

NATIONAL IMMUNIZATION PROGRAM

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COMMITTEE ON APPROPRIATIONS
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FIRST SESSION

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NATIONAL IMMUNIZATION PROGRAM

WEDNESDAY, JULY 16, 1997

U.S. SENATE,
SUBCOMMITTEE ON LABOR, HEALTH AND HUMAN
SERVICES, AND EDUCATION, AND RELATED AGENCIES,
COMMITTEE ON APPROPRIATIONS,
Washington, DC.

The subcommittee met at 10:33 a.m., in room SD-124, Dirksen Senate Office Building, Hon. Dale Bumpers presiding.
Present: Senator Bumpers.

NONDEPARTMENTAL WITNESSES

STATEMENT OF PETER PARADISO, VICE PRESIDENT OF SCIENTIFIC AFFAIRS AND RESEARCH STRATEGY, WYETH-LEDERLE VACCINES AND PEDIATRICS

OPENING REMARKS OF SENATOR DALE BUMPERS

Senator BUMPERS. First I want to thank the chairman, Senator Specter, for calling today's hearing to discuss the development of new pediatric vaccines and the role industry and Government should take in ensuring that these new vaccines are made available to our Nation's children. I know he shares my commitment to improved preventive health care for children and to make the investments necessary to ensure that all children have ready access to vaccines that protect them from illness and death.

Today's hearing is an opportunity to celebrate breakthroughs on several fronts. In 1992 the public health community was reeling in the aftermath of a 3-year measles epidemic that resulted in 55,000 cases of measles and 132 deaths, mostly among preschool aged children. Coverage rates for preschoolers were abysmally low in many areas and this committee was struggling to find the resources to provide CDC with the tools to respond to the crisis.

Today, just 5 years later, we will hear testimony that the United States has achieved the highest coverage rates in recorded history. Even better news is that disease rates are at a new low and there is evidence that measles transmission in this country has been interrupted.

We will also hear exciting news about development of new vaccines that will protect our children against deadly and other costly diseases. One of the most promising products in the pipeline is a rotavirus vaccine that will have a dramatic effect on illness and death in young children. Worldwide, rotavirus kills 2,000 children every single day. In the United States alone, rotavirus is respon-

sible every year for 50,000 hospitalizations and 20 deaths among children under age 5.

Two vaccine manufacturers have rotavirus vaccines in the late stages of development and it is likely that at least one of those vaccines will be available as early as next year. We will hear today about these and other exciting developments that hold the promise of preventing thousands of cases of diseases and death among our young children.

As new vaccines have been introduced, industry has also made considerable progress in combining vaccines as a way of reducing the need for doctor visits and additional injections. Two combinations have come onto the market in the last year and at least 12 additional combinations are in some stage of development. Even beyond the human costs associated with death and disease in young children, the benefits of new vaccines and new combinations are clear. Immunization is still the most cost-effective preventive health strategy available. The cost-benefit ratio for vaccines varies from \$2.60 saved for every \$1 spent for pertussis vaccines to \$14.40—let me reread that.

The cost-benefit ratio for vaccines varies from \$2.60 saved for \$1 spent for pertussis vaccines to \$14.40 saved for \$1 spent for measles, mumps, and rubella vaccine.

But along with the benefits of this new generation of vaccines, there are new challenges. How can we maintain our high coverage levels in the face of a far more complex schedule? How can industry and Government improve collaboration to ensure that products are brought to market in a timely way? What steps should we take to reduce the risks of complications associated with a new generation of overlapping combination vaccines?

In this era of tightening budgets at the State and Federal level, how can we accommodate the increased costs associated with new products? How can the Federal Government make purchasing decisions in a way that provides maximum flexibility to the States and at the same time ensures competitive prices for new products?

We will not be able to answer all of these questions this morning, but I know that our witnesses will have a great deal to offer as we debate these issues over the next several years. I have asked Dr. Peter Paradiso of Wyeth-Lederle to lead off with an overview of where industry is today in development of new products. Dr. Walter Orenstein will follow with an update on coverage and disease rates and a summary of the challenges CDC has identified in implementing an improved and much expanded vaccination schedule. Then Dr. Michael Osterholm brings us the perspective of the State health community, which along with private pediatricians is on the frontline in delivering an increasingly complex regimen of vaccines.

After each of the witnesses has delivered his testimony, I will ask each of them to remain on the panel so we can discuss a number of the questions. I want to personally thank all of you on behalf of myself, the subcommittee, and, frankly, the American people for being here this morning and taking the time to prepare testimony on an increasingly new set of complex problems that we are faced with.

SUMMARY STATEMENT OF DR. PETER PARADISO

Dr. Paradiso, please lead off.

Dr. PARADISO. Thank you. Mr. Chairman, I am Dr. Peter Paradiso, vice president of scientific affairs and research strategy for Wyeth-Lederle Vaccines and Pediatrics, one of four companies in the childhood vaccine market. Before I begin, I would like to especially thank you, Senator Bumpers, for your long-time involvement and interest in childhood immunization issues. All of us who work to develop childhood vaccines will surely miss you and your input when you retire.

I will condense my submitted remarks to focus on three major topics: first, the positive effect that newly developed vaccines are currently having in the prevention of childhood disease; second, the promise of control of even more vaccine-preventable diseases over the course of the next decade; and third, to the extent time permits, the influence of Vaccines for Children [VFC] Program on vaccine research and development.

A decade ago, if I were sitting in this witness chair I would be able to discuss three very good childhood vaccines—OPV, MMR, and DTP. These vaccines have saved the taxpayers countless billions of dollars in direct and indirect costs over the years. They have now been joined by an impressive array of new products made possible by biotechnology that continue the tradition of safe and effective vaccines. These include a new acellular pertussis vaccine that responds to parent and provider concerns about adverse reactions, hepatitis B vaccine for infants that is greatly increasing protection against liver disease, and most recently a varicella vaccine to protect children against chicken pox.

All these vaccines are extremely safe, effective, and, an important consideration in the new world of managed care, also highly cost effective.

I would like to spend a few minutes discussing another of the new vaccines, the Haemophilus influenza type b, [Hib], conjugate vaccine whose development I was intimately involved in, as an example of the benefits attainable for society through childhood immunization. Prior to the development of the Haemophilus influenza type b conjugate vaccine, Hib infected 1 of out every 250 infants, 5 percent of patients died, and 30 percent suffered permanent central nervous system injury. Hib was the predominant cause of childhood meningitis, the leading cause of acquired mental retardation, and a major source of deafness and other neurological defects in children.

It was known for many years that antibody directed at the sugar saccharide coating on the surface of the bacteria would protect against disease. Unfortunately, young infants at the highest risk for disease are unable to respond to saccharide. If you look at the first chart, you will see a cartoon of conjugate technology that was used to develop the Hib conjugate and that is now being used to develop vaccines for pneumococcus and meningococcus, which we will hear more about today. The two components are the protein, with the big "P" there on the top—and that is a component because children as young as 2 months of age can respond to protein vaccines, like diphtheria, tetanus, and pertussis vaccines. The squiggly

green line is a representation of the sugar that coats the surface of the bacteria. If you make antibody to the sugar, then you will kill the bacteria and protect the children.

Unfortunately, children under 2 years of age cannot make or respond to the sugar. So what the conjugate technology did was to take the protein and attach it covalently to the sugar in a permanent way, so that when the child recognized the protein it also recognized the sugar because it was attached. The result was that infants were able to make a response to the sugar and protect against the Haemophilus b disease by attacking the surface of the bacteria.

This conjugate technology actually resulted in an immune response that nature did not naturally do from an infection and so children were unable to be protected.

The next chart shows the chronology of the development of Haemophilus vaccine. The bacteria was recognized in the late 1800's and it was really in the 1930's that people recognized that it was the sugar on the surface that was the important part of the bacteria to try to make a response to. But you can see there were many years in the use of that knowledge, and in 1973 it was shown that the sugar would work in older children, but would not work in younger children, and that something different was needed if you were going to protect the youngest infants who were at the greatest risk.

So in 1990 a vaccine that used that conjugate technology was shown to be effective in very young infants, and within a very short period of time—and here I have listed 1994—the disease was under control in the United States.

You can see on the next chart what I mean by that. In the United States in the 1980's, analysis by the Centers for Disease Control showed that there were approximately 20,000 cases of Haemophilus b disease every year and about 12,000 of those were meningitis. You can see that in the year 1991, a year after the introduction of conjugate vaccines, there was already a dramatic reduction in the total number of cases of Haemophilus disease, and that continued to go down, so that by 1993–94 about 95 percent of the disease was gone.

In 1992 they started recording the cases in children under 5 where the majority of these 20,000 cases were, and you can see that impact is even more dramatic.

The next slide shows you why the impact for this conjugate vaccine was even more dramatic than we would have expected by the amount of vaccine that was used. This is a population in northern California, where we did our efficacy trial for the conjugate vaccine. You can see that it shows from the year 1984 to the year 1995 the cases of Haemophilus b disease in various age groups within the population. The first arrow, red arrow, shows the time at which the polysaccharide vaccine was used, and it did not have much of an impact on total disease. The second arrow, the middle arrow there, shows when we started doing our efficacy trial, and now you can start to see a reduction in the number of cases of disease.

The yellow line here is the highest incidence in kids 17 to 18 months of age. The third red line is when the vaccine was actually introduced universally around the country in this population. What

is really remarkable about this slide and what it illustrates is that not only are the kids who were targeted protected, but also the kids who were not vaccinated or only partially vaccinated, and you can see that from the blue line, as well as the older children from the green line, who were also protected from disease.

PREPARED STATEMENT

The reason that they were protected was because the vaccine eliminated the carriage of the bacteria in the population. This effect is known as herd immunity, where you actually by vaccinating a majority of the population can protect the whole population because you have eliminated the bacteria. Those children are not carrying it, they do not spread it to their friends and siblings. So what you get here is a far more dramatic effect than you measured initially in your efficacy trials because you are protecting people in contact with those who have been vaccinated.

[The statement follows:]

PREPARED STATEMENT OF PETER PARADISO

Mr. Chairman and members of the subcommittee, thank you for the opportunity to testify today regarding vaccine research and development and the pipeline of new vaccines that will be introduced in the next decade and beyond. I am Dr. Peter Paradiso, Vice President of Scientific Affairs and Research Strategy for Wyeth-Lederle Vaccines and Pediatrics. Together with its predecessor companies, Wyeth-Lederle has developed and manufactured childhood vaccines for more than a century. Wyeth-Lederle is part of Wyeth-Ayerst, a division of American Home Products, which is one of the world's largest research-based pharmaceutical and health care products companies. American Home is a leader in the discovery, development, manufacturing, and marketing of prescription drugs and over-the-counter medications. It has a global presence in vaccines, biotechnology, agricultural products, animal health care and medical devices.

THE BIOTECHNOLOGY REVOLUTION

The 1990's have been an era of great progress in vaccine research and development. If I were sitting before this Subcommittee a decade ago, the story I would tell would be quite different. In the mid-1980's, the question was not which vaccines would be available in the future, but whether vaccines would be available at all. The industry confronted a severe liability crisis which threatened not only its financial well-being but public confidence in childhood immunization. Action taken by Congress at that time provided a measure of relief from the cloud of vaccine liability, and the advent of managed care has placed a new premium on preventive interventions like vaccines.

As a result of these changes in the environment, the vaccine industry is healthier than at any time during the past several decades. Nevertheless, there are still only four companies serving the American childhood vaccine market—Wyeth-Lederle and Merck (both U.S. companies), Pasteur Merieux Connaught, and SmithKline Beecham. In spite of being the most cost-effective approach to health care, vaccines account for only 1 to 2 percent of the U.S. pharmaceutical market, and even with robust growth over the next decade, vaccines will still account for only a small portion of the pharmaceutical market.

Congressional action and changes in the marketplace have been key elements of the progress in immunization. The primary impetus for new vaccine development, however, has been the availability of new tools provided by biotechnology. A decade ago most vaccines consisted of either inactivated or attenuated live organisms. For many diseases, these relatively straightforward approaches were adequate to stimulate immune responses. But for other diseases, the infant immune system did not respond to products manufactured in the traditional ways. New techniques, such as the use of recombinant or conjugation technology, have opened up many new possibilities for development of vaccines to deal with this problem.

An example with which this Subcommittee is familiar is the use of conjugation technology to prevent *Haemophilus influenzae* type b (Hib) disease—most notably meningitis—in infants. In the 1980's, several companies developed and brought to

the market Hib polysaccharide vaccines. These vaccines were purified capsular polysaccharide vaccines similar to the pneumococcal polysaccharide vaccines that are currently used in adults. Although the Hib polysaccharide vaccines were very safe, they were not effective in children younger than 18 to 24 months of age. Because Hib disease occurred mostly in children younger than 18 months, particularly those in day care settings, the polysaccharide vaccine was of limited utility. Therefore, it became a public health priority to develop a Hib vaccine that would benefit young infants who are at greatest risk of the disease.

In the second generation of Hib vaccines, a protein carrier is conjugated, or chemically linked, to the Hib polysaccharide. The benefit of these vaccines is that they can be effectively administered to infants as young as two months of age, thereby offering protection at the time of greatest exposure to disease. Prior to the development of conjugation technology, protecting young children from this disease was simply a dream. The conjugation technology that is necessary for the production of these Hib vaccines is now being used in the development of other new vaccines, including one that will protect against *Streptococcus pneumoniae*, also known as pneumococcus, which causes meningitis, bacteremia, pneumonia, and nearly 50 percent of childhood ear infections.

Although the principal explanation for progress in vaccine development lies in new scientific methods, government policies do matter. A favorable environment for vaccine research depends on a productive relationship between industry and government. Because the federal government is the largest single purchaser of childhood vaccines and also sets policy for the use of childhood vaccines, its power to influence vaccine development is great.

In order to maintain a healthy environment for vaccine research and development, we believe the government should coordinate with industry in the establishment of research priorities and in the conduct of research; pay a fair price for vaccines; support the use of preventive vaccines by the public; encourage a diversity of scientific approaches to the development of vaccines; support industry efforts to market vaccines globally; and strongly defend the safety of government-approved vaccines.

Industry, in turn, must respond to public health priorities in setting its research agenda; supply vaccine reliably and at a reasonable price; respond to provider concerns about immunization schedule confusion; and responsibly address public concerns about vaccine safety. I will return to our vision of an appropriate relationship between industry and government in more detail after reviewing vaccines recently introduced to the market and those that soon will be introduced.

NEW VACCINES

For many years after the initiation of the Section 317 immunization program, the federal government purchased only measles-mumps-rubella (MMR) vaccine, diphtheria-tetanus-pertussis (DTP) vaccine, and oral polio vaccine (OPV), and the task of fully immunizing a child was a matter of administering six shots and five oral doses of vaccine during the first five years of life. The members of the Subcommittee are well-acquainted with those vaccines and their benefits. Those vaccines have prevented much illness and loss of life, and they also have impressive cost-benefit ratios—1:11 for DTP and 1:14 for MMR.¹ It is also worth noting that the worldwide use of OPV has resulted in the eradication of wild polio disease from the Western Hemisphere and great progress in the global effort to eradicate polio by the year 2000.

Since 1990, four new vaccines and several new combination products have been introduced, and the potential to prevent childhood disease and save health care dollars has expanded dramatically. However, the introduction of new products has also created problems for the federal and state governments, pediatricians, public health officials, and parents. Providers and parents sometimes express concerns about the "confusion" created by a multitude of new vaccines and suggest they need a "simpler" schedule. While we agree that combination vaccines would simplify the immunization schedule, some thought should be paid to efforts to improve parent and provider education regarding changes and additions to the immunization schedule so that acceptance of new products occurs promptly. The use of new vaccines prevents children from suffering from disease and saves the health care system millions of dollars. Surely we can find a way to educate parents and providers concerning appropriate use of these life-saving products.

¹Hinman A.R., Koplan J.R., Pertussis and pertussis vaccines. *JAMA* 1984;251:3109–3113; White C.G., Koplan J.P., Orenstein W.A. Benefits, risks and costs of immunization for measles, mumps, and rubella. *AJPH* 1985;75:739–744.

Recently-introduced vaccines and their benefits are:

Haemophilus influenzae type b vaccine

Prior to the development of a Hib conjugate vaccine, *Haemophilus influenzae* type b, or Hib, infected one of every 250 infants; 5 percent of patients died; and 30 percent suffered permanent central nervous system injury. Hib was the predominant cause of childhood meningitis, the leading cause of acquired mental retardation, and a major source of deafness and other neurological defects in children. In the early 1990's, introduction of several Hib conjugate vaccines, including one developed and manufactured by Wyeth-Lederle, virtually eliminated Hib meningitis. In addition, the vaccine has resulted in savings of approximately \$2.5 billion annually in direct and indirect costs associated with Hib disease. As discussed above, this vaccine is the result of conjugate technology that was perfected only a few years before the vaccine's introduction.

