0.993 (0.875, 1.012)
345	Epilepsy	162	0.991 (0.979, 1.004)
Renal conditions			
593.9	Unspecified disease of kidney	67	1.009 (0.985, 1.033)

CDC

Exposure - influence high categories at 3 months

Code	Description	RR + 95% CI (Ref = 0 ug)	
		No HepB in first month	
		n	RR
Neurologic developmental disabilities:		1416	1.007 (1.002, 1.012)
299.0	Autism	69	1.001 (0.981, 1.022)
307.0	Stammering & stuttering	51	1.029 (0.999, 1.060)
307.4	Sleep disorders	67	1.009 (0.987, 1.031)
313	Disturbance of emotions specific to	126	1.500 (0.973, 1.035)
313.1	Misery and unhappiness disorder	31	Not estimated
313.8	Mixed emotional disturbances		1.000 (0.973, 1.035)
314.0	Attention deficit Sy	208	1.007 (0.995, 1.014)
315	Specific delays in development	1001	1.008 (1.002, 1.014)
315.39	Developmental speech delay	663	1.006 (0.991, 1.014)
315.9	Unspecified delays in development	224	1.002 (0.991, 1.014)
Other neurologic conditions:			
343.x	Infantile cerebral palsy	60	1.007/0.985, 1.029)
345	Epilepsy	116	1.000 (0.985, 1.016)
Renal conditions:			
593.9	Unspecified disease of kidney	46	Not estimated

CDC

Exposure - influence 0 category at 3 months

Code	Description	RR + 95% CI (Ref. = 0 ug)	
		Excluding 0 exposure	
		n	RR
Neurologic developmental disabilities:		3130	1.007 (1.004,1.011)
307.2	Tics	103	1.022 (1.003, 1.042)
314.0	Attention deficit Sy	367	1.009 (1.000, 1.019)
31531	Language delay	348	1.020 (1.010, 1.030)
315.39	Speech delay	1509	1.009 (1.001, 1.017)
315.9	Unspecified delays	527	1.009 (1.001, 1.017)

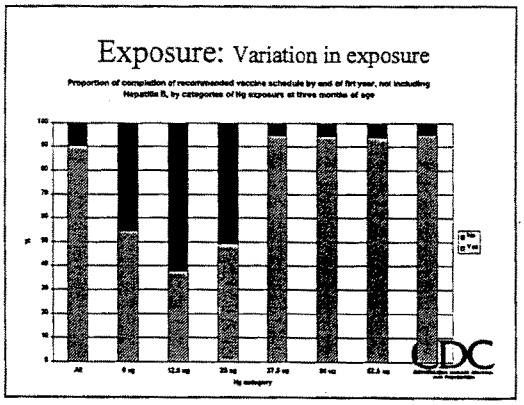
CDC

Exposure: correlation between exposure measures

	1 month	2 months	3 months	6 months	12 months
1 month	1	0.36	0.45	0.16	0.16
2 months		1	0.41	0.34	0.28
3 months			1	0.71	0.74
6 months				1	0.80
12 months					1

CDC

Exposure: Variation in exposure



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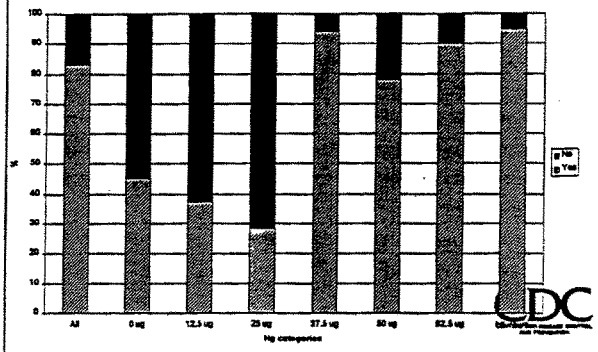
Exposure: Variation in exposure

Proportion of completion of recommended vaccine schedule by end of first year, including Hepatitis B, by categories of Hg exposure at three months of age



Exposure: by birthweight NDD

Exposure	Sub-analysis	RR + 95% CI
Cumulative at 3 months		1.005 (0.999, 1.012)
Cumulative at 3 months	Stratified on BW (categories of 250g)	**1.007 (1.001, 1.014)**
Birthweight in kilos		0.92 (0.81, 1.05)
Cumulative/Birthweight		**1.025 (1.010, 1.040)**
Cumulative/Birthweight	Stratified on BW (categories of 250g)	**1.024 (1.003, 1.046)**

CDC

Exposure: by birthweight ADD

Exposure	Sub-analysis	RR + 95% CI
Cumulative at 3 months		1.005 (0.982, 1.020)
Cumulative at 3 months	Stratified on BW (categories of 250g)	1.006 (0.982, 1.030)
Birthweight in kilos		0.86 (0.53, 1.37)
Cumulative/Birthweight		1.025 (0.872, 1.081)
Cumulative/Birthweight	Stratified on BW (categories of 250g)	1.025 (0.948, 1.112)

CDC

Exposure: by birthweight Speech

Exposure	Sub-analysis	RR + 95% CI
Cumulative at 3 months		1.005 (0.996, 1.014)
Cumulative at 3 months	Stratified on BW (categories of 250g)	1.006 (0.998, 1.015)
Birthweight in kilos		1.20 (1.06, 1.36)
Cumulative/Birthweight		0.987 (0.968, 1.006)
Cumulative/Birthweight	Stratified on BW (categories of 250g)	1.011 (0.985, 1.037)

CDC

Exposure: by birthweight Unspecified delay

Exposure	Sub-analysis	RR + 95% CI
Cumulative at 3 months		1.018 (1.001, 1.035)
Cumulative at 3 months	Stratified on BW (categories of 250g)	1.019 (1.003, 1.036)
Birthweight in kilos		0.51 (0.38, 0.68)
Cumulative/Birthweight		1.057 (1.039, 1.076)
Cumulative/Birthweight	Stratified on BW (categories of 250g)	1.067 (1.014, 1.122)

CDC

Outcome - multiple diagnoses

Number of common cases in some disorders (cycle 6)

	2990	3070	3140	31539
2990	66	0	7	23
3070		59	2	15
3140			158	20
31539				830

CDC

Outcome repeated diagnoses

- Diagnosed more then once:
- Autism: 40%
  - (GHC: 22%, NCK: 43%)
- Speech delay: 37%
  - (GHC: 64%, NCK: 22%)
- ADD: 39%
  - (GHC: 24%, NCK: 48%)

CDC

RRs repeated diagnoses

Code	Description	RR + 95% CI (Ref. = 0 ug)	
		Diagnosed more than once	
		n	RR
Neurologic developmental disabilities:			
307.2	Tics		
314.0	Attention deficit Sy	190	1.008 (0.996, 1.019)
31531	Language delay		
315.39	Speech delay	618	1.013 (1.005, 1.021)
315.9	Unspecified delays		

CDC

Cohort selection -
Excluded congenital - perinatal disorders

Main exclusion codes:

7469: Unspecified heart anomaly

7708: Other respiratory problems after birth

7706: Transitory tachypnea of newborn

7671: Scalp injury

7793: Feeding problems newborn

CDC

Cohort selection -
Excluded congenital - perinatal disorders

	Excluded infants	ALL infants
NDD	1.001(0.996, 1.006) (n = 953)	1.005 (1.002, 1.008) (n = 4060)
ADD	1.001(0.986, 1.016) (n = 91)	1.006 (0.999, 1.013) (n = 486)
Speech delay	1.005 (0.996, 1.014) (n = 349)	1.007 (1.003, 1.011) (n = 1882)
Unspecified delay	1.005 (0.997, 1.013) (n = 366)	1.005 (1.002, 1.008) (n = 903)

CDC

Cohort selection -
Excluding recipients of < 2 polio by 1 yr

Code	Description	RR + 95% CI (Ref. = 0 µg)	
		Any number of polio	
		n	RR
Neurologic developmental disabilities:		3340	**1.007 (1.004, 1.010)**
307.2	Tics	105	**1.023 (1.006, 1.040)**
314.0	Attention deficit Sy	376	**1.010 (1.002, 1.009)**
31531	Language delay	356	**1.021 (1.012, 1.030)**
315.39	Speech delay	1557	**1.007 (1.003, 1.012)**
315.9	Unspecified delays	587	1.006 (1.000, 1.012)

CDC

Bias: medical care utilization

Exposure category	Well child <3m	Well child <12m	All <3m	All < 12m
1	0.7	2.6	1.6	8.0
2	1.3	4.1	2.6	11.8
3	1.3	3.5	3.1	10.9
4	1.6	4.0	2.7	10.5
5	1.4	3.5	2.4	9.5
6	1.4	3.2	3.0	10.5
7	1.6	3.6	3.6	11.9

CDC

Bias: medical care utilization

Number of outpatient visits per additional 12.5 µg of cumulative mercury exposure at 3 months

Year of birth	GHC	NCK
1992	0.4	0.2
1993	2.7	-0.5
1994	1.7	0.5
1995	1.5	0.0
1996	0.9	0.7
1997	1.4	0.3

Linear model of the above, adjusted for HMO, year and month of birth:
All outpatient visits: 0.55 per 12.5 µg of cumulative mercury at 3 months

CDC

Bias: medical care utilization

Number of well child visits per additional 12.5 µg of cumulative mercury exposure at 3 months

Year of birth	GHC	NCK
1992	0.1	0.0
1993	0.5	-0.1
1994	0.4	0.0
1995	0.4	0.1
1996	0.4	0.2
1997	0.1	0.0

Linear model of the above, adjusted for HMO, year and month of birth:
Well child visits: 0.15 per 12.5 µg of cumulative mercury at 3 months

CDC

Bias: medical care utilization

	Number well visits	Hg 3 mo adjusted	Hg 3 mo stratified
ADD	1.07 (1.02, 1.13)	1.007 (0.999, 1.016)	1.008 (1.000, 1.016)
Speech delay	1.16 (1.13, 1.19)	1.007 (1.003, 1.012)	1.006 (1.002, 1.011)

CDC

Bias: medical care utilization

- SES :Race - ethnicity

category	Mean cumulative exposure at 3 months (ug)	% of total
Asian	48.8	6.5
Black	45.7	3.7
Hispanic	46.5	6.9
Native	62.5	0.0 (n=3)
White	49.5	82.8

CDC

Bias: medical care utilization

- SES :Yearly Household Income

category	Mean cumulative exposure at 3 months (ug)	% of total
< 15K	48.4	6.8
15 – 24 K	47.7	1.1
25 – 49 K	49.7	66.9
50 – 74 K	48.1	10.8
>= 75 K	47.9	14.3

CDC

Bias: temporal trend:
Relative risk associated with exposure at 3 months of age: tests for trend by calendar year

	Speech delay	ADD
1992	1.004 (0.993, 1.016) n = 201	1.009 (0.997, 1.022) n = 137
1993	1.013 (1.003, 1.023) n = 354	1.014 (0.999, 1.029) n = 130
1994	1.013 (1.003, 1.023) n = 378	1.007 (0.983, 1.030) n = 62
1995	1.003 (0.994, 1.012) n = 334	1.005 (0.970, 1.041) n = 22
1996	1.006 (0.993, 1.019) n = 217	0.981 (0.952, 1.011) n = 17
1997	1.009 (0.987, 1.032) n = 39	0.981 (0.939, 1.025) n = 6

CDC

Bias: temporal trend:
tests for trend by calendar year by logistic regression (speech delay)

- For all ages : RR 1.006 (1.004, 1.010)
- Under 1 year: 1.006 (0.985, 1.027)
- 1 – 2 years: 1.010 (1.000, 1.020)
- 2 – 3 years: 1.007 (0.999, 1.014)
- 3 - 4 years: 1.009 (0.999, 1.019)
- > 4 years: 1.002 (0.990, 1.014)

CDC

Alternative diagnoses

Code	Diagnosis	Cases	Mean age
37230	Unspecified conjunctivitis	16805	
5589	Non-infectious gastro-enteritis	23018	
9599	Unspecified injury	3369	
V655	Worried well	1141	20
734	Flat feet	379	32

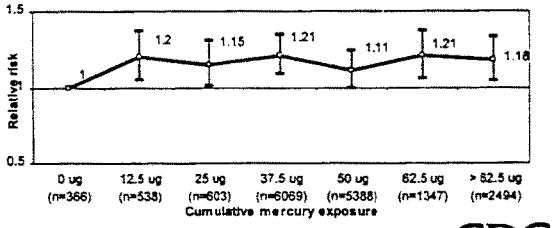
CDC

Alternative diagnoses

Description	RR + 95% CI		
	1 month	3 months	Hib combined - sep
Conjunctivitis		1.001 (1.000, 1.001)	0.93 (0.85, 1.02)
Gastro-enteritis		1.001 (1.001, 1.002)	0.94 (0.87, 1.03)
Injury		0.997 (0.995, 0.998)	0.86 (0.66, 1.04)
Worried well	0.992 (0.981, 1.002)	0.998 (0.995, 1.004)	1.05 (0.26, 4.48)
Flat foot	0.989 (0.974, 1.004)	0.997 (0.989, 1.004)	0.96 (0.36, 2.54)