Acellular pertussis vaccine

For decades, we have used a very effective whole cell pertussis vaccine to protect children against whooping cough. In the mid-1980's, parents began to refuse use of the whole cell pertussis vaccine because of the perception of adverse events associated with the vaccine. Declines in immunization rates led to pertussis outbreaks. It later became clear that whole cell pertussis vaccine posed little if any risk of serious reactions, but public confidence in the vaccine was damaged. Accordingly, public health experts identified their number one immunization priority to be the development of a pertussis vaccine that was composed of purified parts of the bacterium, rather than the entire inactivated organism. This acellular pertussis product was thought to be safer than the whole cell vaccine. The vaccine industry responded by developing a number of new acellular vaccines. Three acellular products for infant use have been introduced in the last year, and additional entrants to the market are possible. The new acellular pertussis vaccines have fewer side effects—both local ones like redness and swelling and systemic ones like fever—than the whole cell pertussis vaccine, and their development was seen as critical to ensuring continued parent and public confidence in the childhood immunization program.

Hepatitis B vaccine

Hepatitis B is a very serious liver disease, predisposing infected individuals to liver cancer. A plasma-derived hepatitis B vaccine has been available in the United States since the 1970's, but the vaccine was not widely accepted because of concerns about its safety and the reliability of supply. Development of a recombinant product began in 1975, and the recombinant vaccine was introduced to the market in 1986 by Merck and SmithKline Beecham. This vaccine was originally recommended for use in high risk individuals, including infants, or those born to mothers infected with hepatitis B, but this strategy was not effective at reaching all of those at risk.

In the United States, hepatitis B is most commonly transmitted through sexual contact or intravenous drug use. It is not routinely considered a disease of childhood. However, the absence of a routine adolescent immunization program has convinced many public health experts that administration of hepatitis B vaccine at infancy is appropriate to ensure vaccination compliance. After initial resistance to use of the vaccine, most pediatricians and others immunizing infants have added it to the infant schedule. A recent report indicates some problems in tracking and monitoring the infants born to hepatitis B mothers and recommends stronger centralized tracking and case management systems. The difficulties associated with the perinatal immunization program for these mothers and infants underscore the need for universal hepatitis B immunization as part of routine immunization services.² The importance of this vaccine is further supported by a study that documented the reduction in incidence of liver cancer in Taiwanese children since the institution of a universal hepatitis B vaccination program.³

Varicella vaccine

In 1995, after more than twenty years in development, Merck's varicella, or chickenpox, vaccine was approved by the Food and Drug Administration (FDA). The vaccine is now recommended for routine use to protect children from chickenpox. Although normally a relatively mild disease, chickenpox afflicts a small fraction of patients with much more serious symptoms, including bacterial infections of skin lesions, pneumonia, dehydration, encephalitis, and hepatitis. Parents lose a consider-

² CDC. Program to prevent perinatal hepatitis B virus transmission in a health-maintenance organization—Northern California, 1990–1995. *MMWR* 1997;46:378–380.

³ Mei-Hwei Chang, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. *NEJM* 1997;336: 1855–1859.

able number of work days when their children have chickenpox, and use of the vaccine prevents not only the disease but also parents' lost work days. An analysis of the vaccine's cost-effectiveness concluded that routine use of the vaccine will save \$400 million a year in total societal costs.⁴ Hospitalizations for varicella and the costs of those hospitalizations have been found to be greater than estimated in the original cost-effectiveness study,⁵ so the total savings associated with use of the vaccine are probably also higher than the initial calculation.

Hepatitis A

Hepatitis A is a highly contagious disease which is usually spread by fecal-oral transmission. In the U.S., hepatitis A is cyclical, but the rate of incidence has increased gradually since the early 1980's. Disease symptoms may vary considerably, from mild and transient to severe and prolonged, and may include fever, nausea, vomiting, and diarrhea, followed by jaundice in many adults. A new hepatitis A vaccine has been approved for use in the United States, but this vaccine is not recommended for routine use in young children. The vaccine is recommended for use by travelers to countries where hepatitis A is endemic and for certain other populations.

THE VACCINE PIPELINE

The promise of the vaccine pipeline is truly impressive. New products will protect children and adults against an increasing number of diseases; influence the practice of pediatric and adult medicine; meet the challenge of antibiotic-resistant infections; and revise our thinking about vaccines, which may be used as therapy rather than just as prevention.

I will confine my remarks today primarily to pediatric vaccines. Although several of the pediatric vaccine companies also have active HIV, herpes, *Helicobacter pylori*, and melanoma vaccine development efforts, to name a few, I will not discuss those R&D pipelines today. Among the new pediatric vaccines that are in the pipeline are:

—*Rotavirus*.—Rotavirus is the most common cause of severe diarrhea among children and strikes virtually every child by the age of four. The direct medical costs associated with rotavirus are more than \$400 million annually—primarily the result of the fact that young children can get dangerously dehydrated very quickly—and the total societal costs are over one billion dollars annually. In less developed countries, rotavirus is a major killer of young children. My company has recently filed an application for a new vaccine that will protect children against 80 percent or more of serious diarrhea caused by rotavirus.

—*Streptococcus pneumoniae*.—Perhaps the most pressing issue facing pediatricians today is the emergence of antibiotic-resistant strains of *Streptococcus pneumoniae*, which is a major cause of pneumonia and meningitis in infants and the number one cause of otitis media, or ear infection, in all children. According to the Centers for Disease Control and Prevention (CDC), the way to address the looming problem of antibiotic resistance in *S. pneumoniae* is to develop vaccines which will prevent infection with the organism.⁶ Industry is committed to the development of a pneumococcus vaccine for infants, and this vaccine will respond to the public health crisis of antibiotic-resistant strains of *S. pneumoniae*.

Vaccines to protect against *S. pneumoniae* will have a significant impact on pediatric practice, because as many as half of all sick-child visits are attributed to ear infections, and as many as half of those infections are caused by *S. pneumoniae*. Globally, *S. pneumoniae* is the largest cause of pneumonia in young infants, and pneumonia is the single largest cause of deaths.

—*Sexually transmitted disease vaccines*.—Several companies are pursuing vaccines that will protect adolescents against sexually transmitted diseases. The vaccine that is probably closest to the market is the herpes simplex vaccine, although work on a vaccine to prevent human papilloma virus disease—including cervical cancer—is also proceeding. Some have suggested that hepatitis B vaccine, which is now given to infants, should instead be routinely delivered to older children, as is done in Canada, and serve as the “anchor” for a combination vaccine product to protect against sexually transmitted diseases.

⁴Lieu TA, et al. Cost-effectiveness of a routine varicella vaccination program of U.S. children. *JAMA* 1994;271:375–381.

⁵Seward presentation on varicella vaccine, Advisory Committee on Immunization Practices, June 16, 1997.

⁶Breiman R.F., et al. Emergence of drug-resistant pneumococcal infections in the United States. *JAMA* 1994;271:1831–1835; CDC. Defining the public health impact of drug resistant *Streptococcus pneumoniae*: report of a working group. *MMWR* 1996;45 (no. RR-1).

While some are concerned that it will be difficult to achieve high vaccination compliance among adolescents, others believe vaccines present an opportunity to keep adolescents in the health care system or to make schools the site for preventive care for adolescents. Additional vaccines that might be administered in adolescence—but which are not as far along in development—include vaccines to protect against Epstein-Barr virus and cytomegalovirus.

- Respiratory syncytial virus.*—Respiratory syncytial virus (RSV) is the major cause of lower respiratory tract illness in infants and young children. It is often associated with pneumonia and bronchiolitis. RSV produces sizable epidemics in major urban centers during the winter season, resulting in an average of 100,000 hospitalizations and approximately 5,000 deaths annually. Several companies have research efforts directed at development of an RSV vaccine, and clinical trials are underway.
- Lyme disease and rabies.*—At the most recent meeting of the Advisory Committee on Immunization Practices (ACIP), there were presentations from vaccine companies regarding the development of a vaccine to prevent Lyme disease and a vaccine to prevent rabies. These vaccines are outside the group of products that might be commonly thought of as childhood vaccines, but I mention them to illustrate the range of research on new preventive vaccines.
- Influenza vaccine.*—There is also ongoing research on an influenza vaccine for children. This project is noteworthy not only because it would be the first flu vaccine that is effective in children but also because of its route of delivery. One promising candidate vaccine could be administered as a nasal spray instead of an injection, thereby easing its administration and perhaps improving compliance with the requirement of annual reimmunization against influenza.
- Adult immunization.*—An area of great interest is the development of new vaccines and improvement of existing vaccines for adult use. Currently, influenza vaccine and pneumococcal vaccine are recommended for use in adults, although compliance with the adult recommendations—despite ready Medicare payment for senior citizens—is still low. Research is concentrated on improving those vaccines so that usage could be encouraged. In addition, there is a great deal of interest in use of the acellular pertussis vaccines—only recently approved for infants—as a booster in adults. There are still several thousand cases of pertussis in the United States annually, and many believe the disease will not be brought under control until adults are immunized and no longer carry the organism.
- Other age-appropriate immunization strategies.*—Aside from adult immunization, there are other cohorts who are legitimate targets for immunization beyond those currently contemplated in the immunization program. One way of dealing with the proliferation of new antigens and the accompanying increase in injections is to identify certain diseases as preventable through either maternal—i.e., prenatal—or adolescent immunization. Infections with organisms like Group B streptococcus and RSV in infants during the first months of life may be preventable through maternal immunization, and vaccines to prevent sexually transmitted diseases could be delivered in adolescence.
- Combination vaccines.*—All vaccine companies are investing considerable resources in the development of new combination products that will reduce the number of injections required for full immunization. Several of the vaccines you are familiar with are combination vaccines—for example, diphtheria-tetanus-pertussis vaccine and measles-mumps-rubella vaccine are combination vaccines. Even polio vaccine is technically a combination vaccine because it contains three strains of polio virus. Public health experts are pressing for more antigens to be combined into one shot.

Vaccine companies enjoyed great success when we combined diphtheria-tetanus-whole cell pertussis vaccine with Hib vaccine, and pediatricians and public health providers enthusiastically accepted that new combination, which simplified the immunization schedule by reducing the number of injections required at the 2-month, 4-month, and 6-month visits. Our success on that combination might have left pediatricians and others with the impression that developing combination vaccines is a relatively straightforward and easy process. Instead, we have found the next logical combination product to be a real scientific challenge. When acellular pertussis vaccines were introduced for toddlers—and recently for infants—vaccine companies turned their attention to developing a Hib-containing combination that would include acellular pertussis vaccine in place of the whole cell pertussis vaccine.

Those vaccines have posed very difficult development problems. Although we are not certain of the mechanism of interference, in most cases the acellular pertussis component of the vaccine seems to decrease the immunogenicity of the Hib component in infants who are administered the combination product, compared to those

who receive the vaccines separately. Companies are trying new strategies to eliminate this interference problem and are also developing combinations of Hib with vaccines other than DTaP that will not result in decreased protection, compared to separate vaccines.

Because of the complexity of the infant immunization schedule, companies now evaluate new candidate vaccines in ways we did not in the past. We look closely at the route of administration of the vaccine: is it possible to administer the vaccine orally, in order to avoid an additional injection, and is the vaccine a good candidate for combination with other antigens? Vaccine companies are developing new technologies for vaccine development, including new adjuvants that will enhance the responses to vaccines and reduce the number of doses required for protection against disease, and time release mechanisms that will allow delivery of a full immunization series in a single shot. I am confident that we will be successful in keeping the schedule as simple as possible while enhancing its medical value.

ROLE OF THE GOVERNMENT IN VACCINE RESEARCH AND DEVELOPMENT

There has been a great deal of rhetoric in recent years about how government and industry must be partners in the vaccine development process. As a vaccine researcher and developer for 13 years—in a start-up biotechnology company and in a vaccine division that has been part of two large corporations—I have strong views about how government policies affect the ability of private vaccine companies to provide a reliable supply of vaccines and develop new vaccines. If public-private collaboration is to be successful, there must be balance and predictability in the relationship between industry and government.

The Federal Government as Vaccine Purchaser

Prior to enactment of the Vaccines for Children (VFC) program in 1993, the federal government had been for many years the single largest purchaser of vaccines in the U.S., with federal purchases, at dramatically discounted prices, ranging up to 50 percent of the total market. The equilibrium that existed prior to VFC no longer exists, and the federal share of vaccine purchase appears to be steadily increasing. Aside from the volume of VFC purchases, other elements of the program are having an impact on industry sales and revenue, with an almost inevitable future effect on vaccine research and development.

Whether a vaccine company is a small start-up operation or an existing division of a large corporation, development of new vaccines will occur only if revenues from vaccine sales are available to support the R&D effort. The imposition of outright price controls on vaccines under contract with CDC as of May 1993 has been a cause of concern among vaccine developers, both for its immediate impact and for its precedential effect. This concern has been voiced not only by the major manufacturers but also by smaller biotechnology companies with vaccines or vaccine-related products in development.

When VFC was enacted, there were specific inducements to industry included in the legislation. The prices of new vaccines were to be controlled by the market, not by government. Moreover, industry was promised rapid uptake of new vaccines by virtue of the fact that the VFC entitlement did not require congressional action. In addition, rather than the former winner-take-all practice in federal contracting, the legislation provided for multiple suppliers, a measure that was intended to provide stability in market share where more than one company had an approved vaccine.

With respect to decisions to cover new vaccines, the VFC statute gave unusual authority to the CDC's ACIP in order to ensure that decisions would be based not on budgetary considerations but on the public health. The VFC Conferees stated: The Conferees intend that the Advisory Committee on Immunization Practices be allowed to conduct its work in an objective manner, concerned only with issues of public health and medicine. While decisions regarding the list of recommended vaccines will, undoubtedly, have some budget implications for the program and the Secretary, it is the Conferees' intention that the ACIP's work be rigorously separated from such concerns.⁷

Intent on avoiding previous circumstances in which vaccines had been recommended by the ACIP but not purchased promptly by the federal government because of budgetary concerns, Congress effectively made the decision to cover vaccines under VFC automatic once the ACIP had made its recommendation. In fact, the Conferees stated their specific intention "that the Secretary provide for Feder-

⁷ 139 Cong. Rec. H6173 (daily ed. Aug. 5, 1993).

ally vaccine-eligible children the same vaccines that are recommended for children with their own source of payment.”⁸

Unfortunately, at some point in the implementation of the VFC program, this congressional intent appears to have been lost. Now, the ACIP is being encouraged to conduct a rigorous cost-benefit analysis before making a decision about VFC purchase. A consideration of the costs and benefits of a vaccine is routinely part of the ACIP discussions surrounding the development of a recommendation for general usage of a vaccine, but the advisory committee is now repeating that analysis—in fact, in some cases asking for additional data on costs and benefits—before making a purchase decision. This approach has resulted in a delay in the acceptance of certain new vaccines—most recently, the varicella vaccine—while ACIP weighs matters of cost.

This is troubling to manufacturers because we now have a very large purchaser of vaccines that does not necessarily accept its own decisions regarding routine vaccine usage and delays the uptake of new products. The whole idea undergirding the VFC program was to make the same vaccines available to all of America’s children, whether rich or poor, whether in the private or the public sector. Yet the two-step process by which the ACIP is reviewing new vaccines—first making a general recommendation, then proceeding to consider whether the vaccine should be covered by VFC—is inherently creating a two-tiered immunization system. With respect to varicella vaccine, the ACIP has issued a very broad recommendation, but has bridled at the same scope of coverage for purposes of VFC purchase. We hope Congress will give the CDC and ACIP some direction about its intent when it drafted the VFC program and its hope that new vaccines would be quickly integrated into the new program.

Another potentially troubling aspect of VFC implementation involves contracting approaches or ACIP policy statements that might serve to restrict availability of individual vaccine products to providers. This stems from a desire to lessen perceived “confusion” among providers regarding new vaccines and the new vaccine schedule. Either through restrictive contracting or through encouragement to limit choices, the prospect is raised that providers may not have the full range of options in selecting specific vaccines. Industry regards this as a potential breach of the legislation’s promise of multiple suppliers for each antigen. In our experience, providers are able to make sound choices among the available products. Like any prudent purchasers, providers reward quality and convenience in use while keeping an eye on product price. Restricting provider choice is a step backward that is inconsistent with the spirit of VFC.