CDC

Relative risk associated with exposure at 3 months of age: Unspecified conjunctivitis (ICD9 37230)



Trend: 1.001 (1.000, 1.001)

CDC

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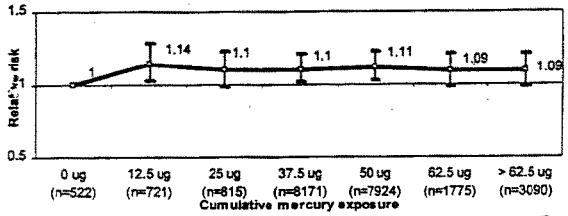
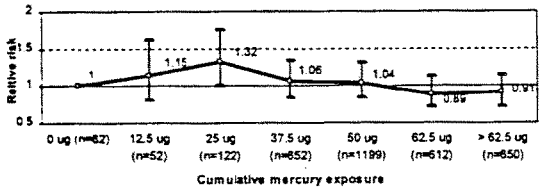
Relative risk associated with exposure at 3 months of age : Non specific non-infectious Gastro-enteritis (ICD9 5589)



Trend: 1.001 (1.001, 1.002)

Relative risk associated with exposure at 3 months of age : Unspecified injury (ICD9 9599)



Trend: 0.997 (0.995, 0.998)

Prematures

Code	Description	Cases	RR + 95% CI		
Prematures: (n = 6953)			1 month	2 months	3 months
Neurologic Developmental Disorders		562	0.970 (0.956, 0.985)	0.994 (0.990, 0.998)	0.986 (0.980, 0.992)
315.39	Speech delay	155	0.995 (0.971, 1.019)	0.994 (0.986, 1.002)	0.994 (0.982, 1.005)
315.9	Unspecified delays	300	0.951 (0.930, 0.973)	0.994 (0.988, 0.999)	0.980 (0.973, 0.987)

Code	Description	Cases	RR + 95% CI	
Prematures: (n = 6953)			6 months	Hib comb -sep
Neurologic Developmental Disorders		562	0.998 (0.995, 1.002)	2.89 (1.35 – 6.18)
315.39	Speech delay	155	0.999 (0.992, 1.007)	0.77 (0.10, 5.86)
315.9	Unspecified delays	300	0.997 (0.992, 1.002)	4.46 (1.81, 10.94)

CDC

Thimerosal or other effect:

DTP separate vs combined

Code	Descripuon	RR + 95% CI (Ref. = DTP-Hib combination)
Neurologic developmental disabilities		1.20 (0.84, 1.72)
299.0	Autism	1.25 (0.36, 4.35)
307.0	Stammering & stuttering	2.05 (0.25, 18.63)
307.4	Sleep disorders	2.15 (0.43, 10.86)
313	Disturbance of emotions specific to	1.50 (0.40, 5.67)
313.1	Misery and unhappiness disorder	Not estimable
313.8	Mixed emotional disturbances	1.53 (0.40, 5.67)
314.0	Attention deficit Sy	1.79 (0.70, 4.58)
315	Specific delays in development	1.17 (0.77, 1.78)
315.39	Developmental speech delay	1.28 (0.78, 2.10)
315.9	Unspecified delays in devesoproent	0.81 (0.29, 2.24)
Other neurologic conditoons		
343.x	Infantile cerebral palsy	1.95 (0.48, 7.87)
345	Epilepsy	1.66 (0.58, 4.73)
Renal conditoons		0.13 (0.00, 4.05)
593.9	Unspecified disease of kidney	0.01 (0.00, 7.31)

CDC

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Thimerosal or other effect:
Number of antigens as exposure

	Antigens 1 month	Antigens 3 months
NDD	1.07 (1.01, 1.13)	1.04 (1.02, 1.06)
Tics	1.11 (0.82, 1.52)	1.16 (1.01, 1.34)
ADD	1.06 (0.88, 1.26)	1.06 (0.99, 1.14)
Speech delay	1.11 (1.02, 1.20)	1.04 (1.01, 1.08)
Unspecified delay	1.04 (0.90, 1.21)	1.04 (0.98, 1.10)

CDC

Thimerosal or other effect:
Number of shots as exposure

	Shots 1 month	Shots 3 months
NDD	1.09 (1.02, 1.17)	1.10 (1.05, 1.15)
Tics	1.18 (0.81, 1.72)	1.39 (1.07, 1.81)
ADD	1.06 (0.87, 1.29)	1.13 (1.00, 1.27)
Speech delay	1.15 (1.04, 1.27)	1.10 (1.03, 1.18)
Unspecified delay	1.07 (0.90, 1.28)	1.10 (0.98, 1.21)

CDC

RRs for HepB and Hib thimerosal free

Disorder	At 3 months	at 6 months
ADD	Not estimable	1.07 (0.50, 2.29)
Language delay	Not estimable	**2.78 (1.08, 7.20)**
Speech delay	0.71 (0.44, 1.38)	1.28 (0.89, 1.84)
Speech or language delay	0.75 (0.49, 1.16)	**1.43 (1.00, 2.03)** p = 0.05
Unspecified delay	1.48 (0.74, 2.97)	1.42 (0.77, 2.63)
NDD	0.92 (0.67, 1.26)	1.25 (0.98, 1.61) p = 0.08

CDC

0 at 1-3 - (ref) vs 2? at 1-3

0 - 3-6 - (ref) vs 5? - 3-6

regardless of what they got at birth

[a reluctantly performing analysis ...]

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Discussion of Initial Analyses and Re-Analyses of Thimerisol and Developmental Delay in the Vaccine Safety Datalink Cohort

Philip Rhodes
Centers for Disease Control

June 7, 2000

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Outline

VSD Study

Evaluating thimerisol effects vs other effects

Difficulties with early analyses
- Exclusion criteria
- Uncertainties about low exposure groups
- Importance of clinic practices at NCK

Re-definition of cohort to be studied
- At one month
- At three months

Re-analyses of exposure-outcome relationships

Conclusions

Limitations/ Further Efforts

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Vaccine Safety Datalink Study

Good at evaluating exposures-- outcomes where

1) Outcome is acute, medically well defined, high probability of coming to medical attention and has a clear onset occurring a short time after the exposure

2) Effect of the exposure on the outcome is transitory

3) Exposures are nearly universal but there is sufficient variation in the age at exposure

   e.g. seizures after DTP or MMR

Hard to evaluate exposures-- outcomes where

1) Outcome is chronic, not medically well-defined or onset is not well-defined

2) Exposure is nearly universal, i.e. only a small unrepresentative sub-group do not have the exposure

   e.g. Attention deficit disorder after MMR

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Vaccine Safety Datalink Study

Where is thimerisol - developmental delay on this continuum?

Outcomes studied here vary on their medical certainty and likelihood of coming to medical attention

autism vs speech delay

Outcomes are chronic and onset is not well defined

Exposure is nearly universal and completely unvaccinated form an unrepresentative sub-group

Hopeless?

No – there is variation in the amount of thimerisol by type and manufacturer of vaccine

Important to distinguish whether differences in cumulative thimerisol exposure at some age are due to: 1) policy vs 2) self-selection (e.g. lateness in getting vaccinated, reluctance to accept vaccination and/or other medical care)

Original Exclusion Criteria

Born into HMO
Followed continuously for > 1 yr, first follow-up only

Not premature or low birth weight
Not have one of many possible perinatal conditions

No HBIG
Two or more polio vaccines by age 1

All exclusions had good intent

Prematures/ low birth weight may be less likely to receive HepB or other vaccines at an early age and may be more likely to have some outcomes of interest

Children receiving less than two polio vaccines in first year may not be accessing system as often as others

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Problems with Exclusion Criteria

Perinatal Exclusion Codes

Differential usage by HMO

NCK 19.2 %
GHC 6.7 %

Also differential usage or occurrence across birth f facilities in NCK : Range 13 - 36 %

Some of the ICD-9 codes likely represent fairly minor events e.g.

767.1 Scalp injury at birth
6060 at NCK
24 at GHC

779.3 Feeding Problems
3895 at NCK
548 at GHC

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Problems with Exclusion Criteria

Prematurity Codes 765

Different usage of prematurity/ low-birth weight code

NCK 5.3 %
GHC 1.8 %

36% of those excluded at NCK > 2.5 kg
5% for GHC

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Original Exclusion Criteria

Two or more polio vaccines at 1 yr
First enrollment > 1yr

Some events occur by 1 year of age
Need to exclude these or have odd situation where exclusion follows event of interest

OK for events such as speech/lang delay that occur after one year

Polio exclusion is a reasonable attempt to control for HMO usage

Enrollment Date Problems

NCK has moderate number of children with multiple enrollment periods

Second or later periods not used in current study

Substantial numbers of events/vaccines are recorded at times where children are not 'enrolled

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Thimerisol Status at 100 and 107 Days
Children <=25 at 93 Days in Original Cohort

Per Cent Changing after 7 or 14 Days Further Follow-up

	93 days	N	100 days	107 days
NCK	0	2302	27%	42%
	12.5	2826	18 %	27%
	25	2989	6%	11%
GHC	0	181	19%	31%
	12.5	215	27%	38%
	25	894	1%	2%

Mean Time Since Last Well Child Visit (ICD9 V20.*)
By Length of Follow-up and Hg at 3 Months
GHC - Original Cohort

	Hg at 3 Months							
	0-25		37.5-50		62.5		>=75	
	N	Avg Lag	N	Avg Lag	N	Avg Lag	N	Avg Lag
First Follow-up								
12-18 m	888	104	6129	96	2754	81	2961	88
19-24 m	675	158	7446	143	1359	127	1368	130
25-36 m	1098	250	14832	225	264	164	255	201
37-48 m	1783	382	12072	348	81	370	105	370
>48 m	1513	455	10978	439	84	460	74	413

VSD Cycle 7
DRAFT

B01331

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Clinics at NCK

NCK has clinics over a wide geographic area in Northern California

Birth facilities and clinics often have different policies

Use of Hep B vaccine in first month of life
For all children born into HMO 1992-1998

Range : 4% – 85% Mean 43%

Great differences in exposure groups at three months by clinic e.g. Four clinics listed below, all > 4000

Clinic	I	II	III	IV	V
11	54	5	7	23	10
31	22	13	41	15	9
35	24	6	52	5	12
72	25	1	48	2	24

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Clinics at NCK

Variations in outcome by clinic

All Developmental Delays

In all children followed longer than 4 years
Overall 4.4%

32 clinics : Range 1.6 – 8.7%

	# Clinics
< 3 %	3
3 – 4%	9
4 – 5%	11
5 – 6%	3
6 – 7%	1
> 7 %	4

Common Combinations at 3 Months and Numbers of Children in Original Cohort

	Hep	DTP*	HIB	Hg	NCK	GHC
I	1	Comb		37.5	33,004	—
II	0	1	1	50	4,328	1,990
III	2	Comb		50	28,628	—
IV	1	1	1	62.5	9,199	2,213
V	2	1	1	75	9,427	9,165
Total					**84,586**	**13,368**

Five Exposure Group Approach:

Clarifies questions that may be answerable by the current data and where the information may be obtained

Thimerisol Difference = 37.5

I vs V – Differ on 1 vs 2 HepB and DTP-HIB combination vs separate DTP (or DTaP), HIB
Only possible at NCK

Thimerisol difference = 25

I vs IV – Both have 1 HepB, differ on DTP-HIB combination separate DTP (or DTaP) , HIB
Only possible at NCK

III vs V – Both have 2 HepB, differ on DTP-HIB combination separate DTP (or DTaP) , HIB
Only possible at NCK

II vs V – Both have separate DTP , HIB , differ by 2 HepB
Possible at both NCK and GHC

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Reanalyze Data Based on:

1) Five exposure groups

2) At one month, consider exclusions based on Hep B usage within the group considered for exclusion , for outcomes occurring mostly after one year consider two polio exclusion

3) At three months base exclusion primarily on ability to get into one of the five exposure groups
– Except exclude children receiving DT by three months

4) Use clinic as an additional stratification variable at NCK

5) Consider data quality issues e.g. some children at NCK receive unusual vaccines based on their month of birth i.e. separate DTP and HIB during calendar periods when >99% of the rest receive DTP-HIB combination

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NCK + GHC
Outcome = Speech/Lang Delay 315.3*
Relative Rates and P-values

Analysis	Thimerisol at One Month		
	RR	Chi-Sq	P-value
Original	1.20	12.1	0.005
+ Clinic	1.15	4.1	0.04
+ Exclus	1.09	2.1	0.14
- Prem (<1.75 kg)	1.14	5.4	0.02
- Polio <2 At 1 year	1.09	2.2	0.14

Stratify by month of birth, Control for gender
Reference Group = No thimerisol in first month