The Federal Government as a Research Funder

An ideal theoretical division of research responsibility between the public and private sectors would have the federal government fund basic research while industry supports clinical or applied research. In practice, however, the relationship is more complicated. Vaccine companies perform a substantial amount of basic research, especially in areas that have generally not been explored by others. At the same time, the federal government has been a major funder of a variety of clinical vaccine research.

As a general proposition, industry should take responsibility for financing and conducting the clinical trials that lead to FDA approval of vaccines for routine use in children. We believe that the federal government has a role to play in some clinical research. For example, certain clinical trials would not be undertaken if the federal government did not choose to fund them. The trial of adult acellular pertussis vaccines that the National Institute of Allergy and Infectious Diseases (NIAID) has recently agreed to fund may be one such example. Federal maintenance of a clinical trials network has also contributed to the high degree of clinical trials expertise and ready availability of an infrastructure for conducting trials, and that effort could not be readily duplicated in the private sector.

However, the federal government should not fund trials of products where companies are willing to support the trials. This is an unnecessary commitment of federal resources, and it creates a situation in which the government may give one company an advantage over others. The advantage is not restricted to the results of the trial but also to what amounts to an endorsement of a product. In addition to providing an immediate advantage in terms of avoiding the substantial cost of a clinical trial, government funding creates a perception that one product may be favored over others in the process of review and approval by other government agencies, including both FDA and the ACIP.

⁸ 139 Cong. Rec. H6173 (daily ed. Aug. 5, 1993).

The Federal Government As Defender of Childhood Immunization

Despite the fact that public confidence in the safety of childhood vaccines is much higher than prior to enactment of the injury compensation system, there remain small but vocal groups who are quick to exaggerate problems with these products, which are overwhelmingly safe and effective. It does not take much misinformation to dissuade parents from immunizing their infants. Several years ago, for example, the selection of a hearing-impaired Miss America led to public statements that her disability was the result of a DTP shot in infancy. Fortunately, her pediatrician corrected the public record by noting that in fact Miss America was deaf as a result of a childhood Hib infection. Now, of course, Hib conjugate vaccines make this condition largely a thing of the past.

We believe the federal government should take as one of its primary responsibilities the defense of childhood immunization against irrational fears unsupported by data. At present, vaccines are under attack from a variety of sources who are willing to take advantage of the most remote theoretical possibility of adverse reactions. Federal agencies should utilize their not insubstantial public relations capacities to deal promptly and aggressively with scientifically unsound assertions that threaten public confidence in vaccines.

The Federal Government's Role in Global Immunization

As important as childhood immunization is in the United States, it can no doubt accomplish even more in developing countries around the globe. Financial aid from the U.S. and the significant private sector support of organizations like Rotary International will never be adequate to address all the global opportunities for prevention of disease through immunization. Wyeth-Lederle, which has been mostly a domestic supplier of vaccines, would like to do our part to prevent disease in developing countries where the need is most acute.

Several of our new vaccine products could have their greatest impact in the developing world, but there are many hurdles before we can become an effective global vaccine company. One concern that could be alleviated by U.S. governmental action is that relating to differential pricing of products between developing and developed countries. During the 1993 debate over the VFC program, vaccine companies were unfairly targeted as selling products in the U.S. at a higher price than abroad. Our company, which at that time sold very little vaccine internationally, could truthfully say that our prices in the U.S. were no higher than in other countries.

For the future, however, that cannot be the case if we expect life-saving vaccines to reach the developing world. Those countries simply lack the resources to pay fair value for new vaccines like those to prevent rotavirus or pneumococcal disease. As a result, prices in the United States and other developed countries must be high enough essentially to subsidize the cost of delivering the same vaccines to developing countries. In fact, European-based vaccine companies have long supplied vaccines like DTP, OPV and measles to world health agencies at greatly discounted prices. Polio eradication would not be possible if this had not been true. The practice of subsidizing revenues from sales in less developed countries with revenues from sales in developed countries should not subject a company like mine, which is seeking to globalize what has been a domestic business, to unfair criticism. U.S. government policy should specifically recognize the legitimacy of differential pricing as a way of meeting our moral obligation to the less fortunate countries of the world. Furthermore, as the global polio eradication campaign demonstrates, control of diseases overseas can have a direct beneficial impact on disease levels in the U.S.

CONCLUSION

This is an exciting time for vaccine research and development. Over the course of the next few years, there will be a number of new vaccines that will protect American children from dreaded diseases. A decade ago, Members of this Subcommittee were concerned that suppliers of the three childhood vaccines then in use would desert the market and the federal government would be searching for emergency vaccine supplies.

Now, providers' and consumers' complaints relate more often to the wealth of new products and the confusion of the immunization schedule. Industry is confronting the challenge of schedule confusion by working hard to develop new combinations that will not compromise the effectiveness of the separate products, and the federal and state governments must be very involved in educational efforts regarding schedule additions and changes.

From time to time, there are proposals to develop comprehensive research and development plans for new vaccines under the auspices of this or that government agency. The history of vaccine research and development does not support the no-

tion that government planning makes a significant contribution to the process. Instead, vaccines have been developed as a result of solid basic science forming a foundation for clinical development. When the science is ready, the vaccines will follow—and not before.

In my testimony, I have recounted only research successes or promising avenues of exploration. For all these successes, there are many more projects that have not borne fruit in the form of new products. Vaccine research is risky and can thrive only when those supporting it—including both the federal government and the investment community—understand and accept those risks.

For the industry to remain a reliable supplier of vaccines and developer of new products to protect against additional disease, we must have a stable, predictable, and cooperative relationship with the government if it remains the major purchaser of vaccines. We believe that a true partnership can produce exciting new possibilities for preventing childhood disease.

APPENDIX 1

HIGH-RISK POPULATIONS ARE PROTECTED

Improvements in immunization coverage have reached populations with a high burden of vaccine-preventable diseases and low immunization coverage. Measles among preschool children has been a marker for underimmunization. The disease had disproportionately affected urban areas and racial and ethnic minority populations during the resurgence of 1989–1991 as a result of undervaccination of preschool children. However, measles has now virtually disappeared from these populations. Between 1989 and 1991, 55,622 cases were reported across the country. In contrast, between 1993 and 1996, 2,072 cases were reported. In New York City during the 1989 to 1991 resurgence, there were 3,144 reported measles cases, but only 51 cases were reported from 1993 to 1996.

Improved immunization coverage against measles is a major reason for these decreases. Studies of children who were two years of age during the mid to late 1980's in 15 large urban areas, documented a median measles vaccination coverage of 67 percent, ranging from 52 to 78 percent. In contrast, data from the same 15 urban areas from the 1995 NIS documented a median coverage of 89 percent, ranging from 81 to 97 percent.

Successful Strategies

CDC and its partners are implementing strategies that work. Improved coverage is a result of State and local areas' implementing proven strategies that increase immunization rates. In Chicago, for example, a 1994 survey of five Housing Authority units showed that MMR coverage among 19- to 35-month-old children was 62 percent. A 1996 follow-up survey showed that MMR coverage had increased to 76 percent. This increase intensified linkages with the U.S. Department of Agriculture's Special Supplemental Nutrition Program for Women, Infants, and Children (WIC), using outreach workers to bring children into the health care system, and using a mobile van to improve access to care.

Linking the WIC program with assessment of immunization status has been highly effective in increasing coverage in areas of underimmunization. For example, data from three cities, between June 1995 and May 1996, found that immunization coverage of WIC participants improved 24 to 33 percentage points within 12–15 months of starting interventions (Table 4).

TABLE 4.—RESULTS OF WIC/IMMUNIZATION LINKAGE EFFORTS IN SELECTED CITIES

Location	Number of sites	Percent of births in WIC	Preintervention results	Postintervention results	Project period
Chattanooga	4	55	57	84	12
Boston	12	35	39	63	15
Chicago	48	55	56	89	12

Note: Children 24 to 27 months of age.

Despite these successes, underimmunized populations continue to exist, and we must continue efforts to further address these areas.

Pockets of need are being identified and addressed

CDC has been working closely with States and urban areas to improve coverage. In 1997, all States were required to describe how they will identify concentrations

of underimmunized populations and the measures they will take to improve coverage. CDC suggests various means of identifying underimmunized populations, such as use of coverage data from local surveys, clinic assessments, and/or use of surrogate measures including poverty status, which has been shown to correlate with low immunization coverage. Proven approaches, such as linking immunization with the WIC Program, clinic and provider assessments with feedback of results to decisionmakers who can improve performance, reminder and recall systems, and immunization registries are being employed by States and urban areas. In addition, they are implementing other innovative strategies, such as increased outreach and education.

Other CDC activities are also aimed at improving coverage and reducing disease. At the direction of Congress, CDC awarded funds last year to support childhood demonstration projects in community health networks in three urban areas, Detroit, San Diego, and New York City, and one rural area consisting of four counties in Colorado. These projects will demonstrate whether an academic medical center, as a leader of a community health network, can raise immunization coverage by using interventions to improve clinic immunization practices and conducting outreach.

Also at the direction of Congress, CDC awarded immunization funds to four school-based demonstration clinics in New York, West Virginia, South Dakota, and Wisconsin to determine if these school-based clinics can help raise immunization rates in their communities. Finally, in collaboration with the U.S. Department of Housing and Urban Development, CDC recently awarded funds to support immunization demonstration projects in public housing authorities, where children at risk of underimmunization are likely to reside. Selected cities include Kansas City, Little Rock, Chicago, and Philadelphia. These projects will be important in determining methods to improve immunization coverage among children living in public housing.

HIB VACCINE ON TRIAL IN GAMBIA

Senator BUMPERS. Dr. Paradiso, I am reluctant to interrupt you, but I just read a thing in the World Health Organization where the Hib vaccine is on trial in Gambia.

Dr. PARADISO. Yes.

Senator BUMPERS. Why—and it says that from all appearances it is going to be as effective in African countries as it is in industrialized nations.

Dr. PARADISO. Yes.

Senator BUMPERS. What is the difference? I found that intriguing.

Dr. PARADISO. The major difference is that Haemophilus b in developing countries and in Africa, where this was done in the Gambia, the biggest problem is in pneumonia, and Haemophilus b causes pneumonia in that population. So the question was, first of all, whether in that population those children would respond to conjugates at a very young age the same way people in developed countries do, and the answer to that was yes, and you do prevent the same kind of disease we see here.

But what they also found out was that they also prevented against pneumonia, and they found out that a large portion of pneumonia was from Haemophilus on the basis of how much pneumonia went down as a result of vaccinations.

So the World Health Organization has now targeted Haemophilus conjugate as the next vaccine to add to their program, along with hepatitis B, for global immunization.

The vaccine pipeline contains a wealth of new products, which I have described in some detail in my written statement. We also have prepared a few charts for the research pipeline for the four vaccine companies currently serving the U.S. pediatric population.

The first charts shows the products that are under development at SmithKline Beecham and at Wyeth-Lederle Vaccines, my com-

pany. The second chart, on the other side, show the vaccine development for Merck Co., as well as Pasteur Merieux Connaught.

I am not going to go over this list of vaccines, but it shows you the impressive array of vaccines that are currently in some point of research and development within these companies. They include vaccines, for instance, they include vaccines for adolescents, for sexually transmitted diseases, for elderly where we are recognizing that they become susceptible to childhood diseases again as they get older and their immune systems become compromised. So there is an impressive array of vaccines that all these companies are working on and that the public sector is working on to take advantage of the cost effectiveness of vaccines.

Because I have limited time today, I will discuss only the two new antigens which will probably be introduced into the childhood immunization schedule soon. The conjugation technology which I spoke to you about and that was necessary for the production of the Hib vaccines is now being used to develop several new vaccines, including one that will protect against streptococcus pneumoniae, also known as pneumococcus, which causes meningitis, bacteremia pneumonia, and nearly 50 percent of childhood ear infections.

One of the most pressing issues facing pediatricians today is the emergence of antibiotic-resistant strains of pneumococcus. In some locations nearly 40 percent of strains are resistant. According to the Centers for Disease Control, the way to address the looming problem of antibiotic resistance to pneumococcus is to develop vaccines that will prevent infections by the organism. Industry is committed to developing these vaccines. Several companies are dedicating considerable resources to this effort and a number of candidate vaccines are already in clinical trials.

The pneumococcal vaccine will include seven or more strains of streptococcus pneumoniae, thereby providing protection from a broad spectrum of pneumococcal infections.

Streptococcus pneumoniae vaccines were identified in 1986 by a special panel of the Institute of Medicine as one of the five high priority category vaccines for the developing world. This designation is explained by the fact that pneumococcus is the largest cause of pneumonia in young infants globally and pneumonia is the single largest cause of deaths worldwide.

Another vaccine that the Institute of Medicine panel included in the high priority category for the developing world as a candidate for accelerated development in the United States is the rotavirus vaccine. Rotavirus is the most common cause of severe diarrhea among children and strikes virtually every child by the age of 4. The direct medical costs associated with rotavirus are more than \$400 million annually, primarily the result of the fact that young children can get dangerous dehydrated very quickly, and the total societal costs are over \$1 billion annually.

The impact of rotavirus goes beyond our borders. In less developed countries rotavirus is a major killer of young children.

The rotavirus vaccine also answers the concern of immunization providers that researchers reduce the number of injections required for full vaccination and utilize oral and other routes of delivery whenever possible. My company has recently filed an application

for a new oral rotavirus vaccine that will protect children against 80 percent or more of serious diarrhea caused by rotavirus.

This is an exciting time for vaccine research and development. Over the course of the next few years there will be a number of new vaccines that will protect American children from dreaded diseases. A decade ago, members of this subcommittee were concerned that suppliers of the three childhood vaccines then in use would desert the market and the Federal Government would be searching for emergency vaccine supplies. Now, in contrast, there is reference to an embarrassment of riches as the question is how to smoothly integrate the new life-saving products into the childhood immunization schedule.

As these comments suggest, biotechnology is revolutionizing childhood immunization. Another important influence on the vaccine research and development is the increased participation of the Federal Government. No example of Government involvement in the process has made a greater impression on vaccine companies than the Vaccines for Children Program enacted in 1993. As you know, the VFC Program was of great concern to the vaccine industry because it gave the Government unprecedented power to purchase vaccines and impose price caps. We argued at the time of the enactment of VFC that the combination of price controls and expanded public market might have a devastating impact on vaccine research and development.

In response, the administration offered and Congress incorporated into VFC certain features intended to allay these concerns. In order to provide stability in the marketplace and support vaccine research and development, VFC envisions contracts with multiple suppliers and promises that new vaccines will not be subject to a price cap. Moreover, companies introducing new vaccines were led to believe that their products would have the benefit of immediate uptake by the VFC program as coverage would be virtually automatic once an ACIP recommendation had been issued.

To avoid a repeat of situations where the Federal Government failed for extended periods of time to purchase new recommended vaccines, notable examples being hepatitis B, acellular pertussis for toddlers, and combination DTP-Hib, coverage decisions were delegated to the ACIP. Congress believed that the ACIP would be driven only by public health and medicine and not by budgetary considerations. Therefore, Congress directed the Secretary to ensure that those children who are eligible for VFC would automatically receive the same vaccines as those generally recommended by the ACIP and received by children in both the public and the private sector.

Unfortunately, at some point in the implementation of the VFC program this congressional intent appears to have been lost. In implementing VFC, CDC has instructed the ACIP to follow a two-step process. This has resulted in a very difficult task for committee members, whose expertise is in medicine and public health. Their decisions should be based on their expertise.

Rather than relying on general recommendations developed strictly on public health grounds, the ACIP now engages in a second evaluation that seems to involve reconsideration of cost effectiveness. This approach has resulted in delay in the acceptance of

certain new vaccines, most recently the varicella vaccine, while ACIP weighs matters of costs.

We do not believe that Congress intended the current two-step process that CDC is employing for VFC coverage decisions. How does this affect vaccine research and development? The lead time for the development of new vaccines is extremely long. Companies can expect to wait a decade or more before new basic research is translated into vaccines in the marketplace. Before investors will dedicate resources to potential new products, they must have some assurance that there will be a market for them.

With the advent of managed care, most of us are secure that our products will be welcomed in the private sector as cost-effective alternatives to hospitalization and other expensive treatment interventions. We need to also be confident that the Federal Government will be a stable and reliable purchaser of our new vaccine products and accept new vaccines at a fair price, at least as long as the Government remains our major customer.

The promise of new vaccine R&D is impressive. Vaccines are among our most humane and effective medical tools and, unlike most other interventions, are not only cost effective but cost beneficial. However, they will save neither children nor costs if they are not used. Industry is doing its part by making vaccines available. Government's role should be to ensure that they are used through public education, support for vaccine research where appropriate, and a reasonable and balanced purchase program.

Thank you for this opportunity, and I welcome your questions.

Senator BUMPERS. Thank you very much, Dr. Paradiso, for that excellent statement.

STATEMENT OF WALTER A. ORENSTEIN, M.D., DIRECTOR, NATIONAL IMMUNIZATION PROGRAM, CENTERS FOR DISEASE CONTROL AND PREVENTION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Senator BUMPERS. Dr. Orenstein.

Dr. ORENSTEIN. Thank you very much, Mr. Chairman. I am Dr. Walt Orenstein, Director of the National Immunization Program at the CDC. I am pleased to appear before the subcommittee to discuss future vaccine development.

I want to thank you personally and the subcommittee for the support and leadership you have provided to assure that our Nation's children are fully protected against vaccine-preventable diseases. Your support has contributed much to our success.

ACHIEVEMENTS IN CHILD IMMUNIZATION INITIATIVE

As you mentioned in your opening statement, this Nation has made unprecedented progress toward our goals of eliminating or reducing vaccine-preventable diseases. Provisional data for 1996 show that record low levels were set or tied for mumps, tetanus, polio caused by wild viruses, and invasive Haemophilus influenza. Fewer than 500 measles cases were reported, down from almost 28,000 cases in 1990, and all of the cases in 1996 are believed to be due to recent importations from abroad.

We also have high immunization coverage among 2-year-old children. Data from the 1995 national immunization survey show that

95 percent of 2-year-old children received three or more doses of the DTP vaccine, 88 percent received three doses of polio vaccine, 90 percent received a dose of a measles-containing vaccine, and 92 percent received three or more doses of *Haemophilus influenzae* type b vaccine. The national coverage rate for the 4-3-1 series was 76 percent in 1995, the highest level ever achieved.

VACCINE DEVELOPMENT

The pace of progress in the area of vaccine development is quickening, as we have highlighted in our first chart, which depicts the cumulative number of changes to the routine immunization schedule since 1975. The schedule has been changing dramatically since the late 1980's. Each vial represents a single change. In the 10 years between 1975 and 1984 only one change to the schedule was made. In contrast, in the 10 years between 1988 and 1997 more than 10 changes were made.

Several new vaccines may become available in the next few years to prevent death and disability from other infectious diseases and, as has already been mentioned, will be considered for universal childhood immunization. These include a vaccine for rotavirus diarrhea, a vaccine against strep pneumoniae, which causes an estimated 7 million ear infections each year in the United States, and even a vaccine for meningococcal disease, another cause of serious meningitis.

ACCOMPLISHMENTS WITH NEW VACCINES

These are wonderful fruits of the revolution in biotechnology, but they pose challenges for those of us in public health who have to implement them.

If you could put on the next chart, please.

As you can see in this chart, in 1987, just 10 years ago, there were just six injections required through 2 years of age. Now in 1997, as shown by the blue shots on the chart, there is a minimum of 11 injections if certain combinations of vaccines are used and as many as 4 more shots, as shown in yellow, if other vaccines are used.

The number of injections can result in three or four separate injections at some visits to one's provider, or more visits, which might compromise compliance.

Next chart, please.

The vaccine manufacturers have responded to this problem by working to combine antigens developed to prevent multiple diseases into combination vaccines. As you mentioned in your opening statement and as shown in the top part of this chart, in 1996 two new combinations were introduced, the DTaP-Hib for toddlers, shown here at the top left, and the Hib-HepB for infants 6 weeks of age or older, shown on the top right. Possibly appearing in the years ahead are many more vaccines, including some which could prevent seven diseases with a single product.

Senator BUMPERS. Let me interrupt you just a moment, Walt.

Dr. ORENSTEIN. Sure.

Senator BUMPERS. Are you saying that those combinations are in existence now?

Dr. ORENSTEIN. That is correct. The Hib-HepB is in existence right now, the one on the top right. The one on the top left is in existence for the fourth dose of the schedule. It is not yet licensed for doses one, two, and three, although we expect that in the near future.

Senator BUMPERS. I understood you to say we had a combination of DTaP, Hib, and HepB.

Dr. ORENSTEIN. No; that is not yet available.

Senator BUMPERS. OK.

Dr. ORENSTEIN. The ones on the—

Senator BUMPERS. I misunderstood this. I had looked at that chart.

Dr. ORENSTEIN. OK. The ones on the bottom are ones that various companies have told us at one point or another that they are seriously considering. I would imagine only a few of these may actually reach the market, but these are the ones that are potentially in the pipeline that we have to be prepared for.

CHALLENGES POSED BY NEW VACCINES

As I said, this is a list of up to 20 products. The benefits of such combination vaccines are clear. More diseases can be prevented with fewer shots. We can decrease immunization visits and increase parental and provider acceptance of new vaccines.

However, we face several challenges, including the potential increased cost of combination vaccines. Developing combination vaccines is neither simple nor cheap, because it must be demonstrated that there are not any potential chemical incompatibilities between ingredients, nor immunologic interference, and that the overall safety and efficacy is not compromised compared to the individual products. Development of combination vaccines may require greater collaboration among vaccine manufacturers. Since not all manufacturers currently make all vaccines, companies will have to acquire rights to include certain components in their new combination vaccines, which could add to the cost of these vaccines.

Actual production costs may be higher because it is necessary to assure all components, both individually and when combined, meet safety and efficacy requirements. Although these vaccines may be shown to be cost saving compared to existing vaccines, some resistance to a higher price may exist. This may occur since the budgetary pocket that purchases the vaccine is often not the pocket which accrues the cost savings in reduced numbers of doctor's visits, parental time lost from work, and reduced costs of caring for prevented diseases.

SAFETY AND EFFICACY ISSUES

Individual vaccines may be cheaper to purchase, but more expensive to deliver.

An important challenge for all new vaccines, particularly new combination vaccines, will be to monitor safety and effectiveness after licensure. New vaccines are usually tested in up to 10,000 people prior to licensure to assure basic vaccine safety and efficacy. These studies are unlikely, however, to detect less frequent adverse reactions that still may be of public health importance when these vaccines are used in millions of children.

To monitor the safety of new and combination vaccines, surveillance of adverse events following licensure must occur to ensure that if new unanticipated adverse events occur, they are detected. In addition, it is critical to scientifically evaluate whether rare adverse events observed following vaccination are actually caused by the vaccine or represent coincidental illness that would have occurred anyway.

The CDC has developed the vaccine safety datalink project, in which four health maintenance organizations link vaccination and medical records of more than 1 million children to provide exactly this scientific basis for evaluation of causation of adverse events.

The effectiveness of new combinations must also be monitored. It may not always be predictable when vaccines can be combined together. We will have to maintain strong disease surveillance to look for evidence that these new vaccines really work by reducing the actual occurrence of disease.

ISSUES RELATED TO STOCKING VACCINES

Another issue related to combination vaccines is the need to determine which vaccines to stock among many potential options.

If you could go to the next chart, please.

For example, the licensure of combined Hib-HepB, shown here at the top of refrigerator 1, and combined DTaP-Hib, shown at the top of refrigerator 2, represented a turning point in immunization practice, as these two products contain overlapping, noncomplementary antigens. They both contain Hib.

In refrigerator 1 on the chart, if HepB-Hib is stocked, a child can be fully vaccinated against five diseases with this vaccine and DTaP alone. That is all that would need to be stocked in that refrigerator. DTaP-Hib is not needed, even when it becomes available for infant vaccination, and in fact using this combination with Hib-HepB would give extra, unneeded doses of Hib, because you can see that Hib is in both vaccines and you only need one Hib.

In contrast, as shown in refrigerator 2, if DTaP-Hib is stocked, HepB alone is needed, rather than the combination Hib-HepB, and DTaP alone is needed.

Choosing what to stock for the individual physician would be easy if the patient stayed with that physician. Unfortunately, patients switch and may have been started on one regimen and then moved into another practice. Thus, until combinations are available containing all the vaccines, physicians and clinics will be confronted with the choice of stocking all vaccines to meet every possibility, as shown in refrigerator 3 here, or stocking a limited number of vaccines, as shown in refrigerators 1 or 2, to help simplify the inventory in a given clinic, and thus occasionally having to give extra doses of some vaccine components.

These choices have cost implications both for the individual physician or clinic and for public health programs. An additional challenge for CDC in the future will be to create procurement strategies which are as economical as possible, while continuing to encourage vaccine manufacturers in the research and development of innovative vaccine technologies.

CDC is testing a procurement strategy for DTaP vaccines which more closely approximates the private sector market. As long as

the ACIP considers each manufacturer's products essentially equivalent from a public health perspective, manufacturers of all licensed vaccines are given access to the public vaccine market and States can then choose which product or products they want to use.

A contract was established with each licensed manufacturer with low guaranteed minimum purchase requirements and manufacturers are able to change the negotiated price every 3 months as long as the price does not exceed the original negotiated price.

In conclusion, a remarkable record of success has been achieved. Vaccine-preventable diseases are at or near record low levels and immunization coverage is at record high levels. New vaccines offer the promise of preventing more and more infectious diseases. Combination vaccines offer the promise of simplifying vaccine delivery so we can assure that children will benefit from all these vaccines.

However, future challenges lie ahead. The development of new and combination vaccines raises issues related to cost, assuring safety and efficacy, and product choices. We welcome these challenges, however. The short-term costs and difficulties should be more than compensated for by the additional protection against diseases conferred by these new vaccines.

PREPARED STATEMENT

With your help and working with our partners in industry, public health, the provider community and others, we are confident that we can overcome obstacles and take advantage of opportunities.

Thank you and I would be happy to answer any questions you may have.

Senator BUMPERS. Thank you very much, Dr. Orenstein, for a highly enlightening statement.

[The statement follows:]

PREPARED STATEMENT OF WALTER A. ORENSTEIN, M.D.

INTRODUCTION

Mr. Chairman, I am Dr. Walter Orenstein, Director, National Immunization Program, for Disease Control and Prevention (CDC). I am pleased to appear before the Subcommittee to discuss fixture vaccine development.

I want to thank you and the Subcommittee for the support and leadership you have provided to assure that our Nation's children are fully protected against vaccine-preventable diseases. I am happy to report great progress, we have record low disease levels and record high immunization rates. Your support has contributed significantly to our success.

Record low levels of vaccine preventable diseases

This Nation has made unprecedented progress toward our goals of eliminating or reducing vaccine-preventable diseases. Reported cases of eight vaccine-preventable diseases have declined by at least 97 percent from prevaccine era peaks (Table 1). Provisional data for 1996 show that record low levels were set or tied for mumps, tetanus, polio (caused by wild viruses), and invasive *Haemophilus influenzae* (for children under 5 years of age). Only one case of diphtheria was reported, and fewer than 500 measles cases were reported. (All of the measles cases are believed to be connected to recent importations.) Pertussis, even though occurring at levels more than 97 percent below prevaccine era rates, is occurring at levels higher than we would wish. It is now, however, predominately occurring in older children, adolescents, and adults, for whom, there are no currently licensed pertussis vaccines. The National Institutes of Health has recently undertaken a study to determine whether new acellular pertussis vaccines available for children can safely protect adults.

TABLE 1.—COMPARISON OF MAXIMUM AND 1996 PROVISIONAL MORBIDITY VACCINE-PREVENTABLE DISEASES

	Maximum cases	1996 provisional cases	Percent change
Diphtheria	206,939	1	– 99.99
H. influenzae, invasive disease (less than 5 years)	¹ 20,000	276	– 98.62
Measles	894,134	488	– 99.95
Mumps	152,209	658	– 99.57
Pertussis	265,269	6,467	– 97.56
Polio (paralytic)	21,269	– 100.00
Rubella	57,686	210	– 99.64
Congenital Rubella syndrome	¹ 20,000	2	– 99.99
Tetanus	² 1,560	27	– 98.27

¹ Estimated.² Mortality.*Record High Immunization Coverage*

We have record high immunization coverage among 2-year-old children. The 1995 National Immunization Survey (NIS) (Table 2), the latest data available, shows that 95 percent of 2-year-old children received three or more doses of the diphtheria/tetanus/pertussis (DTP) vaccine, 88 percent received three doses of polio vaccine (OPV), 90 percent received one dose of a measles-containing vaccine, and 92 percent received three or more doses of the Haemophilus influenzae type b (Hib) vaccine. The national coverage rate for the 4:3:1 series (4 DTP/3OPV/1MMR), a common measure of the basic series of vaccines, was 76 percent in 1995, the highest level ever achieved.

TABLE 2.—1995 IMMUNIZATION LEVELS OF 19- TO 35-MONTH-OLD CHILDREN AND 1996 IMMUNIZATION GOALS

Vaccine	Percentages			
	1992 baseline	1996 goals	1995 coverage	Oct.-Dec. 1995 coverage
DTP 3+	83	90	95	95
OPV 3	72	90	88	90
MCV ¹	83	90	90	91
Hib 3+	90	92	92
Hepatitis B3	70	68	78
4DTP/3OPV/1MMR	55	76	78

¹ Measles-containing vaccine.

Source: 1992 Baseline: National Health Interview Survey, 1992.

1995 Data: National Immunization Survey (NIS), January-December 1995.

Information on successful strategies for achieving high immunization coverage and low disease rates is contained in Appendix 1.

Prospects for future vaccines

We are on the way to reducing or eliminating the vaccine-preventable diseases of today. While continuing to do this, we must also consider the challenges and opportunities of tomorrow.

A thoughtful biology-watcher, Lewis Thomas, predicted that a thousand years from now our era will be known as the Age of Biotechnology, because of our growing ability to purposefully manipulate the molecular structures of living organisms to serve our needs. Nowhere is this technology more evident than in the current arena of vaccine development. Almost a century passed between the very first vaccine—Edward Jenner's preventive for smallpox in 1796—and the second one for rabies by Louis Pasteur in the 1880's. In the hundred years since Pasteur, vaccines for another two dozen diseases—from diphtheria to polio to measles were introduced. Now, the pace of that progress is quickening.

Since 1990, several major changes have been made to the routine childhood immunization schedule, including infant vaccination with *Haemophilus influenzae* type b, hepatitis B, routine early childhood immunization against varicella (chickenpox), and replacement of older pertussis vaccines with safer vaccines. The new "acellular" pertussis vaccines will decrease the fever, soreness, and fussiness that sometimes have followed whole-cell pertussis vaccines, as well as some of the rare but more serious adverse events.

Several new vaccines may become available in the next few years to prevent death and disability from other infectious diseases. These vaccines will also be considered for universal childhood vaccination. Such vaccines include a vaccine for rotavirus diarrhea, which each year results in an estimated 500,000 doctor visits, 50,000 hospitalizations, and approximately 20 deaths among children under 5 years of age.

Studies are also underway to develop vaccine for *Streptococcus pneumoniae* that will work in infants under 2 years of age, for whom current pneumococcal vaccines do not provide protection. The pneumococcus causes an estimated 7 million ear infections, 9,000 serious bloodstream infections, and 1,500 cases of meningitis in American children under the age of 2 years. With the trend toward increased resistance to antibiotics by these bacteria, such new vaccines, if safe and effective, would be very useful. In addition, strains of another bacterium, meningococcus, cause approximately 2,600 cases of meningitis in the United States each year, often in epidemics that frighten the public and require emergency control efforts to diagnose and treat cases and give antibiotic prophylaxis to exposed persons. About 13 percent of those infected die from this devastating disease. Incidence rates are highest in young children. New "conjugated" vaccines for some of these strains show promise to prevent this disease in infants.

Also, on the horizon are potential vaccine technologies that would have been considered science fiction just a decade ago. Small pieces of synthetic DNA have worked as experimental vaccines in animals, and are producing promising immune responses in human volunteers. Plants have been bioengineered to become vaccine factories, potentially reducing manufacturing costs. Even tomatoes, corn, and potatoes have been genetically engineered to express vaccine antigens. Oral vaccine made from re-engineered benign strains of typhoid bacteria has protected against this disease. The benign typhoid strains have also been modified and given orally to protect experimentally against other diseases as well, offering an alternative to shots. Experimental vaccines have been enclosed in microscopic capsules, which might permit them to be released slowly over time to avoid the need for booster shots, or to be taken orally. Adjuvants can increase the effectiveness of some vaccines.