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NCK

Outcome = All Developmental Disorders
Relative Rates and P-values

	Thimerisol at Three Months			
	(50)	(50)	(62.5)	(75)
Analysis	II	III	IV	V
Original	1.34	1.12	1.41	1.35
	(0.13)	(0.03)	(0.03)	(0.06)
+ Excl	1.46	0.97	1.48	1.29
	(0.01)	(0.49)	(0.006)	(0.03)
+ Clinic	1.22	0.97	1.30	1.18
	(0.25)	(0.64)	(0.05)	(0.21)
– Odd Codes	1.19	0.96	1.24	1.17
	(0.42)	(0.52)	(0.20)	(0.35)

Stratify by month of birth, Control for gender
Reference Group = I (37.5)

Draft - may contain error of fact or omission

NCK

Outcome = Speech/Lang Delay 315.3*

Relative Rates and P-values

	Thimerisol at Three Months			
	(50)	(50)	(62.5)	(75)
Analysis	II	III	IV	V
Original	1.64	1.25	1.30	1.21
	(0.07)	(0.001)	(0.25)	(0.38)
Final	1.13	1.04	0.96	1.14
	(0.72)	(0.60)	(0.90)	(0.65)

Stratify by month of birth, Control for gender

Reference Group = I (37.5)

Draft - may contain error of fact or omission

GHC

Outcome = All Neurologic Devel Delay
Relative Rates and P-values

	Thimerisol at Three Months	
	(62.5)	(75)
Analysis	IV	V
Original	0.97	1.23
	(0.89)	(0.30)
Final	1.30	1.28
	(0.14)	(0.16)

Stratify by month of birth, Control for gender
Reference Group = II (50)

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NCK + GHC
Outcome = All Neurologic Devel Delay
Relative Rates and P-values

	Thimerisol at Three Months	
	(62.5)	(75)
Analysis	IV	V
Original	0.99	1.13
	(0.96)	(0.31)
Final	1.10	1.06
	(0.45)	(0.68)

Stratify by month of birth, Control for gender
Reference Group = II (50)

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Conclusions from Re-Analysis

Strong uncertainties about fairness of low exposure groups

Much less concern about exposure groups 37.5 – 75

Evaluation still tricky because of several issues:

1) Small amount of calendar overlap of use of the different policies that lead to the various exposure groups

   May have resulted in a small number of mis-coded children having an undue influence on the results

2) Original exclusion criteria were too extreme

3) Importance of accounting for clinic practices at NCK

Overall: Slight tendency for higher exposure groups to have higher rates but p-values unimpressive (i.e. mostly > .20)

Limitations / Extensions of Current Analyses

Complete rejection of the 0, 12.5 and 25 groups at three months may be too severe -- try to refine assessment of the possible biases in these groups

Conclusions of little or no effect of thimerisol at three months on developmental delay outcomes must be confined here to the restricted range 37.5 - 75

i.e. No way to 'fairly compare' 0 with 50-75 or higher

Better definition of clinic at NCK, i.e. change over time

Check assumption that at NCK children with unusual combinations for their birth cohort are in fact mis-coded

Continue analyses looking at whether relative dose or age at receipt of doses is related to outcomes

Use data from chart reviews to refine case definitions

Re-do analyses as more data becomes available from these two and/ or other sources

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May 2, 2002

The Honorable Dan Burton
Chairman
Committee on Government Reform
2157 Rayburn House Office Building
Washington, DC 20515

Dear Mr. Chairman:

I am writing to ask you to drop your threats to subpoena reams of patient information from the most important national database for monitoring vaccine safety, the Vaccine Safety Datalink (VSD) project. According to the Centers for Disease Control and Prevention, issuance of a subpoena could lead to the collapse of the VSD database, "destroying CDC's ability to scientifically test hypotheses relating to adverse events potentially associated with vaccines." It would also jeopardize the medical privacy of millions of Americans. Despite these risks, you and your staff have drawn up a draft subpoena. I urge you to reverse course and state clearly that you will not subpoena patient data from these medical records.

The database in question is the Vaccine Safety Datalink project, a federal effort established over a decade ago that now combines information from the medical records of eight large health maintenance organizations. HMO officials have expressed their concern that a subpoena would jeopardize the medical privacy of approximately 7.5 million Americans and would lead the HMOs to reconsider their participation in the project altogether.

The consequences of the loss of this database would be grave. It was the VSD project that demonstrated an association between rare cases of intestinal obstruction and the vaccine to prevent rotavirus infection, contributing to its withdrawal from the market. Studies using the VSD also helped make the measles-mumps-rubella, polio, and pneumococcal vaccines safer. In the future, according to CDC, the VSD will "be critical to our ability to monitor the safety of smallpox vaccinations in a timely and accurate manner." For these reasons, top public health officials and experts contacted by my staff uniformly expressed alarm at the possible collapse of the VSD.

A confrontation with CDC over the VSD is needless. In recognition of your interest in

confirming some of the results of VSD studies involving vaccines containing thimerosal, CDC and the HMOs have offered a way for independent investigators to analyze VSD data without compromising medical privacy. You should endorse this approach rather than continue to seek to subpoena the records themselves.

The rest of this letter explains my concerns in more detail.

The Vaccine Safety Datalink System

Understanding whether a particular vaccine is safe, and what side effects it may produce, begins with pre-licensure studies. While the size of these studies has increased in recent years, in some cases adverse outcomes are too rare to be detected before licensure. To identify quickly such rare events, public health officials rely on several mechanisms to monitor adverse effects after approval. The two largest and most important mechanisms are the Vaccine Adverse Event Reporting System (VAERS) and the VSD.

VAERS is a compilation of spontaneous reports of suspected adverse events from parents, health care providers, and pharmaceutical manufacturers. VAERS reports can be a signal that there may be a problem with a vaccine. However, because VAERS is a passive system, it rarely can answer the question of whether a vaccine is truly associated with a problem or at what rate the adverse effect is occurring.

In order to enhance the understanding of rare adverse effects of vaccines, CDC developed the VSD project in 1990. This project now utilizes the databases of eight large HMOs, pooling information from the medical records of approximately 7.5 million people, or 2.5% of the U.S. population. The records include diagnoses, laboratory test results, prescriptions, and immunizations, but do not include the names of patients. Even without the names, however, these data can be combined with information from publicly available sources to identify some patients. For this reason, the HMOs share information from medical records with CDC only after assurances that confidentiality will be strictly maintained.

The VSD yields an enormous benefit to the public health. Using this large and complex database, CDC can quickly design and implement sophisticated studies that take into account confounding factors and use proper control groups. The VSD allows public health officials not only to carry out planned research activities, but also to conduct timely investigations into adverse events.

One example of how the VSD enabled quick action to protect children is the case of the vaccine to prevent rotavirus infection, a cause of severe diarrhea in infants. In 1999, several cases of intestinal obstruction following rotavirus vaccination were reported to the VAERS system. While the number of cases were suggestive of a possible association, it was still unclear

whether these cases were coincidences or truly linked with the vaccine. Very quickly, CDC officials conducted a study using VSD data, which determined that this rare condition was associated with the rotavirus vaccine. The results contributed heavily to the manufacturer's decision to withdraw the vaccine from the market before more children could be injured.[1]

Over the last decade, public health officials and researchers have used the VSD to answer many vaccine-related questions. VSD studies, for example, have supported policy changes that have reduced adverse effects from the MMR vaccine,[2] maintained high levels of polio vaccination using a formulation that does not cause vaccine-associated polio,[3] and enhanced the safety of the pneumococcal vaccine schedule.[4] Other VSD research has examined theories of vaccine harm and failed to find empirical support for them. Such studies have provided evidence that childhood vaccines are not associated with diabetes,[5] that the MMR vaccine is not associated with inflammatory bowel disease[6] or aseptic meningitis,[7] and that the rubella vaccine is not

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[1]P. Kramarz, E. France, F. DeStefano et al., *Population-Based Study of Rotavirus Vaccination and Intussusception*, Pediatric Infectious Disease Journal, 410-6 (April 2001).

[2]R. Davis, E. Marcuse, S. Black, et al., *MMR2 Immunization at 4 to 5 years and 10 to 12 Years of Age: A Comparison of Adverse Clinical Events After Immunization in the Vaccine Safety Datalink Project*, Pediatrics, 767-71 (November 1997).

[3]R. Davis, T. Lieu, L. Mell, et al., *Impact of the Change in Polio Vaccination Schedule on Immunization Coverage Rates: A Study in Two Large Health Maintenance Organizations*, Pediatrics, 671-8 (April 2001).

[4]L. Jackson , P. Benson, V. Sneller, et al., *Safety of Revaccination with Pneumococcal Polysaccharide Vaccine*, Journal of the American Medical Association, 243-8 (Jan. 20, 1999).

[5]F. DeStefano, J. Mullooly, C. Okoro et al., *Childhood Vaccinations, Vaccination Timing, and Risk of Type 1 Diabetes Mellitus*, Pediatrics, E112 (December 2001).

[6]R. Davis, P. Kramarz, K. Bohlke, et al., *Measles-Mumps-Rubella and Other Measles-Containing Vaccines Do Not Increase the Risk for Inflammatory Bowel Disease: A Case-Control Study from the Vaccine Safety Datalink Project*, Archives of Pediatrics and Adolescent Medicine, 354-9 (March 2001).

[7]S. Black, H. Shinefield, P. Ray, et al., *Risk of Hospitalization Because of Aseptic Meningitis After Measles-Mumps-Rubella Vaccination in One- to Two-Year-Old Children: An Analysis of the Vaccine Safety Datalink (VSD) Project*, Pediatric Infectious Disease Journal, 500-3 (May 1997).

associated with chronic joint disease in adults.[8]

The VSD has played a significant role in making the current vaccine supply safer than ever. Your subpoena threats, however, represent a serious risk to the viability of the entire VSD system.

The Committee's Actions

On July 18, 2000, at a hearing entitled "Mercury In Medicine–Are We Taking Unnecessary Risks," Dr. Roger Bernier of CDC testified about the results of studies using VSD data to examine whether exposure to thimerosal in vaccines is associated with developmental delays. According to his testimony, an initial study suggested a connection between thimerosal and certain developmental symptoms. Subsequent studies in the VSD have not confirmed these findings, and further research is ongoing.[9]

On November 21, 2000, you sent a letter to CDC Director Jeffrey P. Koplan asking for VSD data "in both printed and electronic format."[10] After CDC refused, your staff has repeatedly threatened CDC officials with a subpoena for the raw data from the VSD, including asking for the name and address of the person who should receive the subpoena. Earlier this year, on February 21, 2002, your staff faxed to my staff a draft subpoena to CDC for "all records collected under the Vaccine Safety Datalink Project."[11]

In defending the subpoena threats, you have indicated that your interest in obtaining this medical information is to double check the results of the thimerosal study and to conduct independent analyses of vaccine safety. To accommodate this concern, CDC has developed a protocol to allow independent researchers access to VSD data through the National Center for Health Statistics (NCHS) under certain reasonable conditions. These conditions include: (1) the study is approved by the HMOs' Institutional Review Boards charged with assuring the protection of human subjects; (2) the study has a clear protocol; and (3) the study is conducted at NCHS, with the researchers able to leave with their results but not the raw data.

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[8]P. Ray, S. Black, H. Shinefield, et al., *Risk of Chronic Arthropathy Among Women After Rubella Vaccination*, Journal of the American Medical Association, 551-6 (Aug. 20, 1997).

[9]Institute of Medicine, *Thimerosal-Containing Vaccines and Neurodevelopmental Disorders* (Oct. 1, 2001).

[10]Letter from Chairman Dan Burton to Dr. Jeffrey P. Koplan (Nov. 21, 2000).

[11]Draft Subpoena Duces Tecum to Dr. Jeffrey P. Koplan (February 2002).

Despite this reasonable solution, which does not compromise patient confidentiality and would protect the future of the VSD, you have yet to abandon your subpoena threats.

The Threat to Medical Privacy and the VSD

Your draft subpoena asks CDC to "redact personal information, such as names, social security numbers, or other unique identifiers that would allow for the identification of individual patients."[12] However, even without names, social security numbers, and other unique identifiers, the VSD data can be used to identify individuals. The reason is that the dataset includes many non-unique variables, such as birthday, diagnosis, HMO, and date of immunization that can be patched together with information from publicly available sources to identify individuals. CDC explained:

> In order to assess the ease with which an individual could identify a patient's medical record, one of the VSD HMOs conducted an exercise. They imagined a scenario in which an HMO employee had access, via the internet, to the complete VSD database in its current format. If this employee knew that a co-worker was an HMO member, was able to learn the co-worker's birth date (e.g., through an office birthday party), and knew that the co-worker recently broke an arm and required medical attention, then that employee could find the co-worker's record in the VSD file easily. Once the co-worker's file was found, all of that person's medical history – such as information concerning other medical visits, diagnoses (including HIV and mental health status) and prescriptions filled - was available for review by this person. The Principal Investigator at one VSD HMO tested this scenario using his daughter. With her birth date and knowledge that she recently sprained an ankle, an HMO analyst was able to find her records in the VSD data. Such identification of individuals could have devastating consequences to the individual as well as to the HMO.[13]

CDC has informed my staff that the thimerosal study could not be replicated without identifying the diagnoses and medical records of many children who were excluded from the study for scientific reasons because of unrelated serious medical conditions. Identifying these records carries the risk of disclosure of confidential and sensitive medical information. If your desire is to verify the results of the VSD studies, then it is important to acknowledge the very important privacy interests at stake.