The challenges ahead

These are wonderful fruits of the revolution in biotechnology, but they pose challenges for those of us in public health responsible for putting new vaccines to use in preventing disease and reducing the costs of health care to society. For example, the recommended immunization schedule is getting very complex. Just 10 years ago in 1987, the nationally recommended immunization schedule for children through 2 years of age required just 6 injections. The 1997 schedule, however, requires 11 to 15 injections for children through 2 years of age depending on which vaccine combinations are used.

This number of injections can result in 3 or 4 separate injections at some visits to one's health care provider. Anecdotally, we know that some doctors and some parents may be reluctant to immunize children with more than 2 or 3 injections during one visit. So, some injections may get deferred, resulting in additional time and costs for the extra visits, some of which may not be kept, and thereby, potentially decreasing the proportion of children fully protected from disease in a timely manner. Simply increasing the number of visits in the routine schedule could add to costs, including both the direct medical expenses incurred and the indirect costs when parents must take time off from work for the visit.

Combination vaccines—benefits and challenges

The vaccine companies have responded to this problem by working to combine antigens for multiple diseases into combination vaccines. In 1996, two new combinations were introduced: DTaP-Hib for toddlers (recommended at 12–18 months of age) and Hib-HepB for infants 6 weeks and older. Possibly appearing in the years ahead are up to 20 various combination vaccines, such as MMR-Varicella, or DTaP-Hib-HepB.

The benefits of such combination vaccines are clear. More diseases can be prevented while reducing the number of shots, thereby eliminating additional doctor visits, and decreasing related medical costs and parental costs. Along with the bene-

fits of new combination vaccines comes new challenges related to cost, assuring vaccine safety and efficacy, and choices among products.

Cost of combination vaccines

The potential increased cost of combination vaccines will be a major challenge for the future. Developing combination vaccines is neither simple nor cheap, because it must be demonstrated that there are not any potential chemical incompatibilities nor immunologic interference between the ingredients, and that safety and efficacy will not be compromised. (For example, such interference has delayed the licensure of the DTaP-Hib combination vaccine for use in infants.)

Development of combination vaccines may require greater collaboration among vaccine manufacturers. The most desirable vaccine combination would contain the greatest number of components. Since not all manufacturers currently make all different vaccines, vaccine companies will have to acquire rights to include certain components in their new combination vaccines, which could add to the cost of these vaccines. Furthermore, actual production costs to combine these vaccines may be higher than the individual vaccines because it is necessary to assure all components, both individually and when combined, meet safety and efficacy requirements. Also, the product lifetimes may be short as newer, larger combinations replace combination vaccines with fewer components.

Although these vaccines may be shown to be cost-saving compared to existing vaccines, some resistance to a higher price may exist. This may occur since the budgetary packet that purchases the vaccine is often not the pocket which accrues the cost savings in reduced numbers of doctor's visits, parental time lost from work, and reduced costs of caring for prevented diseases. Individual vaccines may be cheaper to purchase but more expensive to deliver.

ASSURING SAFETY AND EFFICACY

An important challenge for all new vaccines, particularly new combination vaccines, will be to monitor safety and effectiveness after licensure. New vaccines are usually tested in up to 10,000 people prior to licensure to assure basic vaccine safety and effectiveness. These studies may not, however, detect less frequent adverse reactions that may still be of public health importance when these vaccines are used in millions of children. Furthermore, new combination vaccines are generally tested in smaller numbers of people prior to licensure. As a hypothetical example, for a vaccine that causes serious reactions once per 20,000 doses, approximately 200 children, in a birth cohort of approximately 4 million, may suffer a reaction. To monitor the safety of new combination vaccines, surveillance of adverse events after licensure must occur to ensure that if new, unanticipated adverse events occur, they are detected. In addition, it is critical to scientifically evaluate whether rare adverse events observed following vaccination are actually caused by the vaccine or represent coincidence of an illness that would have occurred anyway.

CDC has developed the Vaccine Safety Datalink, in which four health maintenance organizations link vaccination and medical records of more than 1 million children, to provide exactly this scientific basis for evaluating causation of adverse events. With the addition of new and combination vaccines, this project will play a critical role in assuring the safety of vaccines.

The effectiveness of new combination vaccines must also be monitored. It may not always be predictable which vaccines can be combined together. For example, researchers were surprised recently when they discovered interference in immune response to Hib vaccine when combined with some acellular pertussis vaccines even though none existed between the whole-cell pertussis and Hib vaccines. For some vaccines such as pertussis-containing vaccines, there is no laboratory test to measure how well a person is protected by the vaccine. When acellular pertussis vaccines are named with other vaccines, chemical alterations may occur which could decrease effectiveness. This is not detectable by tests that are currently available. Therefore, we will have to maintain strong disease surveillance to look for evidence that these new vaccines really work by reducing the occurrence of disease, and be prepared to do more detailed scientific studies if surveillance suggests they are not as effective as expected. CDC can play a major role in these efforts, through its collaborative surveillance efforts with States, using projects such as the Vaccine Safety Datalink to evaluate vaccine efficacy, and by providing technical and epidemiologic skills.

PRODUCT CHOICES

Another issue related to combination vaccines is the need to determine which vaccines to stock among many potential options. For example, the licensure of Hib HepB and DTaP-Hib represented a turning point in immunization practice, as these

two products contain overlapping, non-complementary antigens. If Hib/Hep B is stocked, a child can be fully vaccinated against five diseases with this vaccine and DTaP alone. DTaP/Hib is not needed, even when it becomes available for infant vaccination; in fact, using this vaccine combination would give extra, unneeded doses of Hib since it is in both products. In contrast, if DTaP/Hib is stocked, Hep B alone is needed rather than Hib/Hep B. DTaP alone is also needed. These choices could be easy to make if children stayed with the same provider, but many switch. Thus, until there are combinations containing all the vaccines, physicians and clinics will be confronted with the choice of stocking all vaccines to meet every possibility, or giving extra doses of some vaccines to help keep the inventory in a given clinic or office simple. These choices have cost implications both for the individual physician or clinic and for public health programs. Giving extra doses of some vaccines as parts of combinations will require more resources; however, having to stock all preparations, including some that may be infrequently used, could lead to some vaccine expiration.

An additional challenge for CDC in the future will be to create procurement strategies which are as economical as possible while continuing to encourage vaccine manufacturers in the research and development of innovative vaccine technologies. Since 1994, CDC has established guaranteed minimum purchase contracts with each licensed manufacturer of a childhood vaccine recommended by the Advisory Committee on Immunization Practices (ACIP) for routine use. To ensure that each licensed manufacturer received a portion of the public sector market, the low bidder receives 50 percent of Vaccines for Children Program (VFC) orders, as well as all vaccine orders purchased with Section 317 or State funds. The other bidder receives the other 50 percent of VFC orders, but does not receive any orders with State or 317 funds. Until recently, there had not been more than two licensed manufacturers for any particular product. However, there are now three licensed manufacturers of DTaP vaccine, and ultimately there could be 5 licensed manufacturers. Therefore, it was clear a new approach to vaccine procurement was needed.

CDC is testing a procurement strategy for DTaP vaccines which more closely approximates the private-sector market. As long as the ACIP considers each manufacturer's products essentially equivalent from a public health perspective, manufacturers of all licensed vaccines are given access to the public market, and States can then choose which product or products they want to use. A contract was established with each licensed manufacturer with low guaranteed minimum purchase requirements, and manufacturers are able to change the negotiated price every 3 months, as long as the price does not exceed the originally negotiated price. It is hoped that this procurement strategy will further encourage innovation in vaccine development while providing product choice to States, where choice did not exist in previous contracts.

We are working to anticipate the issues posed by new and combination vaccines. This involves cooperation with our many partners in the diverse community involved in disease prevention through immunization, including public health agencies at local, State, Federal, and international levels; non-governmental organizations of medical providers and others promoting health; managed care groups; vaccine manufacturers; those in academia who provide their expertise and advice; parental advocacy groups; and others.

CONCLUSION

A remarkable record of success has been achieved. Vaccine-preventable diseases are at, or near, record low levels, and immunization coverage is at record high levels. But our effective vaccines are only as good as our ability to deliver them to children and adults in need. By continuing to build a comprehensive system, much as we developed methods to ensure our school-age children are vaccinated, we as a society, and we as individuals, can gain the full benefits vaccines have to offer. Never again should epidemics be the primary motivation of immunization errors of our current vaccines.

The Childhood Immunization Initiative (CII) was designed to increase immunization rates now, and build a system for sustaining gains into the future. As you know, the CII includes five key strategies to improve preschool vaccination rates improving the quality and quantity of vaccination delivery services; reducing vaccine costs; increasing awareness, community participation, and partnerships; improving the monitoring of disease and vaccination coverage, and improving vaccines and vaccine use.

New vaccines offer the promise of preventing more infectious diseases. Combination vaccines offer the promise of simplifying vaccine delivery so we can ensure that children will benefit from all these vaccines. Future challenges do, however, lie

ahead. The development of new and combination vaccines raises issues related to cost, assuring safety and efficacy, and product choices. Immunization schedules are becoming increasingly complex as new vaccines are added. We welcome these challenges, however. The additional protection against diseases conferred by these new vaccines will more than compensate for the short-term costs and difficulties associated with new vaccines. With your help, and working with our partners in industry and public health, we are confident that we can overcome obstacles and take advantage of future opportunities.

Thank you. I would be happy to answer any questions you or other Members of the Subcommittee may have.

**STATEMENT OF DR. MICHAEL OSTERHOLM, STATE EPIDEMIOLOGIST
AND CHIEF, ACUTE DISEASE EPIDEMIOLOGY SECTION, MINNESOTA DEPARTMENT OF HEALTH**

Senator BUMPERS. Dr. Osterholm, welcome to the committee.

Dr. OSTERHOLM. Thank you, Mr. Chairman. Mr. Chairman, I am Dr. Michael Osterholm, State epidemiologist and chief of the acute disease epidemiology section, Minnesota Department of Health. I welcome the opportunity to appear before the subcommittee to discuss both the potential and challenges of the new generation of vaccines that will be available for public and private providers.

Like my colleagues here on the panel, I, too, want to acknowledge you and the subcommittee for your ongoing vision and support of our efforts to protect children against vaccine-preventable diseases. One of the sad days in public health is the day that we heard of your decision not to run again, and a heartfelt thank you to you for all that you have done.

Senator BUMPERS. Thank you very much.

Dr. OSTERHOLM. As you have heard this morning in testimony from my distinguished colleagues, we have made unprecedented progress toward our goals of eliminating or reducing childhood vaccine-preventable disease in this country. No other country in the world has realized this same success. Our most recent track record in protecting the health of our children should give us cause for great celebration.

But we all realize that vaccine-preventable disease efforts are everyday, ongoing, and ever needed if we are to continue to realize that current success. As we anticipate the future, we all recognize this effort will be affected by the increasing availability and use of combination vaccines. At the outset, it would seem that combination vaccines will be a major step forward in reducing the number of injections that a child must receive. This will be particularly important as new and significant public health problems, such as rotavirus, strep pneumo, and Neisseria meningitides infections are addressed in the future.

However, I am here to share with you as a State epidemiologist that the future of vaccine-preventable diseases as viewed from the availability of an ever-increasing number of combination vaccines represents both the best of times and the worst of times.

Some of the challenges and opportunities of combination vaccines have been shared with you by other members of the panel. I concur completely with the recent comments made by Dr. Orenstein regarding some of the issues and these vaccines. However, let me share with you some additional concerns.

Some 5 years ago as a State epidemiologist and someone involved in immunization research, particularly that surrounding Haemophilus influenza type b vaccines, I felt confident that I could de-

scribe with clarity and personal understanding the recommended childhood immunization schedule for Minnesota children. This would include all possible combinations and permutations of necessary immunizations based on the age of the child and previous immunization history. Today, despite the fact that I do this for a living, I find that the same discussion is extremely difficult.

In fact, at a recent meeting that we had among our senior immunization personnel at the Minnesota Department of Health, we all agreed that we have great difficulty in answering questions for both providers and parents when they share with us a child's previous immunization history and request advice on those vaccines needed in the future to comply with the recommended immunization schedule and minimize doses and product number.

If this activity is difficult for those of us who do this for a living, I can only imagine how difficult and frustrating it has become for the private practitioner and the parent.

I have included a copy of a document prepared at the Minnesota Department of Health outlining vaccine product options available for preschool children to meet the recommended immunization schedule. As you can see in this enclosed handout, there are any number of different immunizations that are available to meet specific antigen requirements for a given age. However, one must first determine if we are attempting to optimize in the fewest number of injections for that child or use the fewest number of products by the medical practice or public health clinic.

Depending on which of those two options you decide, it will dictate which product you will give at a given age for that child. In addition, you must consider whether you are providing an immunization for a child with a high risk versus a low risk for hepatitis B virus infection. If one could optimize among the current 19 licensed immunization products available through the Minnesota VFC program, you could provide the fewest number of injections per child at both low and high risk for hepatitis B by using 9 different products. On the other hand, if you are trying to optimize in the fewest number of products, which is 7, this will result in 16 injections, plus two oral doses of vaccine for both high- and low-risk infants for hepatitis B infection.

The vaccines to use become extremely complicated when a child enters a medical practice after having received initial immunizations from a different provider source. Now the original provider source may not have used the vaccines chosen by the current provider. What are the options and what are the possibilities?

Today we have staff at our department that literally spend hours on calls to our immunization hotline assisting clinicians and parents as they wade through this complicated maze of immunization possibilities. In effect, we have become a victim of our own success.

As noted above, as part of the VFC program in Minnesota we currently supply 19 different vaccines to our providers. Enclosed you will find a copy of our vaccine order form. This compares, of course, to the 29 different CDC contracts for vaccines and biologics. All of these vaccine orders are handled by a single pharmacy warehouse under State contract. When this contract was originally initiated, less than one-half of the currently available products were on the market.

Today we find ourselves stocking redundant antigens and multiple vaccine products, of which not all are needed to fully immunize a child. Nonetheless, if you are a provider today you may order any or all of these products, depending on the previous history of immunization among your current patients and your own medical practice protocol.

Not only does the polypharmacy issue become a problem for the State people, but now it becomes a major issue within individual clinics as it relates to needs, space, and equipment for storage of the vaccines. Is this issue really a problem and, if so, why?

It is in Minnesota, believe me. Today over 90 percent of our State's population is in some form of managed care, something that you have heard originally mentioned earlier today as a positive area for vaccine use. This includes different options of managed care, which are the closed panel practices or staff models, or loosely connected preferred provider organizations or PPO's. In Minnesota we have found that as purchasers of health care, particularly large employer groups, change health plans almost on an annual basis due to cost differentials, people are frequently changing their primary health care provider.

Last year in our State, we estimate that more than 25 percent of all individuals in managed care settings, which again is 90 percent of our total population, changed their primary health care provider. We have labeled this population as the churning population. This extremely large number of migrating consumers of health care are bringing with them to their new medical clinics their previous immunization histories, both documented and undocumented.

For the new provider to try to address this maze of previous immunization histories and match them up with future needs is beginning to overwhelm our system. We have documented an ever-increasing number of errors in vaccine administration, errors in vaccine ordering, wasted nursing time in attempting to understand the confusion, high levels of both provider and parent frustration, and last but not least, wasted vaccine.

As they would say back in rural Minnesota, all change is not progress. This is taking a real toll on our public health staff. We have seen a dramatic increase in the number and complexity of our hotline calls, an increased need for satellite or other types of training sessions, for complex algorithms for vaccine administration, and for widespread distribution of provider manuals and guides. And as new and additional vaccines come online, regardless of their VFC status, all this material needs immediate updating.

All this has placed great stress on our public health infrastructure and our ability to assist the community in maintaining age-appropriate immunization levels.

Finally, while immunization levels are at an all-time high, we are witnessing increasing frustration among our medical care providers that is extremely counterproductive to achieving those same overall goals of high immunization, childhood immunization, in the future. As more combination vaccines become available and the number of possibilities and permutations for who gets what vaccine and when, we can expect further stress in this system and I believe substantial reductions in our current immunization levels.

I might add that this is continuing to occur even with the recently harmonized immunization schedule.

So where do we go from here? Unless there are some timely and critical changes to our current national agenda for childhood immunizations, I fear our current success will begin to implode upon itself. What I see as a State epidemiologist for the future is the need to dramatically improve upon our current data management aspects of childhood immunization, particularly as it relates to timely and automated registry systems which follow the child regardless of provider, the need for the automation of vaccine delivery, including the need for necessary equipment and technology for such things as bar code reading of vaccine vials in every physician's office and public health clinic in the country, and, most of all, a need for a standardized antigen package for combination vaccines.