In addition to these privacy threats, a subpoena may threaten the viability of the VSD. Concern by participating HMOs was heightened last summer after a group called SAFE MINDS

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[12]Draft Subpoena Duces Tecum to Dr. Jeffrey P. Koplan (February 2002).

[13]Information sent to minority staff by Centers for Disease Control (Apr. 23, 2002).

filed a request under the Freedom of Information Act (FOIA) for raw VSD data. Researchers from the HMOs wrote to CDC urging the agency not to provide the medical records. Dr. Richard Platt and Dr. Tracy Lieu of Harvard Medical School, for example, sought "explicit assurance that health plans will have ongoing control over any new uses and distribution of their data."[14] These physicians explained that information at stake included HIV diagnoses and other identifiable information that would constitute a profound violation of medical privacy.

CDC responded to these concerns by denying the FOIA requests and then affording the VSD data the highest level of protection for privacy available under public health law.[15] However, representatives of SAFE MINDS claimed in the presence of my staff that a refusal by CDC would be met by a subpoena from you for the same information. Your subsequent subpoena threats led investigators at the participating HMOs to realize that even CDC's protection may not be able to guarantee the confidentiality of the records. As a direct result, according both to CDC and HMO officials, a subpoena may force the HMOs to reconsider their participation in the VSD. According to CDC, "If the currently participating HMOs withdrew from the Project because of lack of assurances of confidentiality, it is extremely unlikely that other HMOs would consider providing such complete and specific data to CDC, thus destroying CDC's ability to scientifically test hypotheses relating to adverse events potentially associated with vaccines."[16]

Because of medical privacy concerns, CDC is working on developing a new secure system that would allow public health officials to review rapidly the databases without ever having possession of highly confidential patient data. However, HMO officials have told my staff that a subpoena from you on existing data at CDC would even threaten their participation in this new system.

The logic is understandable: If millions of their patients lose their medical privacy, then they may lose confidence in their health plan. To convince patients that such a violation would never come to pass again, the HMOs may be forced to terminate the VSD project.

Reaction of Experts and Key Officials

Health officials and experts contacted by my staff uniformly expressed the belief that the

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[14]Letter from Dr. Richard Platt and Dr. Tracy Lieu to Dr. Robert Chen, (July 25, 2001).

[15]CDC has obtained protection under section 308(d) of the Public Health Service Act for Vaccine Safety Datalink data. This protection does not extend to a congressional subpoena, however.

[16]Information sent from CDC to minority staff (Apr. 23, 2002).

VSD is an essential tool to protect children. Dr. Georges Peter, chairman of the National Vaccine Advisory Committee, explained:

> The VSD program has been of vital importance in our continuing efforts to assess causal associations between adverse events in vaccine recipients and specific vaccines. One of the critical elements of the program is the large patient base which allows the investigators to assess possible associations between rare events and vaccines. Without the participation of large HMOs, the sensitivity of the program would be significantly limited and our nation's efforts to continue to enhance vaccine safety efforts would be very much compromised. These scientific studies are necessary for the children and parents who rely on safe and effective vaccines to prevent once common childhood diseases such as poliomyelitis, measles and meningitis."[17]

Dr. Neal Halsey, director of the Institute for Vaccine Safety at Johns Hopkins University, wrote:

> If the subpoena power of Congress is used in a misguided effort to find additional associations with thimerosal exposures, this will undermine the ability of CDC to undertake future research in the area of vaccine safety.[18]

Similarly, Dr. Lou Cooper, president of the American Academy of Pediatrics, noted:

> The Vaccine Safety Datalink (VSD) project has been our best instrument for studying longer term and low incidence consequences of immunization. It is a unique tool, and I am not sure how we could replace it. Any threat to the confidentiality of these data, which are in fact patient medical records, would violate the trust relationships between patients and their doctors and would force the HMOs to withdraw from the program, an irreplaceable loss in our effort to insure vaccine safety. The precedent set by such an action would be a major setback to research on vaccine safety and would have a chilling impact on other vitally needed public health research.[19]

Bioterrorism and the Future of the VSD

CDC officials have said that the loss of the VSD would compromise the agency's ability to protect the American people from future bioterrorist threats. According to CDC:

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[17]E-mail communication from Dr. Georges Peter to minority staff (Apr. 23, 2002).

[18]E-mail communication from Dr. Neal Halsey to minority staff (Apr. 23, 2002).

[19]E-mail communication from Dr. Louis Cooper to minority staff (Apr. 24, 2002).

A study is underway within the VSD to more accurately estimate the number of persons likely to suffer complications from smallpox vaccination. Should the decision be made for its broader use in the U.S., the VSD will be critical to our ability to monitor the safety of smallpox vaccinations in a timely and accurate manner. The VSD can also serve as a valuable tool for monitoring other bioterrorism threats that might result in unusual syndromes, vaccine-derived or otherwise.[20]

The loss of the VSD would also undermine other research priorities. CDC officials told my staff that concerns over your subpoena threaten to derail a number of research projects, including some on developmental delay, another topic you have pursued in committee hearings.

Conclusion

I know you are deeply interested in the safety of immunizations. Indeed, I understand that the reason you are threatening to subpoena the VSD data is that you believe the data may contain important information about the risks of vaccines. But in fact, the issuance of a subpoena would have the opposite effect, jeopardizing the VSD system and thereby reducing vaccine safety. I urge you to reconsider your actions.

Sincerely,

Henry A. Waxman
Ranking Minority Member

cc: Members of the Committee on Government Reform

[20]E-mail communication from CDC to minority staff (Apr. 24, 2002).

May 2, 2002

The Honorable Henry A. Waxman
Ranking Minority Member
Committee on Government Reform
B350A Rayburn House Office Building
Washington, DC 20515

Dear Mr. Waxman:

I am in receipt of your letter regarding a potential subpoena from the Committee to the Centers for Disease Control and Prevention (CDC) for the data from the Vaccine Safety Datalink (VSD) Project. The VSD provides a valuable opportunity to evaluate medical records and look for vaccine adverse events. As part of the Committee's investigation, we have learned that independent evaluation of the overall data or of specific research based on the data has not taken place. Up until this point, data from the VSD has been made available only to a limited number of researchers, hand picked by the CDC. I think we can all agree that if the VSD is to be a valuable scientific tool, the data needs to be made available to a broad range of researchers so that independent verification can take place.

I am pleased with the proposed protocol allowing independent researchers to access the VSD data through the National Center for Health Statistics. We are waiting for assurances that the process will include checks and balances to assure a fair and open sharing of the data within standard research procedures. We are also in communication with the Department of Health and Human Services (HHS) regarding the design of an independent evaluation of the overall VSD project and the published studies. As you may be aware, I have informed HHS that I will hold the proposed subpoena in abeyance. The Committee will continue to monitor the implementation of this protocol to ensure that all researchers are granted fair access to this data so that the best scientific results are produced. While I am not poised to issue a subpoena at this time, I will not foreclose my right to do so at some point if events warrant such action.

It is important to note that in the course of our investigation, we learned that in the ten years of the VSD's existence, the CDC actively tracked 38 conditions. However, speech and language delay, autism, and pervasive developmental delays were not among those tracked. Additionally, several leading research experts have indicated that the CDC's thimerosal study based on the VSD data may have been flawed. The initial study using a large population indicated a potential link between vaccines containing thimerosal (which contains mercury, a toxic substance), tics and language delays. However, a controversial follow-up study using a smaller population claimed to find no such link. These controversies reinforce the need for open access to the data and independent evaluation.

We have seen an explosion in the number of cases of neurological conditions, including autism among children since we have expanded the use of vaccines containing thimerosal. Ten years ago, autism affected 1 in 10,000 children. Today, the NIH estimates that 1 in 250 children is autistic. It is important to note that the effects of mercury are cumulative, and that mercury may remain in a child's body for a long period of time. The cumulative impact of multiple vaccinations received by children needs to be better understood. Some scientists believe that there may also be an association between exposure to mercury in medicines and Alzheimers Disease. This public health crisis demands a concerted research effort to address these issues.

I respect your concerns about medical records and privacy. As you are aware HHS has informed us that access to these medical records can be provided to qualified researchers without exposing the identity of the patients. I would welcome hearing from the HMOs who to date have not communicated their concerns or offered solutions in this area to me or my staff.

I hope this information is helpful.

Sincerely,

Dan Burton
Chairman

Garden Hotel.
Fax 01223. 316605.

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Inflammatory Bowel Disease and measles containing vaccines

(Session 203, Paper 1941)

Robert Davis
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Concern about a possible link between measles virus-containing vaccines and inflammatory bowel disease (IBD) has been raised by a number of past studies, amd was followed by a drop in MMR vaccination coverage rates in the United Kingdom. Because there were a number of methodologic questions regarding these earlier studies, we used the Vaccine Safety Datalink (VSD) project, a collaborative project coordinated by the U.S. Centers for Disease Control and Prevention to study whether MMR or other measles-containing vaccine increased risk for IBD.

Our study focused on a series of questions: was the age of first vaccination with MMR or other measles containing vaccine, or receipt of vaccination itself, associated with an increased risk for Crohn's disease or ulcerative colitis later in life. In addition, we studied whether receipt of MMR or other measles containing vaccine was associated with the acute onset of disease shortly following vaccination.

We performed a retrospective case-control study in four

EXHIBIT 19

large health maintenance organizations (HMOs) that make up the Centers for Disease Control and Prevention's Vaccine Safety Datalink project. This project collects immunization and disease data on approximately 2-4% of all children under 7 years of age in the United States. In order to collect lifetime immunization histories, we limited our study to subjects (cases and controls) who had been enrolled from birth. There were a total of 155 patients with inflammatory bowel disease who had been born between 1958 and 1989 and also enrolled from birth to the onset of disease. Up to five controls were matched by gender, HMO, and birth year.

We found that past vaccination was not associated with an increased risk for Crohn's disease (OR for MMR:0.4;95% 0.08,2.0), ulcerative colitis (OR 0.8;95% 0.18,3.56), or IBD (0.59;95% 0.21,1.69). Risk was not increased among children vaccinated at less than 12 months (OR for MMR 0.61;95% 0.15;2.45) or 12-18 months (OR 0.86;95% 0.28,2.59). Children vaccinated with MMR at >18 months were at significantly decreased risk for IBD (OR 0.16;95% CI 0.04,0.68). Neither past vaccination nor age of vaccination with other measles-containing vaccine was associated with increased risk for Crohn's, ulcerative colitis, or IBD. Risk for Crohn's disease, ulcerative colitis, or IBD was not elevated in the time immediately following vaccination with either vaccine.

In conclusion, we found that neither vaccination with MMR or other MCV, nor the timing of vaccination early in life, increases the risk for inflammatory bowel disease.

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SOAPBOX

14 January 2002

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Measles-containing vaccines and IBD.

Andrew Wakefield, 02 January 2002

In an ironic twist, investigators from the Centers for Disease Control and Prevention (CDC) and the Vaccine Safety Datalink (VSD) Project have confirmed an association between measles-containing vaccines (MCV) and inflammatory bowel disease. Specifically, they have also determined how age at exposure to an MCV may be important in determining the type of inflammatory bowel disease - Crohn's disease or ulcerative colitis - that develops [1].

Before the American Society of Microbiology's millennium meeting, Davis *et al.* reported a retrospective case-control study in which cases (n = 142) with either Crohn's disease, or ulcerative colitis, were compared with unaffected controls (n = 432). The exposure of interest was to an MCV.

When performing the power calculations to determine the necessary size of the study, Davis *et al.* assumed an MCV-exposure rate of 70%. In actual fact, the exposure rate was 93-94%, revealing a fundamental flaw in the study - overmatching.

Exposure of cases and controls to an MCV was so similar that their study, as designed, would never have detected a risk for inflammatory bowel disease, even if this risk were real.

Although these crucial data were presented to the

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American Society for Microbiology (at the Interscience Conference on Antimicrobial Agents and Chemotherapy in November 2000), they received no comment in the subsequent paper published in *Arch Pediatr Adolesc Med.* An explanation is clearly required.

In order to determine whether exposure to an MCV is or is not a risk for inflammatory bowel disease, at the level identified previously [2], power calculations reveal that they would have required at least 3 times as many cases and controls as were included in the study.

The correct power calculations were readily performed using the *Epi.Info* package, downloaded from the CDC website.

Age at exposure and risk

In a recent Israeli study, exposure to measles virus was shown to be associated with an increased risk for Crohn's disease [3]. In addition, measles virus (including vaccine-strain virus) has been amplified and sequenced from intestinal tissues of children with inflammatory bowel disease [4]. However, in the etiology of inflammatory bowel disease, it is likely that it is the pattern of exposure to measles that is more important than exposure *per se*.

Of interest in the Davis study, therefore, was the observation of an association between age at exposure to an MCV (excluding MMR) and the type of inflammatory bowel disease that develops [1]. This observation is entirely consistent with previously reported data, and supports a role for atypical measles virus infection in the etiology of inflammatory bowel disease. Such a claim should not be made lightly, and therefore it is worth reviewing the background to this thesis, that has been described in detail elsewhere [5]-[7].

Age at exposure to natural measles infection is an important determinant of both acute and delayed outcome.

Early measles infection has been reported as a risk factor for delayed disease, including subacute sclerosing panencephalitis (SSPE) and IBD [8]-[10]. For IBD, however, the situation is more complex still; the risk associated with measles virus includes, for example, concurrent exposure to measles and mumps infections in childhood [7] [11].

Studies have used the UK's birth cohort data (British Birth Cohort study 1970 [BCS 70] and the National

Child Development Study [NCDS]), two population-based, nationally representative, and powerful epidemiological instruments. These have shown that, within an early window of risk (measles exposure < 6 years of age) [5], other characteristics of the acute measles exposure determine both the risk and phenotype of IBD that develops.

Younger age at infection (high birth order, e.g. two or more older siblings) (Fig 1) and younger age at exposure to concurrent measles and mumps infection (Fig. 2) are a risk for ulcerative colitis.

Within this early window of risk, older age at infection (low birth order, e.g. no older siblings) (Fig. 1) is associated with an increased risk of Crohn's disease. Higher mean age at concurrent measles and mumps exposure (Fig. 2), and higher age at monovalent measles vaccination (Fig. 3) are also associated with an increased risk of Crohn's [12][13].

Fig 1

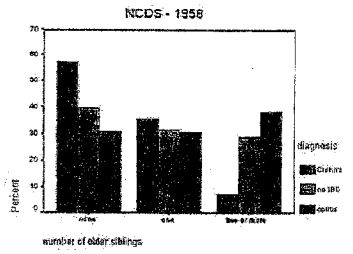


Fig 2

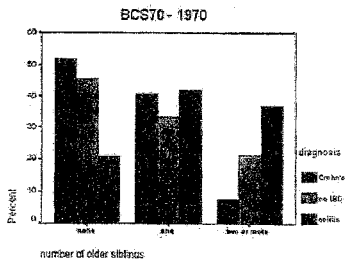
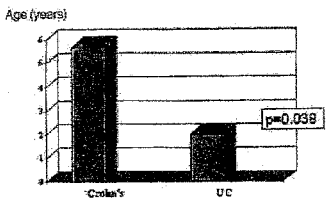


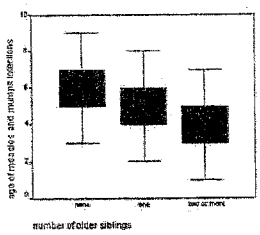
Fig 3



Mean age of concurrent measles and mumps infection in cohort members with IBD (BCS70)

In the BCS 70 cohort, the age of concurrent measles and mumps infection appeared to determine the risk of whether Crohn's disease or ulcerative colitis developed in an individual. For Crohn's disease, the mean age of exposure was greater than for ulcerative colitis. This difference was statistically significant ($p = 0.038$).

Fig 4



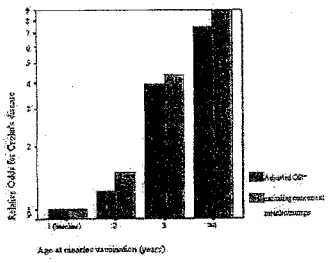
Data for the birth order/family structure versus risk of Crohn's disease or ulcerative colitis were then examined to see if this influenced the age of concurrent measles/mumps infection, as predicted by our hypothesis. This states that those with no older siblings (low birth order) should experience concurrent infections later, whereas those with two or more older siblings (high birth order) should experience the concurrent infection earlier.

The data shown above in Figure 4 indicate that the differential risk for concurrent infection according to number of older siblings is statistically significant ($p<0.001$). Data are adjusted for sex and socio-economic status.

The next question that we addressed was the issue of whether age of exposure to monovalent measles vaccine (the only measles vaccine available in the 1970s in the UK) influenced the risk of IBD in the BCS 70 cohort.

The hypothesis predicted that older age at measles vaccination, within the early window of exposure (0-6 years), would be a risk for Crohn's disease. This is indicated by the data shown in Figure 5.

Fig 5



In this cohort, age at exposure to monovalent measles vaccine, including and excluding those with concurrent measles and mumps infections, appears to be associated with risk of Crohn's disease. This was when adjusted for sex, social class of father at birth, and crowding.

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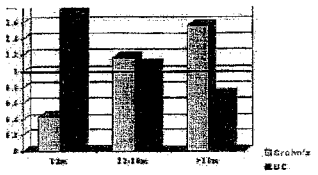
Children exposed the vaccine at an older age are at greater risk (p for trend = 0.017). This is consistent with the fact the response to the vaccine virus is a function of age and, possibly, influences of maternal immunity.

The numbers of cases are small, and therefore independent corroboration was required. This was provided by the Davis study, as shown below.

Fig 6



Age of exposure to measles containing vaccine and IBD risk

The Davis study identifies that those exposed to an MCV (excluding MMR) at a younger age (< 12 months) appear to be protected against Crohn's disease, but at excess risk of ulcerative colitis. Conversely, older age at exposure is a risk for Crohn's disease, but protective against ulcerative colitis. This is exactly as predicted by the previous data and the *a priori* hypothesis.

Analysis of the raw data is required in order to establish whether or not these trends are statistically significant.

The effects of the characteristics of the exposure are likely to reflect age- and dose-dependent influences upon immune responses to the virus that are consistent with models of immunological tolerance, as proposed previously [5]-[7].

The study of Davis *et al.* provides valuable independent confirmation of a possible association between age at measles exposure and the type of IBD that develops.

What needs to be explained, beyond these observations, is the current upsurge of IBD in children, including Crohn's disease, ulcerative colitis, and the recently described autistic enterocolitis.

Questions arising:

1. Were the power calculations for the study, as reported [1], based upon an assumed MCV exposure of 70% in cases and controls, as presented in the original data set?

   If the answer is 'no', please would Davis *et al.* provide the revised assumptions and power calculations.

   If the answer is 'yes', then having performed power calculations for the size of the study based upon an estimated vaccine uptake of 70%, and subsequently finding an actual uptake of 93-94%,

these trends are statistically significant.

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If the answer is 'no', please would Davis et al. provide the revised assumptions and power calculations.

If the answer is 'yes', then having performed power calculations for the size of the study based upon an estimated vaccine uptake of 70%, and subsequently finding an actual uptake of 93-94%, what steps, if any, were taken to reconcile this discrepancy prior to proceeding with the study?

Why were the power calculations, as presented to the American Society for Microbiology, not presented in the paper?

If the answer to question 1 is 'yes', and if no steps were taken to reconcile the discrepancy, why was this not described in the paper as published?

If the answer to question 1 is 'yes', then, based upon the obvious flaw of overmatching, do the authors still consider the conclusions to be valid?

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Sponsor

Measles Shots Safe for Kids

CBS HealthWatch by Medscape

By Dulce Zamora

Sept. 20 (CBSHealthWatch)--Measles-containing vaccines are safe for kids, say researchers of a new study presented at the 40th Interconference on Antimicrobial Agents and Chemotherapy. The study, which used an extensive database of HMO records, contradicts recent research that shows the popular vaccines could cause serious inflammatory bowel disease in children.

"This is the first study looking at vaccines commonly used in the Un States," says Robert L. Davis, associate professor of pediatrics anc epidemiology at the University of Washington in Seattle. "We found there was no evidence of an increased risk of inflammatory bowel disease--and that's Crohn's disease or ulcerative colitis--among chi who received the vaccine at the routine schedule."

Crohn's disease affects any area of the gastrointestinal tract includi small intestine. The most common symptoms include abdominal pa diarrhea. The chronic disease has also been known to stunt growth children. Ulcerative colitis affects the innermost lining of the colon. I who have it usually experience a progressively loosening and blood abdominal pain and a severe urgency to have a bowel movement.

Recent research has indicated that children who get measles-conta vaccines, including the commonly used measles-mumps-rubella sh at risk for acquiring Crohn's disease or ulcerative colitis. The findin caused a significant drop in measles immunizations in the United Kingdom.

To figure out whether measles shots cause inflammatory bowel dis Davis and his colleagues reviewed the Vaccine Safety Datalink Stu

GEN-T941-1CAAC

A Case-Control Study of MMR and Other Measles-Containing Vaccines and Inflammatory Bowel Disease.

Results from the Vaccine Safety Datalink Project

Robert Davis, Piotr Kramarz, Kari Bohlke,
Frank DeStefano, Robert Chen

Measles vaccination and Inflammatory Bowel Disease

Year	Findings
1995 (Thompson)	MCV recipients 3-fold increase of Crohn's & UC
1998 (Wakefield)	Case series of children with non-specific colitis following MCV
1999 (Montgomery)	Early infection and/or vaccine may increase risk for IBD
1998 (Begg)	MCV coverage fall Concern re: serious risks of MMR

Year/Study			
1997/Feeney	Crohn's	1.1	(0.6, 1.9)
	UC	0.8	(0.4, 1.6)
1997/Morris	Crohn's	1.2	(0.5, 2.9)
	UC	1.3	(0.5, 3.7)
	IBD	1.3	(0.6, 2.4)
1998/Miller	No increase Crohn's disease after 2nd MMR campaign		
1998/Pebody	No increase Crohn's disease with increased MMR population coverage		

Measles vaccination and Inflammatory Bowel Disease

- Thompson (1995):
  - –Measles virus-containing vaccine recipients at three-fold increased risk for Crohn's disease and ulcerative colitis
- Wakefield (1998):
  - – 12 children with non-specific colitis, ileal-lymphoid nodular hyperplasia, and developmental disorders after measles-containing vaccine

- Begg (1998):

Fall in vaccine coverage/increase in parents believing MMR posed serious risks

Measles vaccination and Inflammatory Bowel Disease

Thompson:

1964 MRC Schwarz strain vaccine trial

Follow-up through 1994.

Comparison group: 1958 NCDS study

Crohn's	RR 3.01;95% CI 1.45,6.23
ulcerative colitis	RR 2.53;95% CI 1.15,5.58

Measles vaccination and Inflammatory Bowel Disease

Feeney (1997)

140 cases/280 controls

United Kingdom

Crohn's disease	OR 1.08;95% CI 0.6,1.9
U.C.	OR 0.84; 95% CI 0.4,1.6

Measles vaccination and Inflammatory Bowel Disease

Feeney (1997)

Crohn's disease	OR 1.08;95% CI 0.6,1.9
U.C.	OR 0.84;95% CI 0.4,1.6

Morris (1997)

UK 1970 birth cohort study, through age 26

Crohn's disease	RR 1.21;95% CI 0.5,2.9
U.C.	RR 1.31;95% CI 0.5,3.7
IBD	RR 1.25;95% CI 0.6,2.4

Measles vaccination and Inflammatory Bowel Disease

Miller, UK:

- •Computerized hospital discharge statistics,1992
- •No increase in the rate of hospital admissions for Crohn's disease following MMR campaign

Pebody, Finland:

- •Increase in proportion population receiving measles virus vaccine
- •No increase in Crohn's disease among children, adolescents, and young adults

Herman-Taylor,UK:

- •Rise in the rate of Crohn's disease predated introduction of MCV by 20 yrs

Measles vaccination and Inflammatory Bowel Disease

Study Questions:

•Is vaccination with MMR or other MCV associated with increased risk for Crohn's disease or ulcerative colitis?

•Does age at vaccination increase risk for Crohn's disease or ulcerative colitis?

•Is vaccination with MMR or other MCV associated with acute onset (triggering) of Crohn's disease or ulcerative colitis?