This latter recommendation relates to the need for some type of understanding, going, or at the very least regulation, which requires manufacturers to include a core set of antigens in a specified combination vaccine. I recognize this latter recommendation has many obstacles and many opponents. The obstacles include the current licensure process for vaccines via the FDA, concern regarding the incentive for industry to develop new vaccines and economic return, antitrust issues related to collaborative industry efforts, and concern that the Government begin directing vaccine development in a procurement manner similar to that currently used by such agencies as the Department of Defense for other contract items.

However, I can tell you, if we do not address all three of these above issues immediately, the future for childhood immunization in this country will be problematic. In addition, I might add, less crucial but helpful areas that we need to address include State flexibility for ordering among all possible immunization products for VFC and our need for continued 317 grant support for staff to provide the kind of technical assistance to providers and parents I just outlined.

PREPARED STATEMENT

I believe that this subcommittee as part of its ongoing effort to maintain the highest possible levels of immunization among our children can play a role in helping direct us through both the future opportunities and challenges regarding this problem.

Thank you. I will be happy to answer any questions you or other members of the subcommittee may have.

[The statement follows:]

PREPARED STATEMENT OF MICHAEL T. OSTERHOLM

Mr. Chairman, I am Dr. Michael Osterholm, State Epidemiologist and Chief, Acute Disease Epidemiology Section, Minnesota Department of Health (MDH). I welcome this opportunity to appear before the Subcommittee to discuss both the potential and challenges of the new generation of vaccines that will be available for public and private providers. I want to acknowledge you and the Subcommittee for your ongoing vision and support for our efforts to protect children against vaccine-preventable diseases.

Future of Childhood Vaccination from a State Health Department Perspective

As you have heard this morning in the testimony from my colleague, Dr. Walter Orenstein, we have made unprecedented progress towards our goals of eliminating or reducing childhood vaccine-preventable diseases in this country. No other country

in the world has realized this same success. Our most recent track record in protecting the health of our children should give us cause for great celebration. But we all realize that vaccine-preventable disease efforts are everyday, ongoing and ever-needed if we are to continue to realize our current success. As we anticipate the future, we all recognize this effort will be affected by the increasing availability and use of combination vaccines. At the outset, it would seem that combination vaccines will be a major step forward in reducing the number of injections that a child must receive. This will be particularly important as new and significant public health problems such as rotavirus, Streptococcus pneumonia, and Neisseria meningitidis infections are addressed. However, I'm here to share with you as a State Epidemiologist that the future of vaccine-preventable diseases as viewed from the availability of an ever increasing number of combination vaccines represents both the "best of times and the worst of times."

Some of the challenges and opportunities of combination vaccines have also been shared with you by Dr. Orenstein. I concur completely with his conclusions regarding these vaccines. Let me share with you some additional issues.

Five years ago, as a State Epidemiologist and someone involved in immunization research, particularly that surrounding the Haemophilus influenzae type b vaccines, I felt confident that I could describe with clarity and personal understanding, the recommended childhood immunization schedule for Minnesota children. This would include all the possible combinations and permutations of necessary immunizations based on the age of the child and previous immunization history. Today, despite the fact that I do this for a living, I find that same discussion extremely difficult. And in fact, at a recent meeting of our senior immunization program personnel at the MDH, we all agreed that we have great difficulty in answering questions for both providers and parents when they share with us a child's previous immunization history and request advice on those vaccines needed in the future to comply with the recommended immunization schedule. If this activity is this difficult for those of us who do this for a living, I can only imagine how difficult and frustrating it has become for the private practitioner and the parent.

I have included a copy of a document prepared at the MDH outlining vaccine product options available for preschool children to meet recommended immunization schedules. As you can see, there are any number of different immunizations that are available to meet specific antigen requirements for a given age. However, one must first determine if we are attempting to optimize on the fewest number of injections for that child or the use of the fewest number of products by the medical practice or public health clinic. Depending on which of those two options you decide, it will dictate which product we'll use at a given age for that child. In addition, you must consider whether you are providing an immunization for a child with a high-risk versus a low-risk for hepatitis B virus infection. If one could optimize among the current 23 licensed immunization products on the market, you could provide the fewest number of injections for children at both low- and high-risk for hepatitis B by using nine different products. On the other hand, if you are trying to optimize on the fewest number of products, which is seven, this will result in 16 injections plus two oral doses of vaccines for both high- and low-risk infants for hepatitis B virus infection. The vaccines to use become extremely complicated when a child enters a medical practice after having received initial immunizations from a different provider source. Now, the original provider source may not have used the vaccines chosen by the current provider. What are the options and what are the possibilities? Today we have staff at the MDH that literally spend hours on calls to our immunization hotline assisting clinicians and parents as they wade through this complicated maze of immunization possibilities. In effect, we have become a victim of our own success.

In Minnesota, as part of our immunization program, we currently provide 18 different vaccines to our providers. Enclosed you will find a copy of our vaccine order form. All of these vaccine orders are handled by a single pharmacy warehouse under state contract. When this contract was originally initiated, less than half of the currently available products were on the market. Today we find ourselves stocking redundant antigens and multiple vaccine products of which not all are needed to fully immunize a child. Nonetheless, if you are a provider today, you may order any or all of these products depending on the previous history of immunization among your current patients and your own medical practice protocol. Not only does the polypharmacy issue become a problem for the state depot, but now it becomes a major issue within an individual clinic as it relates to needs, space and equipment for storage of these vaccines.

Is this issue really a problem and, if so, why? In Minnesota it is! Today, over 90 percent of our state's population is in some form of managed care. This includes the different options of managed care which are closed panel practices or loosely con-

nected PPOs, staff models or preferred providers. In Minnesota, we have found that as purchasers of health care, particularly large employer groups, change health plans almost on an annual basis due to cost differentials, people are frequently changing their primary health care provider. Last year in our state, we estimate that more than 25 percent of individuals in managed care settings changed their primary health care provider. We have labeled this population as the "churning population." This extremely large number of migrating consumers of health care, are bringing with them to their new medical clinics, their previous immunization histories, both documented and undocumented. For the new provider to try to address this maze of previous immunization histories and match them up with future needs, is beginning to overwhelm our system. We have documented an increasing number of errors in vaccine administration, errors in vaccine ordering, wasted nursing time in attempting to understand this confusion, high levels of provider and parent frustration, and last but not least, wasted vaccine. As they would say back in rural Minnesota, "all change is not progress."

This is taking a real toll on our public health staff. We have seen a dramatic increase in the number and complexity of our hotline calls, the increased need for satellite or other types of training sessions, for complex algorithms for vaccine administration, and for widespread distribution provider manuals and guides. And as new vaccines come on line, regardless of their VFC status, all this material needs immediate updating. All of this has placed a great stress on our public health infrastructure and our ability to assist the community in maintaining age-appropriate immunization levels. Finally, we are witnessing increasing frustration among our medical care providers that is extremely counter productive to achieving an overall goal of high levels of childhood immunization. As more combination vaccines become available and the number of possibilities and permutations for who gets what vaccine and when, we can expect further stress on this system. I might add that this is continuing to occur even with the recently harmonized immunization schedules.

The future

So where do we go from here? Unless there are some timely and critical changes to our current national agenda for childhood immunizations, I fear our current success will be short lived. Frankly, the system will begin to implode upon itself. What I see, as a State Epidemiologist, for the future, is the need to dramatically improve upon our current data management aspects of childhood immunization, particularly as it relates to timely and automated registry systems which follow the child regardless of provider, the need for the automation of vaccine delivery, including the need for necessary equipment and technology for bar code reading of vaccine vials in every physician's office and public health clinic in the country, and most of all, the need for standardized "antigen packages" for combination vaccines. This latter recommendation relates to the need for some type of understanding, agreement or regulation which requires manufacturers to include a core set of antigens in a specified combination vaccine. I recognize this latter recommendation has many obstacles, including the current licensure process for vaccines via the Food and Drug Administration, concern regarding the incentive for industry to develop new vaccines, anti-trust issues related to collaborative industry efforts, and concern that government begin directing vaccine development in a procurement manner similar to that currently used by such agencies as the Department of Defense for other contract items. However, if we do not address all three of these above areas immediately, the future for childhood immunization in this country will be problematic. In addition, I might add less crucial, but helpful areas we need to address include state flexibility for ordering among all possible immunization products for VFC and our need for continued 317 grant support for staff to provide technical assistance to providers and parents.

I believe that this Subcommittee, as part of its ongoing effort to maintain the highest possible levels of immunizations among our children can play a role in helping direct us through both the future opportunities and challenges regarding this problem.

Thank you. I will be happy to answer any other questions you or other members of the Subcommittee may have.

VACCINE PRODUCT OPTIONS AVAILABLE FOR PRESCHOOL-AGED CHILDREN TO MEET RECOMMENDED IMMUNIZATION SCHEDULE (DTaP, IPV/OPV, HIB, HBV [LOW AND HIGH-RISK], MMR, VARICELLA)

Age of child	Vaccination against	Vaccine options	Products available	Fewest injections		Fewest products
				HR (HBV) ¹	LR (HBV) ²	
Birth	Hepatitis B	HBV (hepatitis B)	Merck, RECOMBIVAX HB (ped) ³ Merck, RECOMBIVAX HB (high-risk/ado) ³ Merck, RECOMBIVAX HB (adult) SmithKline Beecham (SKB), Engerix-B (ped) ³	1		1
	Hepatitis B	HBV	Merck, RECOMBIVAX HB (ped) ³ Merck, RECOMBIVAX HB (high-risk/ado) ³ Merck, RECOMBIVAX HB (adult) SmithKline Beecham (SKB), Engerix-B (ped) ³	1		1
1 month	Hepatitis B	HBV	Merck, RECOMBIVAX HB (ped) ³ Merck, RECOMBIVAX HB (high-risk/ado) ³ Merck, RECOMBIVAX HB (adult) SmithKline Beecham (SKB), Engerix-B (ped) ³	1		1
	Hepatitis B	HBV	Merck, RECOMBIVAX HB (ped) ³ Merck, RECOMBIVAX HB (high-risk/ado) ³ Merck, RECOMBIVAX HB (adult) SKB, Engerix-B (ped) ³	1 (≥ 6 mo.)		1
2 to 6 months	Diphtheria Tetanus, Pertussis	HBV + Hib	Merck, COMVAX (2 and 4 months only) ³		2	
	H. influenzae type B	DPT + Hib	Wyeth-Lederle, TETRAMUNE ³ Pasteur Merieux Connaught (PMC) DPT/ACTHib ³			
		DTP	PMC, _____ SKB, _____			
		DTaP	Wyeth-Lederle, TRI-IMMUNOL PMC, Tripedia ³			2
		Hib	Wyeth-Lederle, ACEL-IMUNE ³ SKB, Infanrix ³	3	3	3
		OPV	Merck, PedvaxHIB ³ (2 & 4 mos. only)	2		3
		IPV	PMC, ActHIB ³ SKB, OmniHIB			
		Hepatitis B	Wyeth-Lederle, HibTITER ³ Wyeth-Lederle, ORIMUNE ³			
		Hepatitis B	PMC, IPOL ³	2	2	4
		Hepatitis B	Merck, RECOMBIVAX HB (ped) ³ Merck, RECOMBIVAX HB (high-risk/ado) ³			

Diphtheria	Merck, RECOMBIVAX HB (adult)			
Tetanus, Pertussis	SKB, Engerix-B (ped) ³			
H. influenzae type B	Merck, COMVAX ³		1	
	Wyeth-Lederle, TETRAMUNE ³			
	PMC, DPT/ActHIB ³			
	PMC, _____			
	SKB, _____			
	Wyeth-Lederle, TRI-IMMUNOL			
	PMC, Tripeadia ³ (≥ 15 mos.)			
	Wyeth-Lederle, AceL-Immune ³ (≥ 15 mos.)		1	2
	SKB, Infanrix ³ (≥ 15 mos.)			
	PMC, TrIHIBit ³ (4th dose only)	1		
	Merck, PedvaxHB ³			
	PMC, ActHIB ³			3
	SKB, OmniHIB			
	Wyeth-Lederle, HibTITER ³			
	PMC, ProHIBIT (≥ 15 mos.)			
Polio	Wyeth-Lederle, ORIMUNE ³	(4)	(4)	5
	PMC, IPOL ³			
MMR	Merck, MMR II ³	1	1	6
Varicella	Merck, Varivax ³	1	1	7
Diphtheria	PMC, _____			
Tetanus, Pertussis	SKB, _____			
	Wyeth-Lederle, TRI-IMMUNOL			
	PMC, Tripeadia ³	1	1	2
	Wyeth-Lederle, AceL-Immune ³			
Polio	SKB, Infanrix ³			
	Wyeth-Lederle, ORIMUNE ³	(4)	(4)	5
	PMC, IPOL ³			
MMR	Merck, MMR II ³	1	1	6

¹ HR, infants at high risk for HBV.
² LR, infants at low risk for HBV.
³ Federal contract (n = 17)
⁴ Oral.

Note: Fewest injections: 13 for LR infants and 15 for HR infants, using 9 different products. Total products equal 23. Fewest products: 7, resulting in 16 injections (+2 oral) for both low- and high-risk HBV infants.

RECENTLY LICENSED COMBINATION VACCINES

DTaP-Hib	Hib-Hep B
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POTENTIAL FUTURE VACCINES

DTaP-Hep B	Hib-Pneumococcal
DTaP-IPV	Hib-Meningococcal
DTaP-Pneumococcal	Hib-Pneumococcal-Meningococcal
DTaP-Meningococcal	Hib-Hep B-IPV
DTaP-Hep B-Hib	Hib-IPV-Pneumococcal-Meningococcal
DTaP-Hib-IPV	
DTaP-Hep B-IPV	Pneumococcal-IPV
DTaP-Hib-Pneumococcal	Pneumococcal-Meningococcal
DTaP-Hib-Pneumococcal-Meningococcal	
DTaP-Hib-Hep B-IPV	MMR-Varicella
DTaP-Hib-Pneumococcal-Meningococcal	
DTaP-Hib-Hep B-IPV-Hepatitis A	

REMARKS OF SENATOR BUMPERS

Senator BUMPERS. Thank you very much, Dr. Osterholm. And thank all of you.

Let me just open by saying that this is, in all the 22½ years I have been involved in immunization, this morning is one of the most gratifying times that Betty and I have experienced. The explosion, as Dr. Paradiso outlined, the explosion of new products which are so badly and desperately needed, is an incredible thing.

But as we all know, all progress carries its own unique set of problems, too. So here we are with all these magnificent advances, vaccines for all kinds of new things. Who would have ever thought about a vaccine for pneumonia or for ear infections and so on, or rotavirus? Those things even 10 years ago in my mind would have been absolutely impossible to conjure up or to think about.

TESTING EFFICACY OF VACCINES

So it seems to me that here we are now with all of these advances. And one other thing, Dr. Orenstein, I might mention. You mentioned that it takes 10,000 people participating in a test, but I think your testimony showed, or maybe Mary Ann's memo to me showed, that the testing of combinations to make sure that antigens are compatible only requires 4,000. Is that correct?

Dr. ORENSTEIN. I am not sure exactly what the numbers are. The numbers that actually—what we have seen in prelicensure trials—and Dr. Paradiso may be better able to comment on it—is generally up to 10,000 and not more than 10,000. Some of the studies have involved fewer than 10,000 in the initial trials, but in combinations less than that.

Senator BUMPERS. Yes.

Dr. ORENSTEIN. I do not know if it is 4,000.

Senator BUMPERS. Dr. Paradiso?

Dr. PARADISO. It obviously depends on the incidence of the disease, and so for a disease like Haemophilus b, where the meningitis is fairly rare, we did trials in the 20,000 to 30,000 children range. For acellular pertussis, which is more common, or pertussis is more common, vaccine trials were in the 8,000 to 10,000 range.

Our combination DTP-Hib vaccine was tested in about 4,000 or 5,000 children, and those were predominantly safety trials. Those were trials for vaccines that had two components that had already

been very extensively tested for safety and efficacy, so that was the reason probably that it did not need and does not need to go as high as the vaccines where you are showing efficacy against rare disease and vaccines where you are using products that you have never used before and so you want to get some more primary data.

ANTIGEN COMPATIBILITY

Senator BUMPERS. One of my questions is, does medical science—I assume that medical science allows the researchers who develop these things to make a pretty good educated, calculated guess as to whether certain antigens are going to be compatible or not. Do they or not? Or does that have to be determined simply by test or can you—I mean, you have to do the test, of course, to be sure.

But is there a reasonable certainty that you can reach—can you reach a decision with a reasonable certainty that two antigens are going to be compatible?

Dr. PARADISO. Actually, the history of combination vaccines is that interference is the biggest problem with mixing antigens. It was seen with MMR.

Senator BUMPERS. One interferes with the other?

Dr. PARADISO. One interferes with the other. It was seen with the oral polio vaccine when they first mixed the three types. When we developed a vaccine for DTP-Hib combined—by “we” I mean our company—we mixed a DTP product with Haemophilus b and it worked the first time and we thought we were wonderful and it would always be that easy. What we are learning now is that it is not that easy.

The recent attempts to combine the Haemophilus b vaccine with the acellular pertussis—and virtually every group has seen this—results in interference in the response of the Haemophilus vaccine. We do not know why that is. It was not predicted in any of the animal studies that we did or it was not predicted by anything until you actually got into young infants and you saw that there was a two, three, five, tenfold reduction in the response to the Haemophilus b conjugate. We do not know what that means from a clinical standpoint, but, you know, from the charts we looked at, you are currently controlling that disease not only by protecting the individual, but by protecting the environment and the herd.

So you are very reluctant to make changes that reduce the responses in children without knowing exactly what effect that is going to have on long-term disease.

I agree with Mike, Dr. Osterholm, that it would be wonderful to preset what combinations and what antigens should go into a vaccine, but what we have learned is that we do not know that those will be the ones that will actually be combinable. So we need to be flexible, I think, in what we do.

If I could show a couple of other charts that just illustrate how we think about this. Obviously, as we work now on new vaccines we pay attention to combination vaccines because we know we cannot just keep adding vaccines to the schedule.

NEW VACCINES AND EASE OF DELIVERY

Senator BUMPERS. While he is putting those charts up, Dr. Paradiso, let me ask you this. I saw a segment on one of the news-

casts the other night about the use of the nasal drop in infants. That is a flu vaccine, I take it.

Dr. PARADISO. Yes.

Senator BUMPERS. My question is when can we expect that to come on line?

Dr. PARADISO. Well, I read the same articles. I think that is pretty exciting, from what I have read. That was a flu vaccine that has been given as a spray in children, I think 1 to 5 years of age.

Senator BUMPERS. Yes.

Dr. PARADISO. My reading is that those results were very positive, and so I think the projections were for within the next year or two that they would complete the data that they need for safety and efficacy.

Senator BUMPERS. Who is developing that?

Dr. PARADISO. That is a company called Avron in California.

It is exciting also because there are a number of respiratory viruses that affect young infants, respiratory syncytial virus, parainfluenza virus, that cause up to 5,000 to 8,000 hospitalizations a year in babies. Those can all potentially be given by that same method, as an intranasal spray, and they are being tested. My company, for example, is working on vaccines for respiratory syncytial virus delivered the same way to very young infants. If the protection can be that good, then that is obviously ideal and it does not require an injection and protects against a difficult disease.

Senator BUMPERS. Go to the chart.

Dr. PARADISO. These are looking another way at what Dr. Orenstein and Dr. Osterholm have already talked about, the increase in new products from 1980 to 1990 and what we think we may see in the year 2000. I think first of all we should point out that most recently the introduction of the acellular pertussis vaccines, the recommendation now to use IPV in the infant schedule has caused some increases in the number of injections, increase in the number of possible combinations, and clearly some potential confusion.

My opinion is that those are short-term issues because all of us are working on combinations. If you look at the next slide, our goal and I think the goal of many groups is to reduce back down to two immunizations per infant. There are a couple of different combinations that you could look at that different companies are working on that would do that. If you look at the first shot, which is usually referred to as the DTP or DTaP combination, there are groups working on those various combinations, some of which have all four of those antigens that are currently in use in that combination vaccine.

ISSUES RELATED TO MANUFACTURING COMBINATION VACCINES

Senator BUMPERS. Let me interrupt just a moment. Something just occurred to me. Some of those vaccines are made by different manufacturers. How are we going to let the manufacturers collaborate and cooperate on developing those? You have a patent on one, somebody else has a patent on another one. Yet we are trying to develop combination shots. How do we do that without violating antitrust laws?

Dr. PARADISO. Mostly that has been done through collaborations between the companies, through joint ventures between the companies. Sometimes it is consolidations and buyouts, and there are a number of ways that that happens.

Senator BUMPERS. But each company would have a right to sell the combination, wouldn't it?

Dr. PARADISO. Some companies have all four of those combinations or all of the components that go in. So you're right—

Senator BUMPERS. For example, if I had OPV or IPV and you had Hib and somebody else had DTaP, each one would want to manufacture its own combination.

Dr. PARADISO. Right.

Senator BUMPERS. And would they—that would have to be agreed to, of course, when you start in on the research of the combination vaccine?

Dr. PARADISO. Exactly, exactly.

Senator BUMPERS. Has that worked reasonably well in the past?

Dr. PARADISO. Yes.

Senator BUMPERS. We have some combination shots now.

Dr. PARADISO. Yes; there are, and those are the result of companies' own products and also the result of companies who have gotten together and developed vaccines and provided antigens together for specific products.

POSTMARKETING SURVEILLANCE OF VACCINES

Senator BUMPERS. One other question, Dr. Paradiso. It takes a long time sometimes, does it not, to determine whether or not this combination has any side effects? I mean, what if 10 years from now—if all the studies indicate that this combination shot is fully effective against all of the diseases it is designed to prevent and in 10 years a child gets measles or a child gets Haemophilus influenza b, are those possibilities, that over a 10-, 15-year period, much longer than the experimental stage of it—

Dr. PARADISO. I guess the question is, will they be more likely to get the disease as a result of the combination—

Senator BUMPERS. No.

Dr. PARADISO [continuing]. As opposed to when they were getting the—

Senator BUMPERS. No; I'm talking about efficacy.

Dr. PARADISO. Right.

Senator BUMPERS. To make sure that—we'll say you have a combination of three vaccines, and what I'm concerned about is how can we be sure of the efficacy of all of them when these studies—for example, if there are only 4,000 people and it takes a long time sometimes to determine efficacy. I mean, somebody may not be exposed to anything.

Dr. PARADISO. There are two ways, I think, that that can and is being done. We as part of our licensure approvals agree to do what are called postmarketing surveillance studies, in which we actually follow large populations. Usually now we are talking about populations of 100,000 or 150,000, children who receive the vaccine and then we follow them for rare adverse events—hospitalizations, emergency room visits, things that you would expect to happen in the 1 in 5,000, 1 in 10,000 very rare occurrences.

The second is, as Dr. Orenstein talked about, surveillance by the CDC both for adverse events and for disease rates. I think that those surveillance mechanisms and the support for those surveillance mechanisms are critical. We have had years where funding for that has been interrupted and we had gaps in some of our data. But I think it is critical over the next years that we continue to follow these vaccine-preventable diseases, because it is the only way we know whether we are keeping them under control and whether vaccines that we are using are effective.

ADULT IMMUNIZATION

Senator BUMPERS. You alluded, I think, did you not, to adult immunizations? What is the major impediment to adult immunizations?

Dr. PARADISO. I think adult immunizations are a broad category and in my mind would include adults of so-called middle age. There is a separate category that is women, pregnant women or women of childbearing age who could be protected against diseases or who could protect their young infants from diseases by being immunized. And then there is the elderly, who become more susceptible to quite a number of the diseases, including some of the ones we use in infants.

I think that the biggest impediment is that, especially outside the elderly population, either health care is not sought on a regular basis the way it is in infants or there is just not a recognition that these are populations that we can go after. The population has not been educated that these are diseases that not only affect those populations, but affect babies and other populations.

So a good example I think is acellular pertussis, where I think it is becoming clear that the increases in pertussis around the country are often not in infants, but actually in adults, and the result is that they can continue to spread that disease in the population. So they would be a target for acellular pertussis organizations.

Adults do not like to get immunized. They do not necessarily like to go to the doctor, and they need to be educated of the benefits, both to them and to their children. Potentially pregnant women can be educated that there are diseases that occur solely in infancy, like respiratory syncytial virus and group B streptococcus, where if they were immunized they could pass on that protection to their children.

I think it is important also to make those immunizations part of reimbursement systems, so that the doctors get reimbursed for doing that medical care in a preventive way, rather than therapeutically later on dealing with the infection.

PROGRESS IN LINKS OF IMMUNIZATION AND WIC PROGRAMS

Senator BUMPERS. Dr. Orenstein, let me turn to you for a moment. First of all, let me congratulate you and CDC on these immunization rates. Really, I think the White House is going to have something this week or next. Somebody told me this morning Betty and I had been invited over there for I guess some kind of an announcement about levels. Certainly CDC—I hope you will be there, Walt, even if I do not make it; I will let you speak for me, and I

will try to make it. But CDC deserves tremendous credit, because we have had some rocky times in the last several years, very difficult times.

The fact that these levels are as low as they are right now is a real tribute to you and it is a tribute to the State health offices and a lot of other people. But you are certainly entitled to a lot of it.

I wanted to ask you about some of the high risk demonstration projects that we funded last year. What progress, if any, have we made in linking WIC and immunization services?

Dr. ORENSTEIN. I also would like to thank you for all you have done in terms of helping us improve our immunization coverage and bring disease down. For so many years you have been a champion of this program and kept it going, and certainly, as the others have said before we will miss you when you leave. I cannot tell you enough how much I appreciate all the work that you have done to help us.

Senator BUMPERS. You know, Betty slept in another bedroom for a long time after I introduced that bill to require WIC recipients to prove that their children had been immunized. She thought that was the crassest thing she had ever heard of, so I had to fight her and Hilary and everybody else on that one. But really, I want to see if I can get back in her good graces with your answer this morning. [Laughter.]

OUTREACH ACTIVITIES

Dr. ORENSTEIN. Well, Senator, I know she is meeting this morning with some of our staff to discuss immunization-related issues.

In terms of the demonstration projects that you directed us to do, we have awarded grants to four areas, three urban areas—Detroit, New York City, and San Diego—and one rural area in Colorado. The urban areas combined serve a population of about 40,000 children and involve community health networks of about 43 different sites in these areas.

What they are doing is three things. First is to improve the immunization practices of their own clinics, which already serve substantial populations. That is, to try and reduce missed opportunities for immunization, to implement what we call a fix or repair the assessment of immunization coverage of children who attend their clinics and feed back and stimulate competition to improve immunization coverage, linkage with WIC and a variety of other things.

The second task that they are undertaking is to reach out using their stature as academic medical centers leading these community health networks to involve other health networks within that catchment area to get them to do the same thing.

The third task is to try innovative strategies with outreach.

All of them are coming to the conclusion that registries are extremely important, that it is very difficult to know how to improve coverage without having a better estimate of the overall population that needs to be reached. And they are all looking at trying to build those as well.

But I think we are optimistic. It is early now, but I think this is a step in the right direction. I think what is impressive to us is the enthusiasm of public health officials, academic medical centers,

the community health networks, and others. The brain power that is being brought to this process is a real step in the right direction.

MEASLES ERADICATION

Senator BUMPERS. Let me just say that we have always found that the providers share a good portion of the blame, have in the past, for the difficulty we have had in getting the rates as low as they are right now, because we have found that, as you know, in other studies people would bring their children into clinics 10, 15 times, nobody ever mentioned immunizations to them. So that has been a real problem.

Incidentally, as I look over the various combinations we are looking at, if I were a provider I would probably just slash my wrists and forget the whole thing. This is going to be a nightmare for a while. Presumably and hopefully, this will all wash out in time. But this is another one of those things we were talking about. Not only are combinations maddening as a result of this progress. We have all of these combinations coming on. But you think, if you are a provider out there and what shall you keep in your refrigerator? I thought that was a good chart on the refrigerators.

But in any event, I want an answer to that question on those pockets of resistance that we had run into over a period of time. But I also want to ask you—I think you testified or I have seen some data somewhere that all the measles cases, we believe that all the measles cases last year, for example, were not endemic, but they were imported.

No. 1, how do you know that? And No. 2, if that is in fact true, should we not start on an international eradication of measles, as we have on polio?

Dr. ORENSTEIN. Thank you very much.

Senator BUMPERS. Measles is still the biggest killer of children in the world, is it not?

Dr. ORENSTEIN. Right about 1 million deaths, even with the availability of good measles vaccine.

What we can say is since 1993 we have probably eliminated the indigenous transmission of measles about three times within the United States. The best evidence is in 1993 and comparing it to the years before 1993. Virtually all of the measles viruses isolated during the big epidemic of measles between 1989 and 1991 were of one type. That type has not been isolated in the United States since 1992. All of the viruses that have been isolated have been viruses that have been seen elsewhere in the world, implying that new viruses have come to the United States. None of these types of viruses were found during this earlier period.

The second is our surveillance data that show over prolonged periods in 1993, I believe in 1995, and certainly in 1996 going into 1997, there were very prolonged periods in which no cases at all were reported in the United States. So this is the reason why we think it has been interrupted.

I think that there is substantial progress with measles control abroad, which gives us also some feeling that measles can be eradicated. During our big epidemic of measles during 1990, almost 250 importations from Latin America were detected in the United States, many of them in U.S. citizens who had gone to Latin Amer-

ica and returned. In 1996 there were zero importations detected, even though we detected almost 50 importations from elsewhere in the world. So that we believe measles can be eradicated.

In July 1996 we convened, in cosponsorship with the Pan American Health Organization and the World Health Organization, a meeting to discuss the feasibility of eradication with some experts, and they said it could be eradicated, and actually recommended setting a goal for some time between 2005 and 2010.

One of the big issues to overcome in order to move forward is to get the political will, particularly in the developed world. Most of measles detected now is being exported from countries like Japan, Germany, Italy, and the like, and that is where I think we need to place more effort.

STATE CARRYOVER BALANCES FROM PRIOR YEARS

Senator BUMPERS. Let me ask you an additional question, Walt, about cost. The 317 program has had carryovers for the last several years, and I think the VFC program is up to close to one-half billion dollars a year, is it not?

Dr. ORENSTEIN. The actual appropriation had been that. The actual spending has been substantially below the appropriation.

Senator BUMPERS. Has it?

Dr. ORENSTEIN. Yes.

Senator BUMPERS. Well, that is an entitlement program.

Dr. ORENSTEIN. Right.

Senator BUMPERS. So we do not appropriate money for it.

Dr. ORENSTEIN. Right.

Senator BUMPERS. We give you whatever you need and there is no problem with the carryover there.

Dr. ORENSTEIN. Right.

Senator BUMPERS. But with the 317 program, these carryovers, of course, can be used presumably to cover some of the increased costs that we are facing here. But we are going to have to depend on you to tell us. I do not want us to wind up here putting these new vaccines, and some of them very costly—Varicella is what, \$34 a dose?

Dr. ORENSTEIN. Correct.

Senator BUMPERS. That is twice as high as any other vaccine that I know of.

Obviously, the cost is going to escalate for the 317 funds, for these 317 programs. We are going to have to depend on you to give us a little advance guidance on this, so that we do not wind up in the middle of the year out of money, because, as I say, we are adding a lot of new vaccines and combinations and the cost is going to grow. There will be no problem getting the money appropriated here. All we need to know is what is the right amount to deal with this.

I have more questions here that I would ask. Dr. Osterholm, let me turn to you. You mentioned bar codes. I was intrigued by that, but I did not understand it.

CONFUSION CAUSED BY NUMBER OF VACCINES ON THE MARKET

Dr. OSTERHOLM. Mr. Chairman, today what we are seeing happening in many of our clinics out there, both in terms of the private

practice and public health clinics, is we have people such as certified medical assistants who really have minimal understanding of all this combinations, and they are basically trying to do medical ordering much as we would do today out of a hospital pharmacy, where we would require a pharmacist to actually draw the meds and you would require that there be double or triple checks before those meds are delivered in the hospital setting.

In our clinics today we are finding that, with all the confusion and not understanding what these different vaccines mean—it was very easy when there was an MMR or there was a DPT or there was a polio to do it. So that what this would allow you to do actually is take some of the confusion out of which vaccines are you using and in fact which vaccines do you need.

The ideal system would be if you had a child's total immunization history to that point electronically there, and that it could then print out for you in a program what are the appropriate immunizations you need to either minimize the number of injections or minimize the number of different types of products, and that that could then be reliably verified by what is on the vaccine and what is on the medical charts. In other words, it matches it up and it spits out for you what you need.

We do this in blood banking. We do this in a lot of other areas, where the reliability then is assured through that process, as opposed to having some certified medical assistant make a decision about these are the vaccines we really need here.

BAR CODING OF VACCINES

Senator BUMPERS. Dr. Paradiso, what do you think about that?