Measles vaccination and Inflammatory Bowel Disease

Vaccine Safety Datalink Project:

- Group Health Cooperative (GHC), Seattle, Washington
- Kaiser Permanente of Northern California (KPNC) Oakland, California
- Kaiser Permanente Northwest (NWK), Portland, Oregon
- Southern California Kaiser Permanente (SCK), Los Angeles, California

- Started 1991, 2-4% of U.S. children <6 years old

Measles vaccination and Inflammatory Bowel Disease

- Case-Control study

- Eligible population:
  - Born between 1958 and 1989
  - Enrolled from 6 months of age or younger

- Medical record review of diagnoses of either Crohn's disease or ulcerative colitis: (ICD-9 codes 555.* and 556.*)

- Databases:
  - Hospitalizations (all four sites)
  - Outpatient/Emergency dept visits (three sites)

Measles vaccination and Inflammatory Bowel Disease

Analysis:

- Conditional logistic regression
- Up to 5 controls matched by HMO, gender and birth year

- For Vaccination and Risk for Crohns or UC:
  Diagnosis date by physician

- For Vaccination *triggering* acute onset of symptoms
  Symptom onset date

Measles vaccination and Inflammatory Bowel Disease

Exposure measurement:

•Medical record review of lifetime vaccination history

Power calculations

Assumptions	Case #	OR
Power = 80% (alpha = .05) Exposure 70%	138	2.0
Power = 80% (alpha = .05) Exposure 70%	356	1.5

Measles vaccination and Inflammatory Bowel Disease

Case definitions:

- Definite IBD: **diagnosis by HMO gastroenterologist**
  >= 1 sign/symptom (bloody diarrhea; severe +/or recurrent abdominal pain)
  diagnostic test (pathology; colono/sigmoidoscopy)
- Probable IBD: **diagnosis by non-HMO gastroenterologist**
  >= 1 sign/symptom (bloody diarrhea; severe +/or recurrent abdominal pain)
  diagnostic test (pathology; colono/sigmoidoscopy)

Measles vaccination and Inflammatory Bowel Disease

Case definitions:

•Possible IBD:

diagnosis by non-HMO gastroenterologist

>= 1 sign/symptom OR diagnostic test

•Questionable IBD:

diagnosis by non-HMO gastroenterologist

No documented signs/symptoms or diagnostic tests

Measles vaccination and Inflammatory Bowel Disease

Analysis:

- Up to 5 controls matched by HMO, gender and birth year

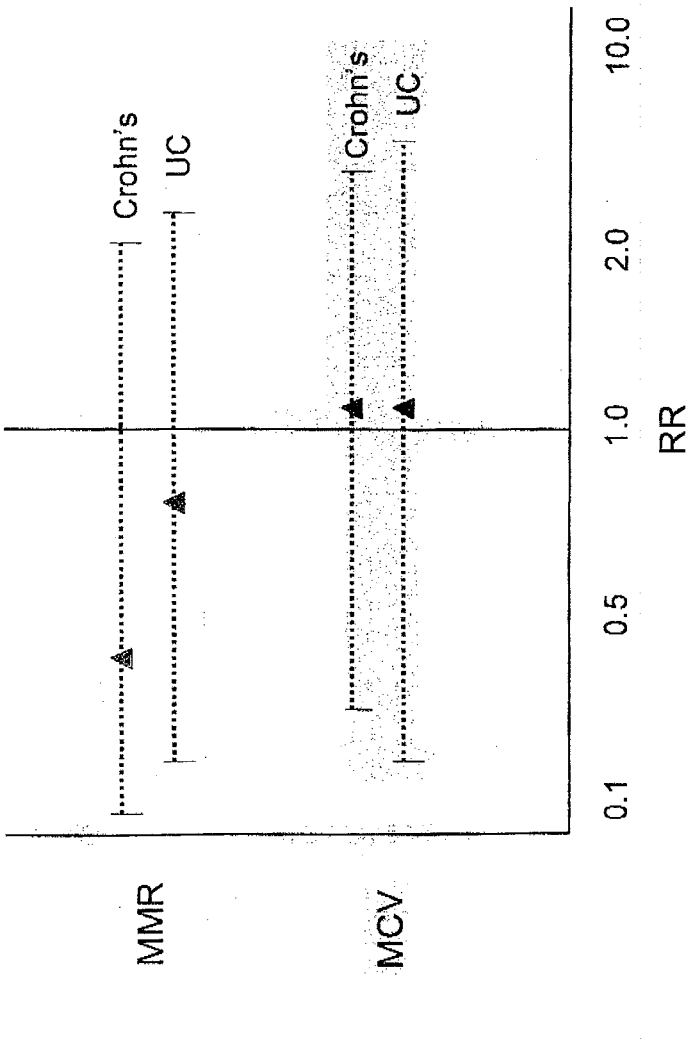
- Conditional logistic regression
  - –accounting for matching/enrollment criteria
  - –adjusted for race

	Cases	
	N	%
	142	
Crohn's	75	(53)
U.C.	67	(47)
Female	74	(52)
Male	68	(48)
Caucasian	95	(67)
Afr/Amer	12	(8)
Other	10	(7)
Unknown	25	(17)

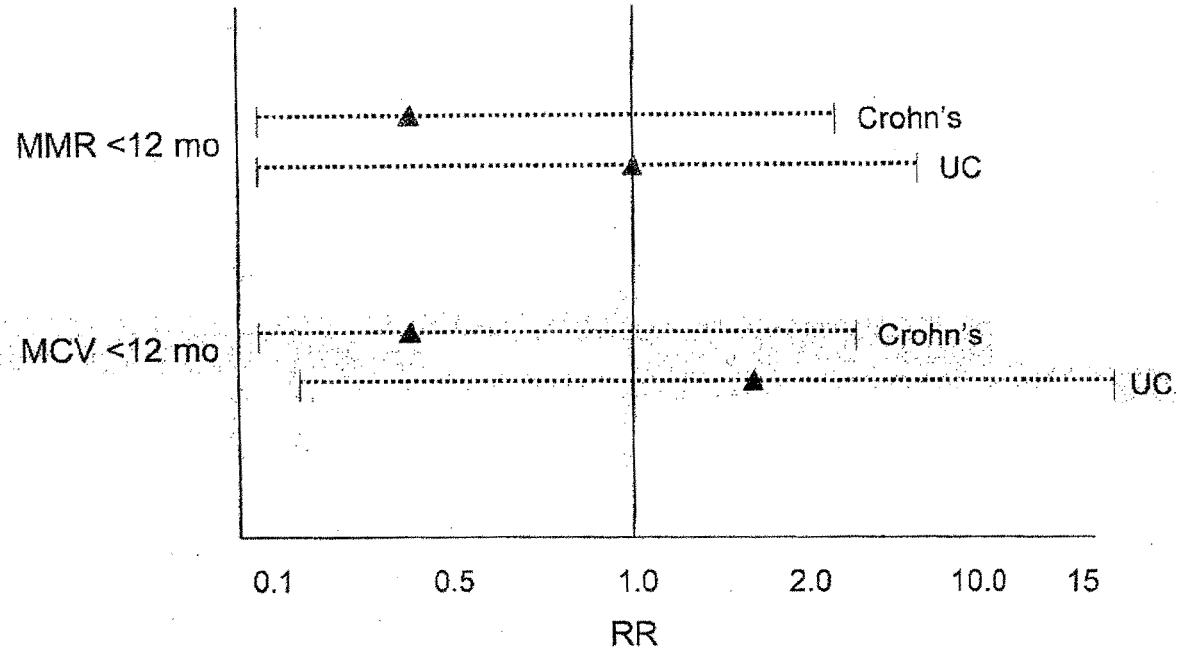
	Cases	
	N	%
	142	
Age		
0-5	7	(5)
6-10	29	(20)
11-14	40	(28)
15-19	43	(30)
20-24	15	(11)
25+	8	(6)

Age of vaccination and IBD risk

Age vaccinated	All IBD	Cases	Controls
MMR < 12 mo	0.61 (0.15,2.45)	6	25
MCV <12 mo	0.77 (0.18,3.37)	5	18
MMR 12-18 mo	0.86 (0.28,2.59)	84	229
MCV 12-18 mo	1.07 (0.35,3.26)	22	62
MMR >18 mo	0.16 (0.04,0.68)	4	54
MCV >18 mo	0.88 (0.24,3.28)	11	30
Unvaccinated	ref	10	26



*Adjusted for race, HMO, gender, and birth year



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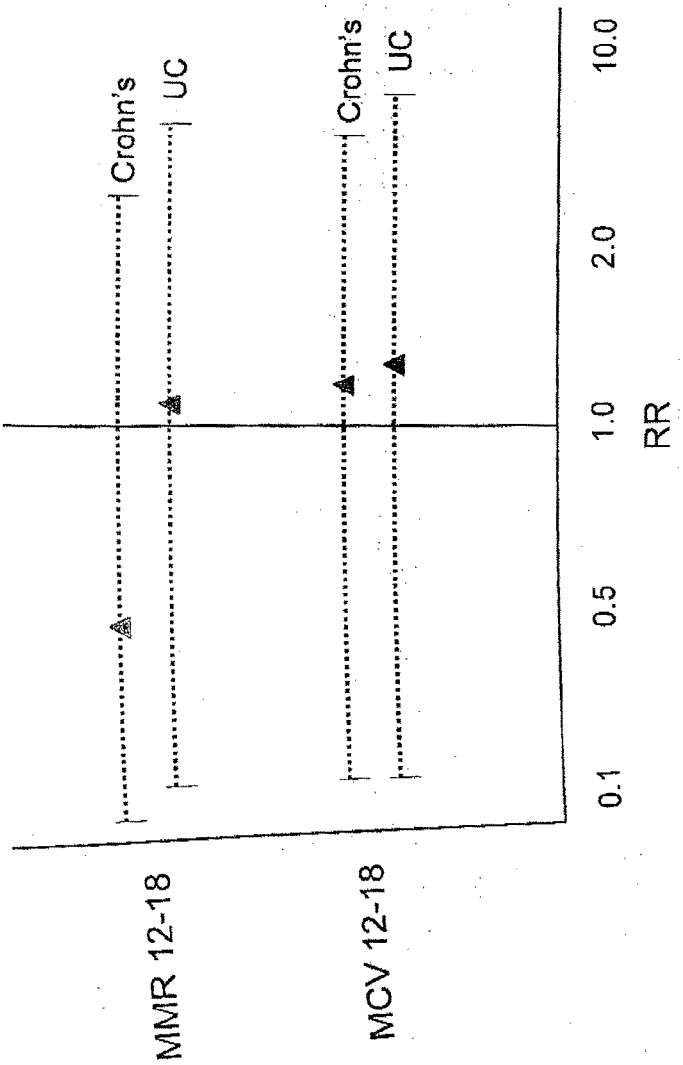
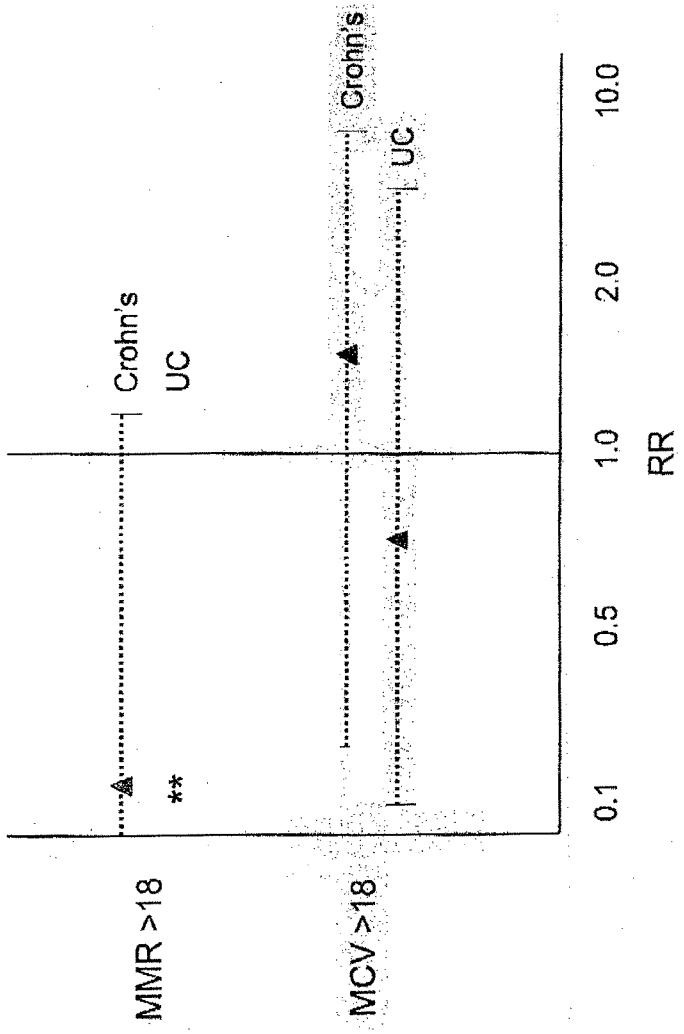


*Adjusted for race, HMO, gender, and birth year



*Adjusted for race, HMO, gender, and birth year

Time window between vaccine & symptom onset

	Crohn's	UC
< 2 months	0.0 (0.0,-)	- (--,----)
< 4 months	0.0 (0.0,-)	- (--,----)
< 6 months	1.9 (0.1,39.2)	0.0 (0.0,-)
< 12 months	0.7 (0.1,8.3)	0.0 (0.0,-)

*Adjusted for race, HMO, gender, and birth year

Measles vaccination and Inflammatory Bowel Disease

Study strengths:

- First study of MMR/MCV in U.S
- Population-based study
- Lifetime medical history: unbiased assessment of vaccine exposure & disease onset

Limitations:

- Little information on children or adults with non-specific colitis
- Inherent limitations of diagnostic accuracy in retrospective study

Measles vaccination and Inflammatory Bowel Disease

- In a population-based sample of cases from four large HMOs, no evidence of elevated risk for IBD immediately following vaccination, or long-term

- Age at vaccination does not elevate risk for IBD

- Concurrent exposure to measles and mumps antigens in vaccines does not increase the risk for IBD

Measles

Search date November 2001

Anna Donald and Vivek Muthu

Key Messages

Benefits of treatment

- Measles is a serious, highly contagious, yet preventable disease. In healthy people who have not been vaccinated against it, measles infection causes pneumonia, brain damage, dementia, or death in about 6% of cases and requires hospital admission in up to 20%. Severity and frequency of complications are higher in people who are ill or malnourished.
- Large cohort studies, large cross-sectional time series, and population surveillance data from different countries have all found that combined measles, mumps, and rubella (MMR) and live monovalent measles vaccination programmes reduce risk of measles infection to near zero, especially in populations in which vaccine coverage is high.
- We found no RCTs comparing clinical effects of MMR versus no vaccination or placebo on measles infection rates. Such trials are likely to be considered unethical because of the large body of whole-population evidence finding benefit from vaccination.
- Unlike live monovalent measles vaccine, MMR additionally vaccinates against mumps and rubella, which themselves cause serious complications (mumps causes orchitis, pancreatitis, meningoencephalitis, deafness, and congenital fetal abnormalities; congenital infection with rubella causes deafness, blindness, heart defects, liver, spleen, and brain damage, and stillbirth).

Harms of treatment

- One systematic review, one RCT, one large population based survey, and one population based study found no evidence of MMR being associated with developmental regression or autism compared with placebo or no vaccine. Large cross-sectional time series have consistently found no evidence of MMR or live monovalent measles vaccine being associated with autism.
- One large, long term population surveillance study and one population based case control study found no evidence that either the monovalent measles vaccine or MMR was associated with inflammatory bowel disease. One large cohort study and two population based case control studies found no association of inflammatory bowel disease with the monovalent vaccine.

Clin Evid 2002;7:331–340.

Measles

- One systematic review and one additional RCT have found that MMR and monovalent measles vaccine are associated with a small and similar risk of self limiting fever within 3 weeks of vaccination compared with 100% risk of acute fever in people with measles.

DEFINITION Measles is an infectious disease caused by a ribonucleic acid (RNA) paramyxomavirus. The illness is characterised by an incubation period of 10–12 days; a prodromal period of 2–4 days with upper respiratory tract symptoms; Koplik's spots on mucosal membranes and high fever; followed by further fever; and a widespread maculopapular rash that persists for 5–6 days.[1]

INCIDENCE/ PREVALENCE Measles incidence varies widely according to vaccination coverage. Worldwide, there are an estimated 30 million cases of measles each year,[2] but an incidence of only 0–10/100 000 people in countries with widespread vaccination programmes such as the USA, UK, Mexico, India, China, Brazil, and Australia.[3] In the USA, before licensure of effective vaccines, greater than 90% of people were infected by the age of 15 years, whereas after licensure in 1963, incidence fell by about 98%.[1] Mean annual incidence in Finland was 366/100 000 in 1970,[4] but declined to about zero by the late 1990s.[5] Similarly, annual incidence declined to about zero in Chile, the English speaking Caribbean, and Cuba during the 1990s with introduction of vaccination programmes.[6,7]

AETIOLOGY/ RISK FACTORS Measles is spread through airborne droplets that persist for up to 2 hours in closed areas following the presence of an infected person. Measles is highly contagious. As with other infectious diseases, other risk factors include overcrowding, low herd immunity, and immunosuppression. People with immunosuppression, children of less than 5 years of age, and adults of more than 20 years of age have a higher risk of severe complications and death, although these also occur in healthy people (see prognosis below).[1] Newborn babies have a lower risk of measles than older infants because of the presence of protective maternal antibodies, although in recent US outbreaks, maternal antibody protection was lower than expected.[1]

PROGNOSIS The World Health Organization estimated that in the year 2000, measles caused 777 000 deaths and a burden of disease of 27.5 million disability adjusted life years.[8] **Disease in healthy people:** In developed countries, most prognostic data come from the pre-vaccination era and from subsequent outbreaks in non-vaccinated populations. In the USA, measles is complicated in about 30% of reported cases. From 1989–1991 in the USA, measles resurgence among young children (< 5 years) who had not been immunised led to 55 622 cases with more than 11 000 hospital admissions and 125 deaths.[1] Measles complications include diarrhoea (8%), otitis media (7%), pneumonia (6%), death (0.1–0.2%), acute encephalitis (about 0.1% followed by death in 15% and permanent neurological damage in about 25%), seizures (with or without fever in 0.6–0.7%), idiopathic thrombocytopenia (1/6000 reported cases), and subacute sclerosing panencephalitis causing degeneration of the central nervous system and death 7 years after measles infection (range 1 month to 27 years; 0.5–1.0/100 000 reported cases).[1,9] Measles during pregnancy

results in higher risk of premature labour, spontaneous abortion, and low birth weight infants. An association with birth defects remains uncertain.[1] **Disease in malnourished or immunocompromised people:** In malnourished or immunocompromised people, particularly those with vitamin A deficiency, measles case fatality can be as high as 25%. Worldwide, measles is a major cause of blindness and causes 5% of deaths in young children (< 5 years).[1,10]

AIMS Preventing measles with minimum adverse effects.

OUTCOMES **Prevention, benefits:** Clinically apparent measles and measles related complications, including death. We have included a proxy outcome (seroconversion — see glossary, p 339) because it is so highly correlated with vaccine efficacy.[11] **Prevention, harms:** Acute fever, febrile seizures, inflammatory bowel disease, developmental regression, autism and clinical measles after seroconversion.

METHODS *Clinical Evidence* search and appraisal November 2001. The authors also searched World Health Organization, US Communicable Disease Control, and UK Public Health Laboratory Service websites and hand searched national and international policy documents. In the benefits section, we have included RCTs and stronger observational studies, given that RCTs have long been considered unethical for assessing the clinical efficacy of measles vaccines (see benefits, p 333). In the harms section, we have included RCTs and robust observational studies (see harms, p 335). In the comments section we have included weaker studies (see comment, p 338). We have included only those studies of the combined measles, mumps, and rubella vaccine (see glossary, p 339) that used the Schwarz strain of the measles virus and only those studies of the monovalent measles vaccine (see glossary, p 339) that considered live attenuated strains of the virus, because of the relative inefficacy of measles vaccines using killed strains.

QUESTION What are the effects of interventions to prevent measles infection?

OPTION MEASLES VACCINATION

We found no RCTs comparing measles infection rates following the combined measles, mumps, and rubella (MMR) vaccine versus placebo or versus monovalent vaccine alone. We found strong evidence from national population surveillance that both MMR and monovalent measles vaccination virtually eliminate risk of measles and measles complications. We found no evidence that MMR or live monovalent measles vaccines are associated with autism or inflammatory bowel disease. We found consistent evidence from RCTs and cohort studies that MMR and live monovalent measles vaccines are associated with small, similar risks of self limiting fever within 3 weeks of vaccination. Measles causes acute fever in 100% of infected children.

Benefits: **Monovalent measles vaccine or combined MMR vaccine versus placebo or no vaccine:** See glossary, p 339. We found two early RCTs of monovalent measles vaccine versus placebo or no vaccine in the UK[12] and USA.[13] Both found efficacy rates of 95% or

greater for vaccines using live attenuated Schwarz[12] and Edmonston[13] strains of the measles virus (Schwarz RCT: 9538 children received live vaccine, 16 239 unvaccinated; Edmonston RCT: 1308 live vaccine, 1271 placebo). We found no RCTs comparing the clinical effects of MMR versus no vaccine or placebo. Such studies have been considered unethical because of previous evidence of the efficacy of measles vaccine and harms of measles infection. We found two RCTs that compared seroconversion (see glossary, p 339) rates of MMR versus placebo.[14,15] The first compared MMR versus placebo in 282 previously non-immune children (92% of whom were ≤1 year old). At 8 weeks, almost all children receiving MMR seroconverted for measles, whereas none of the children receiving placebo seroconverted (measles seroconversion rate 99%–100% with MMR, depending on vaccine batch used).[14] The second trial examined seroconversion with MMR vaccine in 1481 children (1232 MMR, 249 placebo), of whom 446 in the vaccine group were naïve to measles, mumps, and rubella.[15] In this subgroup, seroconversion rates at 8 weeks approached 100%, whereas none of the previously non-immune placebo group seroconverted for measles. One large, retrospective cohort study of the entire US population from 1985–1992 compared measles infection rates in children who were vaccinated versus children whose parents had declined vaccination (17 390 cases from a vaccinated population of 51 264 140 to 52 377 192 from 1985–1992; 2827 cases from an unvaccinated population of 234 040 to 245 887 from 1985–1992).[16] The study did not state what proportion of vaccinated children received monovalent versus MMR vaccine, although MMR was already widely used in the USA by 1985. The study found that although overall measles incidence was low because of herd immunity (see glossary, p 339), vaccination reduced measles infection compared with no vaccination (RR unvaccinated *v* vaccinated 4–170, depending on age group and year of survey). One large, prospective cohort study followed up 9274 children who had been enrolled in a placebo controlled trial of live monovalent measles vaccine in 1964 (36 530 children aged 10 months to 2 years; Schwarz strain vaccine).[17] The cohort study found that by 1990, over a period of 15 years (12–27 years after the trial) and after controlling for subsequent vaccination in initial placebo groups, but not controlling for growing herd immunity following mass vaccination, measles incidence was higher in the unvaccinated group (AR 0.3/1000 person years with vaccine *v* 1/1000 person years with no vaccine; $P < 0.001$). One systematic review (search date not stated, 10 cohort studies, 2 case control) and one subsequent cohort study examined effects of live monovalent measles vaccination on mortality. The review found that live, standard titre monovalent measles vaccination in seven developing countries reduced all-cause mortality by 30–80%, depending on follow up period and country.[18] The more recent study compared a group of children in Bangladesh vaccinated with live, Schwarz strain monovalent measles vaccine versus age matched, unvaccinated children (8135 matched pairs).[19] It found similar results (16 270 children aged 9–60 months; RR for death at 3 years' follow up vaccinated *v* unvaccinated 0.54, 95% CI 0.45 to 0.65). We found

many population based studies from different countries with different healthcare systems and different socioeconomic and demographic distributions. These studies have consistently found measles vaccination coverage to be associated with a steep decline in measles. One cross-sectional time series from the World Health Organization found a global decline in reported measles incidence (which underestimates true incidence) from about 4 500 000 a year in 1980 to about 1 000 000 a year in 2000.[20] The decline was associated with the rise in reported measles vaccination coverage from about 10% in 1980 to about 80% in 2000. One population-based time series of measles incidence from Finland found that in a population of about 5 million people following the introduction of a live monovalent vaccination programme (1975–1981), the number of new measles cases each year fell from an average of 2074 cases in 1977–1981 to 44 cases in 1985. New cases declined to about zero by the mid 1990s. Shortly after introducing the MMR programme in Finland in 1982, rubella and mumps incidence also fell to about zero.[4] One cross-sectional study in a Brazilian city, which was repeated before and after a measles vaccination campaign in 1987 (8163 people, strain not stated) found that reported measles incidence fell from 222/100 000 in 1987 to 2.7/100 000 in 1988.[21] **MMR versus monovalent measles vaccine:** We found no RCTs comparing clinical effects of MMR versus monovalent vaccine in children of the same age. We found one RCT that compared live Schwarz strain monovalent measles vaccine given at 9 months of age followed by MMR at 15 months (442 children) versus MMR only (no prior vaccination) at 12 months (495 children).[22] Pre-vaccination measles seropositivity was higher in the younger, monovalent vaccine group, perhaps because of maternal antibody persistence (pre-vaccine, 8.1% seropositive in monovalent group *v* 1.4% in MMR group; $P < 0.0001$). After 60 months' follow up, measles infection rates were higher with monovalent vaccination followed by MMR compared with MMR alone (AR for infection 2.7% with monovalent plus MMR *v* 0% with MMR; ARR 2.7%; CI not stated; $P < 0.0001$); however, effects may be confounded by the different timing of the vaccinations. We found two RCTs that compared seroconversion rates following live MMR versus Schwarz strain monovalent measles vaccine. The first trial (420 children with no clinical history of measles or mumps, mean age about 15 months) found similar seroconversion rates in both groups after 6 weeks (96.8% with monovalent measles *v* 92.6% with MMR).[23] The second RCT (319 children, mean age 13 months) also found similar seroconversion rates in both groups at 6 weeks (92% with Schwarz strain monovalent measles vaccine *v* 93% with MMR).[24]

Harms:

Acute fever and febrile convulsions: We found one systematic review and four RCTs examining fever as an outcome of vaccination in otherwise healthy children. Results should be interpreted in light of the 100% prevalence of acute fever in children with measles infection. The systematic review (search date 1998) reported that up to 5% of non-immune people develop moderate to high fever (≥ 38.6°C) within 7–21 days of vaccination.[25] The first RCT (cross-over design) compared the acute harms of MMR versus placebo in 1162 homozygous and heterozygous twins (460 children aged