Dr. PARADISO. I think it is a great idea. We use bar coding to do all of our clinical trials, so that each vaccine vial is bar coded and when the child is immunized the bar codes gets put on his record and it gets on the vial and it goes into the computer. The samples from the child get sent with a bar code. You do not write anything.

Senator BUMPERS. You eliminate a lot of human error and get a lot of human information.

Dr. PARADISO. The computer reads all the information and spits it back.

Senator BUMPERS. That sounds pretty fascinating to me. Of course, that is up to you all, I assume, to do that. I do not think we are going to take that upon ourselves here, to order you to do it. It seems to me that that is just something that ought to be done by the pharmaceutical companies.

IMMUNIZATION REGISTRIES

Dr. PARADISO. Well, yes, but in terms of the registries that allow the tracking, these are systems that need to be developed.

Senator BUMPERS. Yes.

Dr. PARADISO. We can put the bar codes on, but it needs to be fit within a system.

Senator BUMPERS. Dr. Osterholm, you talked about the automatic tracking system. Several years ago you did not much endorse this notion before this committee. Have you changed your mind?

Dr. OSTERHOLM. Mr. Chairman, I think that may be a slight misinterpretation.

Senator BUMPERS. It probably is.

Dr. OSTERHOLM. What I was trying to do is predict history for you, and in fact I can tell you that one of the more memorable meetings I have had in my career was with your wife, who in 1991 or 1992 was in a meeting with me at the Carter Center. Obviously, I have the same respect for Mrs. Bumpers as I do you, and I was trying to share with her that I did not believe that the climate was right in the United States for mass proliferation of a smart card with everybody's record on it, as has been promoted by many people.

She I think misinterpreted that, as maybe this committee did, that I was speaking against it. I was merely trying to say the reality is this is not going to happen. Well, here we are 5 years later and it has not happened.

Senator BUMPERS. You are right.

Dr. OSTERHOLM. And I have run into that same problem in my own State legislature trying to get registry efforts through, in which there is a segment of society that says: Stay out of my life, I do not want you in there. So we continue to struggle with that.

Do I think registries are the right thing and the best thing for public health? Absolutely. So what I am trying to do is kind of, I think you might say, bridge the gap between reality and what is ideal and what can we find. So I very strongly support the registry approach. I think that, given a State like ours, where I mentioned 25 percent of the children in managed care each year are changing health plans, moving that data with them has been very difficult. This would be ideal.

So we very much promote the idea and we believe it has to start at a State and local level, and that has been very difficult. I think Mrs. Bumpers, who has probably shared with you that, if you look at the Robert Wood Johnson effort, that I am on the executive committee of the All Kids Count Program and, as much as I think that there have been some real pluses, I am still disappointed that 5 years into that effort we still do not have a major national initiative and a real groundswell of support to put these into place.

What we have had are local providers, which have been great. But we need to do much more in this area.

TRACKING IMMUNIZATIONS OF CHILDREN

Senator BUMPERS. Well, I agree with that. Tracking is working to some extent in some areas. You know, I do not know that we will ever be able to develop a total tracking system. It obviously will never work perfectly. But every time you get a child in the tracking system so that you know exactly where that child is in the immunization schedule and everything, you are just that much better off, because there are so many people who are changing providers all the time and it is just impossible to keep up with what the child has been immunized against and what he has not been immunized against.

I always thought Betty was kind of a Johnny One Note on that. She just talked about that incessantly for years. And she is still enamored of this fellow down in Mississippi, I guess, who started the first tracking system. It has much to be said for it, but it has not—

we just have not committed to it is the reason it has not worked, and maybe we never will.

But as I say, for everybody that goes into the tracking system, that is a big plus.

I think that just about covers most of the questions I had except some that I do want to—oh. For all of you, let me ask this question. The role of the advisory committee is changing as the vaccine market changes and recently the advisory committee decided to request and review a new cost-benefit analysis on Varicella vaccine, which was approved by the committee last year.

COST BENEFIT OF VACCINES

Is it appropriate for the advisory committee, which is an independent panel of scientists, to make economic decisions related to cost-benefits? And should the committee confine its advisory role to safety, efficacy, and public health criteria?

Shall I repeat that question? Do you understand what I am saying? Dr. Paradiso, are you familiar with that committee? I used to hear about it every night when Betty went, but I do not hear much about it any more.

Dr. PARADISO. Yes; I am. I think it is fair to say that that is a committee of public health experts and medical experts, and their job has traditionally been to make recommendations on vaccines on the basis of medical need. Cost effectiveness or cost-benefit has been part of that analysis and obviously it is related to the need and to the requirement for a vaccine and on the basis of the disease.

I think the difficulty that the group is—the difficult position they are put in is when, once they have decided that there is a public health need and that the vaccine should be recommended, if they have to then go back and redecide on the basis of the dollars that are going to be spent, then that puts them in a difficult situation where potentially they could be preventing coverage for certain portions of the population, either while they are making that decision or forever if the recommendation is not made.

So it seems to me that the goal for that committee and what Congress' intent was for them to make that decision once, to decide whether a vaccine should be recommended universally, and if it is then that becomes part of the entitlement program you mentioned. I think that creates a situation that the committee can deal with, and it allows them to act on the basis of their expertise.

Senator BUMPERS. You want to comment on that, Dr. Osterholm?

Dr. OSTERHOLM. Well, I think from the standpoint of cost benefit I guess the issue really becomes one of what we mean just by cost benefit, if we are talking about dollars as the meaning here. I think that—

Senator BUMPERS. Well now, let me interrupt you just a moment to make this question a little more interesting. You know, it was the committee that decided how we ought to mix OPV's and IPV's, and so far as I know that is the regimen we are now following. Is it not, Walt?

Dr. ORENSTEIN. That is correct.

Senator BUMPERS. In the country on how we give oral and intravenous polio vaccines. And I thought that was an appropriate role

for them. They are scientists. I never understood why Betty was on that committee. She just really had no business being on it. In a way, she learned a lot. But that is a scientific committee who makes really important recommendations, as they did in that case.

I am not saying that they should not be precluded from doing cost studies, because in these combinations the combination we pick is going to have everything to do with the cost of this program. If you can eliminate the doctor—if you can make one doctor visit and get five antigens, as opposed to making three visits, you save a lot of money.

So it seems to me that it is hard to extricate the two, but I just wanted to know whether you thought this group of scientists really had any business working on anything except safety and efficacy and should add cost-benefit analyses to their studies?

Dr. OSTERHOLM. Actually, I appreciate that additional information, because actually I was going to try to take the question in that very direction.

Senator BUMPERS. Well, feel free to go any direction you want.

PROBLEMS RELATED TO VACCINE DELIVERY

Dr. OSTERHOLM. And again, I do not mean to presume here, but I will there to help provide why I think Mrs. Bumpers played a key role on that committee as a group of scientists. Imagine today if you had a petroleum company that could make the world's best gas, that had the most clean kind of burning gas, that had the most power, they had the engineers that could build the best gas stations, et cetera, et cetera, but they really screwed up on the pumps and nobody knew how to use them.

So when it came time to put your gas in the car nobody went there because they could not figure out how the devil to make the pump work. Sometimes that is just kind of Joe Citizen that helps them with that.

I think what this committee actually needs to do is have more Joe Citizen approaches to the world to help people understand that you can have the best vaccine in the world, you can have the most elaborate delivery system, but in fact the people are not going to use it or they are going to be so confused as to how to use it that they do not use it. That is where the problem is.

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES [ACIP]

I think ACIP, if I had to say one observational kind of statement about ACIP is I think we need to look much more at combination vaccines. This should not be a government versus industry or public health versus private sector or consumer versus whatever. This is about in the end how do we get the most vaccine in the most kids, which satisfies everybody's outcome.

I think the combination vaccines, as I said in my testimony this morning, is a major problem. I think what Mrs. Bumpers does is bring a reality to that very point that says: "Do not give me the best and most number of antigens there if I cannot get it into kids; I have got to get it into kids." So I think that that committee needs to do much more in looking at that very prospect.

Senator BUMPERS. Well, my crack ace aide Mary Ann Chaffee agrees with you on that, too.

Dr. OSTERHOLM. Then it must be right.

MEMBERS OF ACIP

Dr. ORENSTEIN. I just wanted to clarify. Who are the members of ACIP and whether they are scientists versus other kinds of people? The ACIP presently consists of 10 people. Of that group, four of them are public health officials, two State epidemiologists, one State health officer, and a local health officer who administers an immunization program.

VACCINE DELIVERY ISSUES

It has people on it who are university scientists, who are involved with actual vaccine-related research. And it has plans to increase its membership from 10 to 12 to include more people who have expertise in immunization delivery in the private sector.

I think it is extremely important that they take cost-benefit and cost-effectiveness issues into account in their recommendations because these issues are independent—their recommendations go beyond what the Government purchases. These are recommendations that basically affect public health practice and even practice in private medicine. So I think they need to understand when they make a recommendation whether this is something that will be acceptable.

In terms of whether their recommendations should automatically be funded, it is a very controversial one, I think, as you point to, because one of the things that they do not take into account is what else in the budget might suffer in promoting the vaccine side of it. The advantage for us in the immunization program is that we can more rapidly, even with the two-step process, more rapidly implement and have more assurance that we can implement it when they make their decisions.

So these are the two balancing factors that need to be considered in their decisions.

ACIP RECOMMENDATIONS

Senator BUMPERS. A final question: Are we going to be looking to the advisory committee to determine which combinations would be most viable?

Dr. ORENSTEIN. I think what the advisory committee is doing is trying to work with a whole group of people to develop a set of recommendations for combination vaccines. Industry is participating in that discussion.

Senator BUMPERS. Of course.

Dr. ORENSTEIN. These are complicated kinds of things. Whether the committee will say, we will take only this five-combination vaccine, I doubt this will happen. If there are certain data that show the merits of that far exceed the merits of any other combination available, I think the committee would recommend it.

But I think what I see happening is a much more murky process, where it will not be crystal-clear which combinations are better than others. I think what the committee is attempting to do is to settle on some basic principles, the principles being: One, the preference, whenever feasible, for combination vaccines to avoid extra

injections and potential extra visits; second, they are addressing issues of interchangeability so that the physicians have guidance on that. The third issue they are talking about is giving permission to limit the inventory or formulay if necessary, such as in refrigerator 1, which was the simplest one in my example.

ADVANTAGES OF TRACKING IMMUNIZATIONS OF CHILDREN

Another issue they are saying is, at times, for simplicity's sake, it may be necessary, it may be acceptable to administer extra antigens, such as would occur using the two Hib combinations discussed earlier. Also the ACIP will push for getting better data systems to determine what the child previously received and, therefore, put the doctor in a better position to determine what the child needs. And we have been talking with industry about bar coding, but, as Dr. Paradiso points out, far more is needed to try and determine what a child has actually had.

One of the things and one of the advantages of potential registries in the future is that we can build in algorithms so that, given what a child has, it can automatically tell a doctor or a nurse, this is what you should be giving. Right now it can be, as Dr. Osterholm, I think, pointed out beautifully, it can be extremely confusing. If we can automate through an electronic system, that would be of help.

That is what I think the committee will do. I think there is another committee——

Senator BUMPERS. Well, FDA has to do this first, do they not?

Dr. ORENSTEIN. Correct.

Senator BUMPERS. FDA is going to have to approve the combination first.

Dr. ORENSTEIN. Correct.

Senator BUMPERS. Based on the tests submitted by the pharmaceutical company.

Dr. ORENSTEIN. Correct. And then what one will have to look at is what the other issues are in terms of recommendations versus use. What I think the committee in the past has done, and which I think they will continue to do is, if there are clear indications one is better than another, the committee will recommend the better vaccine. If it is not, the committee will allow choice. But even in choice, I think we, at CDC, have an obligation to begin helping States figure out what they should purchase.

One of the things that we are working on at CDC is to develop economic models that will help States. They can plug in things to figure out which vaccines to purchase. For example, there was a lot of controversy when the first DTP-Hib vaccines came out. One of them was premixed, one of them you had to mix. The one that was premixed was a little bit more expensive. We made a decision that, since they both protected against the same diseases, go ahead and get the cheaper version. I think many States were upset by that.

We are working with the States to allow some flexibility in choice such that, if, in fact, it takes more nurse time to mix then they actually save with the unmixed version, they can buy the premixed product. Those are the kinds of things I think we will need to do in the future.

NEW APPLICATIONS FOR FDA APPROVAL

Senator BUMPERS. Dr. Paradiso, does Wyeth-Lederle have any applications before FDA right now on new applications?

Dr. PARADISO. Yes; we have an application for a DTaP-Haemophilus b combination, also for use in toddlers. We are the premixed group for that combination as well as the first one.

THE EFFICACY OF COMBINATION VACCINES

Senator BUMPERS. I must say, I think I would opt for the premixed.

Dr. PARADISO. I guess what we feel that we need to see is that those providers are able to choose the vaccine on that basis. We took the extra effort to make it premixed because it would be more user-friendly and it would give us an edge over the competition. And if the Government is going to be the major purchaser of vaccines and we lose that edge, then it takes the incentive out of doing that extra step and trying different combinations.

For the list, we will be working on a lot of those. We cannot work on all of them. But we cannot predict which ones are going to work. So it is a gamble for us. The fact that there are so many groups working on it sort of spreads out the gamble.

We, as the other companies, are global vaccine groups and so we are thinking of other markets. Other markets do not use hepatitis B, other markets do not use IPV, have different—some do not use acellular pertussis. So there will be an array of combinations that will be developed for various populations and that will be available for use in the United States. I think it is my feeling that if the committee is going to make kind of recommendations, it should be predominantly what antigens that they would like to see in those mixtures or in the total sum of the mixtures, what antigens would they like to see for kids at 2 months of age; and second, how many shots do they think they can tolerate. And if the answer is two, then it is our job to fit all of them into two shots. If it is three and we can get provider acceptance of that, then that is a different scenario.

I think the goal should be to reduce the number of shots, as everybody does, and to set a standard in that way.

Senator BUMPERS. Do any of you have answers to questions you wish I had asked?

Dr. OSTERHOLM. Well, maybe if I could elaborate on this point that was just made. I think that one of the concerns that we still have in Minnesota, a State with a very expanded VFC program—offering all three of the DTaP's, for example—is that we still have to interface with the private sector, where kids will come from. So if a particular pharmaceutical company aggressively markets a particular combination vaccine which may not in the wisdom of everyone else be the most compatible or the most schedule-friendly vaccine and a child comes from a practice where that vaccine was administered because of a cost advantage initially to that private practitioner and now comes back into another system that is primarily VFC, we now still have to respond to that. In other words, we still have to be sensitive.

So we cannot set our VFC program, for example, in isolation because we are mixing and matching clients all the time. I think this is a very important consideration, and what we see today is one pharmaceutical company or two pharmaceutical companies aggressively marketing one or two of the combinations, which then makes it inconsistent with all the rest.

We need to help standardize that because that is what is causing the confusion. And I think the pharmaceutical industry is underestimating the backlash that is going to occur in the next 2 to 3 years around this. I can tell you right now in pediatric meetings, meetings of family practitioners, this is the highest frustration level issue we have. It is not even in Minnesota how much they are being reimbursed in managed care in general. It is around immunizations and the confusion.

What we are afraid we are going to see in the very near future is people saying, this is just so difficult for us, so confusing, we are going to send all of them to you guys; you all in the public sector, just take this. We have worked hard in Minnesota for years to keep our children in their clinic homes and to try to keep them in the private sector and support that ongoing relationship, and they have about had it.

STANDARDIZATION OF VACCINE DELIVERY

So I think that somebody has to provide the national leadership to say that we have to come together somehow and start to understand how we can standardize around this, and that cannot be automatically knee-jerk interpreted by the industry as meaning we are going to regulate it to say you have to have this. That cannot be at the Government level saying that we cannot do anything about it.

Somewhere somebody has to come together, or the consumers will do it for us and we will be back here talking about lots of cases of disease, because we will have watched the ebb and flow of immunization levels.

Senator BUMPERS. Dr. Osterholm, when I send each of you written questions I would like for you to put what you said in writing and any elaboration on that in writing to me.

Dr. OSTERHOLM. I would be happy to.

CONCLUSION OF HEARING

Senator BUMPERS. It is a very interesting point you just made and it makes a lot of sense.

Gentlemen, I thank you all very much for your time and fine eloquent statements this morning. I think this is extremely helpful to me and it will be to the committee and the Congress.

Thank you again for being here, the subcommittee will stand in recess subject to the call of the Chair.

[Whereupon, at 12:08 p.m., Wednesday, July 16, the hearing was concluded, and the subcommittee was recessed, to reconvene subject to the call of the Chair.]