1 year, of whom 1.3% had been previously vaccinated; 702 aged ≥ 2 years, 95% of whom had been previously vaccinated or experienced measles).[26] One member of each twin pair was randomly selected and allocated to MMR vaccination followed 3 weeks later by placebo, or vice versa. The other twin was allocated to the opposite combination. The trial found that among children aged 14–18 months, MMR was more likely to cause fever than placebo within 21 days (AR fever, 12% in MMR group *v* 4% in placebo group; OR for fever ≥ 39.5°C 2.83, 95% CI 1.47 to 5.45; OR for fever ≥ 38.5°C 3.28, 95% CI 2.23 to 4.82; OR for fever ≥ 37.5°C 2.66, 95% CI 1.66 to 3.08). The second and third RCTs, which compared MMR versus Schwarz strain monovalent measles vaccine in infants with no history of measles, found no difference in fever rates between the two groups.[23,24] The fourth RCT compared Schwarz strain monovalent measles vaccine given at 9 months followed by MMR at 15 months versus MMR alone at 12 months.[22] It found similar rates of fever for monovalent measles vaccine and initial MMR, although results may be confounded by the age difference between the two groups (AR for fever 8.7% with monovalent vaccine *v* 11.2% with MMR; P value not provided). One retrospective cohort study in 679 942 children from four US health maintenance organisations found that children who had received MMR were more likely to experience febrile convulsions at 1–2 weeks after MMR than children of the same age who had not been vaccinated, although the estimated increase in absolute risk was small (RR for febrile seizure 8–14 days after vaccination 2.83, 95% CI 1.44 to 5.55; ARI of febrile seizure, estimated by comparison with background seizure risk in all children aged 12–24 months, 0.025%; NNH 4000; CI not provided).[27] However, the study found no increase in risk within the first week or from 2–4 weeks following vaccination (RR for first wk 1.73, 95% CI 0.72 to 4.15; RR for 15–30 days 0.97, 95% CI 0.49 to 1.95). Seven years' follow up of 543 children with febrile convulsions in the initial month of follow up (22 following MMR, 521 who had not been vaccinated) found no difference between MMR versus no vaccination for subsequent seizure (RR 0.56, 95% CI 0.07 to 4.20). Similarly, among 271 children with febrile convulsion in one of the four participating health maintenance organisations, the study found no evidence that MMR vaccination prior to seizure increased risk of learning disability or developmental delay compared with no vaccination prior to seizure (RR after adjusting for age at first febrile seizure 0.56, 95% CI 0.07 to 4.20). We found one study that reported results of population based surveillance of harms of MMR in all 1.8 million people vaccinated over a 14 year period in Finland.[28] Surveillance was passive, relying on healthcare personnel to be aware of the surveillance programme and to report adverse events that they felt might be associated with MMR. Throughout the surveillance period, the programme was advertised in seminars, the media, and medical press. Acute reactions were more likely to have been reported than long term effects. The study found that fever was associated with MMR in 277 children (AR 0.02%). Children with fever not brought to the attention of health professionals would have escaped detection. Febrile seizure was reported in 52 cases (AR 0.003%), of which 28 cases could have been caused by MMR according to predefined clinical and

serological criteria (AR 0.002%). **Developmental regression or autism:** The RCT comparing harms of MMR versus placebo found no evidence that MMR was associated with acute developmental regression (see glossary, p 339).[26] We found one systematic review of observational studies of different kinds that found no association between MMR and autism.[29] The review included two large cross-sectional time series. Neither found evidence that MMR is associated with autism, but that incidence of autism has been increasing independently of MMR coverage. The first study examined MMR vaccine coverage (see glossary, p 339) among children aged 14–17 months enrolled in Californian kindergartens and born between 1980 and 1994, and autism caseloads referred to the state developmental services department over the same period.[30] The study found that MMR coverage at 24 months rose slightly (from 72% in 1980 to 82% in 1994; 14% proportional rise); however, referral rates for new autism cases increased disproportionately in the same period (from 44/100 000 births in 1980 to 208/100 000 live births in 1994; 373% proportional rise). Referral rates to the department may not accurately reflect incidence of autistic syndromes. The second study, which took its data from a national UK general practice registry, found that the risk of autism among boys increased in the period from 1988–1993, whereas MMR coverage remained almost constant at about 97% over the same period (AR of first diagnosis of autism aged 2–5 years 0.008%, 95% CI 0.004% to 0.014% for cohort born in 1988 *v* 0.029%, 95% CI 0.020% to 0.043% for cohort born in 1993).[31] A third population based study identified 498 children diagnosed with autism born in eight health districts in the UK between 1979 and 1988.[32] The study found that incidence of autism increased over this period. However, there was no step increase or change in the rate of increase of incidence following the start of the MMR vaccination programme or after MMR coverage levelled off at almost 100%. The long term population based passive surveillance study from Finland similarly reported no cases of developmental regression in 1.8 million people vaccinated with MMR.[28] It also reported no cases of autism in the long term, although the study may have limited reliability for detecting long term adverse effects. **Inflammatory bowel disease:** We found one systematic review (search date 1998) of six large observational studies from different developed countries.[25] The review found no evidence of an association between inflammatory bowel disease and MMR and measles vaccines. We found three additional studies. The first was a retrospective cohort study comparing rates of ulcerative colitis, Crohn's disease, and inflammatory bowel disease (assessed by postal questionnaire) in 7616 people who had received live monovalent measles vaccination versus those who had not received measles vaccination by the age of 5 years (mean age at vaccination 17.6 months, standard deviation 7.4 months). People were those available from an original population based cohort of 16 000 children born in the first week of 1970 in the UK.[33] The study found no difference for risk of ulcerative colitis, Crohn's disease, or inflammatory bowel disease between people (aged 26 years at the time of the study) who had received monovalent measles vaccine and those who had not, whether or not the result was adjusted for sex,

socioeconomic status, and crowding (AR for Crohn's disease 0.25% with vaccine *v* 0.31% without, adjusted OR 0.7, 95% CI 0.3 to 1.6; AR for ulcerative colitis 0.16% with vaccine *v* 0.27% without, adjusted OR 0.6, 95% CI 0.2 to 1.6; AR for inflammatory bowel disease 0.41% with vaccine *v* 0.58% without, adjusted OR 0.6, 95% CI 0.3 to 1.2). The second (the long term, prospective population based passive surveillance study from Finland) reported no cases of inflammatory bowel disease associated with vaccination in 1.8 million people vaccinated with MMR followed up for 14 years.[28] The third was a case control study of 142 people with definite or probable inflammatory bowel disease from members of four US health maintenance organisations (67 people with ulcerative colitis and 75 with Crohn's disease).[34] Cases were identified by computerised search of electronic records and manual abstraction of medical records (from 1958–1989 for 3 organisations and from 1979–1989 for 1; people who were not organisation members between 6 months of age and disease onset were excluded). The study found that people with inflammatory bowel disease were not more likely to have received MMR than people without inflammatory bowel disease taken from the same health maintenance organisation and matched for sex and year of birth (OR for Crohn's disease 0.40, 95% CI 0.08 to 2.00; OR for ulcerative colitis 0.80, 95% CI 0.18 to 3.56; OR for all inflammatory bowel disease 0.59, 95% CI 0.21 to 1.69). The study similarly found no evidence of an association between all measles containing vaccines, Crohn's disease, ulcerative colitis, or all inflammatory bowel disease. **Measles risk after seroconversion:** One systematic review of cohort studies (search date 1995) examined risk of measles infection at least 21 days after vaccine induced seroconversion (monovalent or polyvalent vaccine).[11] It identified 10 studies that met inclusion criteria. In the subset of six cohort studies examining live vaccine, where vaccination status was cross checked against medical records, risk of clinical measles infection in children who had seroconverted after vaccination was about zero (0 infections out of 2061 people exposed; 95% CI not provided).

Comment: **Benefits:** Many case control studies conducted during measles outbreaks have found that live measles vaccination (monovalent or MMR) protects against infection, with protective efficacy of about 95% or higher. Given the evidence for benefit already described, we have not included further details of these studies. In addition, and although not the focus of this topic, it should be noted that the MMR vaccine also protects people from mumps and rubella, which cause serious complications in non-immune people (mumps causes orchitis, pancreatitis, meningoencephalitis, deafness, and congential fetal abnormalities; congenital rubella infection causes deafness, blindness, heart defects, liver, spleen and brain damage, and stillbirth). **Harms:** In addition to the more reliable evidence described above, we found two case series. The first was a time sensitive, population based series of 473 children with childhood autism (see glossary, p 339) or atypical autism (see glossary, p 339) born between 1979 and 1998 and registered in five health districts in London, UK.[35] Of these children, 118 had documented evidence of developmental regression. The study found no trends for risk of developmental regression with respect to year of birth

from 1979–1998, although MMR vaccination was introduced in 1988. The study found that MMR vaccination was just as likely to precede or follow documented parental concerns about development, suggesting that the temporal relation of vaccination and onset of developmental problems was not compatible with a causal association (443 children with autism in whom timing of first parental concerns recorded; 26% vaccinated prior to parental concern about development *v* 26% vaccinated after parental concerns expressed; P = 0.83). The second series raised the question of a possible relation between MMR and developmental disorder in 12 children with bowel symptoms.[36] The series was retrospective (parents surveyed up to 8 years after vaccination), small; lacked a control group; and was selective in its sample. For these reasons, we found that the study does not establish MMR as a cause of inflammatory bowel disease, autism, or development regression, and that its hypothesis has been satisfactorily tested by scientifically reliable studies (see harms above).

GLOSSARY

Acute developmental regression Rapid loss of acquired developmental skills.
Atypical autism shares clinical features with autism but does not meet ICD-10 or DSM-IV diagnostic criteria.
Childhood autism ICD-10 or DSM-IV autism (comprising communication difficulties, problems with social interaction, and behavioural problems) in children aged under 3 years.
Combined measles, mumps, and rubella (MMR) vaccine Vaccine with components that aim to raise immunity to measles, mumps, and rubella infections. Contains live attenuated measles virus (Schwarz strain).
Herd immunity Background level of immunity in the community. A high level of herd immunity reduces risk of infection even in non-immune individuals, because there is no pool of at risk individuals who may transmit the infectious agent.
Live monovalent vaccine Commonly known as the single measles vaccine. Uses live, attenuated virus (most commonly Schwarz strain), and only to bring about measles immunity.
Seroconversion Development in the blood of specific antimeasles antibody. Seroconversion is a proxy for clinical efficacy.
Vaccine coverage Prevalence of vaccination in the community.

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Study Dismisses Fears Over Vaccine

By Emma Ross
AP Medical Writer
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LONDON — British experts have reviewed five decades of research on the vaccine for mumps, measles and rubella and have concluded there is no link to autism or bowel disease, as some parents have feared.

The review was commissioned by the British Medical Association after the number of British toddlers getting the shots began to drop, sparking fears that measles might make a comeback.

Experts say the new study and other recent authoritative reviews show definitively that there is no evidence of a connection between the inoculations and developmental and bowel problems in children, and that parents should be reassured the shots are safe.

However, parents who believe their children have been harmed by the vaccine, known as MMR, were not convinced.

Several groups, including the World Health Organization, the U.S. Institute of Medicine, and Britain's Medical Research Council have reviewed evidence investigating a possible link between the vaccine and autism, but the latest project, published Tuesday in the Internet version of the journal Clinical Evidence, is the most comprehensive.

"We looked through over 2,000 studies on millions of children, covering 50 years of research," said lead investigator Dr. Anna Donald, whose company, Bazian Ltd., analyzes the quality of medical research. The company was contracted by the publishing arm of the British Medical Association to conduct the review.

"The science is very rigorous and this really does give a green light to MMR," she said. "The science on this issue is over; the scientific debate is dead."

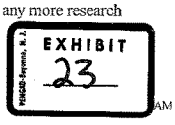
However, Ann Coote from Jabs, a British-based support group for parents who believe their children have been damaged by the MMR vaccine, said she believes the issue has not been settled.

"It's not new evidence. It's only old evidence rehashed," she said. "That's what's annoying parents – if we've got all this money to throw away on keeping on reviewing things, haven't we got the money to start new research and look into it once and for all?"

Fears over the MMR vaccine intensified in 1998 after a British study raised the possibility of a connection between the vaccine and developmental problems in 12 children with bowel ailments. The study was conducted about eight years after the children had been vaccinated.

By February of this year, MMR immunization in British 2-year-olds had dropped to 84 percent, well below the 95 percent specialists say is needed to prevent measles from returning. The decline prompted the British health authorities to launch a campaign to persuade parents the vaccine is safe.

Donald said there is no doubt more research on autism is needed, but she would not endorse any more research into the link between autism and MMR.



"This is a terrible distraction from limited funds that need to be looking at autism itself and not at something that has been answered more convincingly than most things we have ever tried to look at," she said.

Dr. John Clemens, a medical officer in the immunization program at the World Health Organization, said WHO will continue to monitor future vaccine safety studies but the U.N. health agency sees no need to spend more money to further investigate a link to autism.

Dr. Neal Halsey, director of the Institute for Vaccine Safety at Johns Hopkins University, said scientists should try to determine whether measles viruses linger in the intestines or other tissues, but the outcome of such studies would not alter his opinion that MMR is safe and effective.

On the Net: http://www.cdc.gov/nip/vacsafe/concerns/autism/default.htm Letter

http://www.jabs.org.uk