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VACCINES SAVE LIVES: WHAT IS DRIVING PREVENTABLE DISEASE OUTBREAKS?

HEARING

OF THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS

UNITED STATES SENATE

ONE HUNDRED SIXTEENTH CONGRESS

FIRST SESSION

ON

EXAMINING VACCINES, FOCUSING ON PREVENTABLE DISEASE OUTBREAKS

MARCH 5, 2019

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C O N T E N T S

STATEMENTS

TUESDAY, MARCH 5, 2019

VACCINES SAVE LIVES: WHAT IS DRIVING PREVENTABLE DISEASE OUTBREAKS?

Tuesday, March 5, 2019

U.S. SENATE,
COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS,
Washington, DC.

The Committee met, pursuant to notice, at 10:02 a.m., in Room SD–430, Dirksen Senate Office Building, Hon. Lamar Alexander, Chairman of the Committee, presiding.

Present: Senators Alexander [presiding], Isakson, Paul, Cassidy, Roberts, Scott, Braun, Murray, Casey, Baldwin, Murphy, Warren, Kaine, Hassan, and Smith.

OPENING STATEMENT OF SENATOR ALEXANDER

The CHAIRMAN. The Senate Committee on Health, Education, Labor, and Pensions will please come to order. Senator Murray and I will each have an opening statement, and then we will introduce our witnesses. After the witnesses' testimony, Senators will each have five minutes of questions.

It was not long ago, when I was a boy, that I remember the terror in the hearts of parents that their children might contract polio. I had classmates who lived in iron lungs. The Majority Leader of the United States Senate, Mitch McConnell, contracted polio when he was very young. He has a poignant story about his mother, did not know what to do, but she took him to Warm Springs because that is where President Roosevelt went. And for a long period of time, when he was two or three years old, she massaged his legs several hours a day, which is hard to imagine if you remember toddlers. And that is why he is able to walk today. Thousands of others are not so lucky.

Following the introduction of a vaccine in 1955, polio was eliminated in the United States in 1979, and since then, from every country in the world except three. Polio is just one of the diseases we have eradicated in the United States thanks to vaccine. Before the vaccine for measles was developed, up to four million Americans each year contracted the highly contagious, airborne virus. In 2000, the Centers for Disease Control and Prevention, CDC, declared measles eliminated from the United States. In the 1980s, smallpox was declared eradicated from the world by the CDC and the World Health Organization. These stories of polio and measles and smallpox are a remarkable demonstration of what modern

medicine can accomplish in the lives of millions of people in our country and in the world.

Four years ago, this Committee held a hearing on vaccines. That was following the 2014 outbreak of measles, the worst outbreak since the disease was declared eliminated in 2000. Even though 91 percent of Americans had been vaccinated for measles in 2017, according to the CDC we continue to see outbreaks of this preventable disease because there are pockets in the United States that have low vaccination rates. Last year, there were 372 cases of measles, the second highest number since 2000.

So far this year, there have been 159 cases reported and outbreaks confirmed in Washington State, New York, Texas, and Illinois. We know some Americans are hesitant about vaccines, so today I want to stress the importance of vaccines. Not only has the Food and Drug Administration found them to be safe, but vaccines save lives. Vaccines have been so successful that until recently, Americans have lived without fear of getting measles, polio, or rubella. We have made significant strides in improving vaccination rates. In 2009, about 44 percent of Americans had received vaccines for seven preventable diseases, all of which I will now try to pronounce, diphtheria, tetanus, pertussis, polio, measles, mumps, and rubella, haemophilus, influenza type B, hepatitis B, chickenpox, and pneumococcal according to the CDC. Today, over 70 percent of Americans are vaccinated against all seven of these diseases.

Vaccines protect not only those who have been vaccinated, but the larger community. This is called herd immunity. There is some young people who cannot be vaccinated. They are too young, or they have a weak immune system because of a genetic disorder, or they are taking medicine that compromises their immune system like cancer treatment. Vaccines protect those who cannot be vaccinated by preventing the spread of disease. However, low immunization rates can destroy a community's herd immunity. While the overall vaccination rate nationwide is high enough to create this herd immunity, certain areas, the pockets of the country where vaccination rates are low, are vulnerable to outbreaks.

There is a lot of misleading and incorrect information about vaccines that circulates online throughout social media. Here is what I would like for parents in Tennessee to know—parents in Washington, parents in Texas, everywhere in the country. Vaccines are approved by the Food and Drug Administration. They meet the Food and Drug Administration's gold standard of safety. The advisory committee on Immunization Practices makes recommendations on the use of vaccines in our country and annual child and adult vaccine schedules. This advisory committee is made up of medical doctors and public health professionals from medical schools, hospitals, and professional medical organizations from around the country. They are among the best our country has to offer. They have dedicated their lives to helping others. These recommendations are reviewed and approved by the CDC Director, and are available on the CDC website. There is nothing secret about any of these signs, and countless studies have shown that vaccines are safe.

Internet fraudsters who claim that vaccines are not safe are preying on the unfounded fears and daily struggles of parents, and they are creating a public health hazard that is entirely preventable. It is important for those who have questions about vaccines, especially parents, to speak with a reputable health provider. As with many topics, just because you found it on the internet, does not mean that it is true. The science is sound. Vaccines save lives, the lives of those who receive vaccines and the lives of those who are too young or vulnerable to be immunized. Before I turn this over to Senator Murray, I want to add that the National Childhood Vaccine Injury Act of 1986 required the Department of Health and Human Services to submit a report to Congress within two years after the legislation was signed into law.

The HELP Committee has received two reports from the Department submitted to Congress May 4th, 1988 and July 21, 1989. I ask consent that the reports be submitted to the Committee record so they can be more accessible to the public.

[The following information can be found on pages 54 and 126 in Additional Material:]

The CHAIRMAN. Senator Murray.

OPENING STATEMENT OF SENATOR MURRAY

Senator MURRAY. Thank you very much, Mr. Chairman.

As Washington State and several other states grapple with measles outbreaks, this issue cannot be more timely. I remember in 2000, when measles was officially eliminated from the United States, and what welcomed news that was for families across this country. And I remember the years of efforts that actually led to that victory.

Before the vaccine was available, measles outbreaks used to spread through communities like wildfire. If you were old enough to drive, odds were, you had already had measles. But today, vaccines that protect against measles have been in use for over 50 years. Like other vaccines, we know the vaccine is safe, it is effective, and it saves lives. Which is why today a generation of students are starting College, almost none of whom had to worry about a measles outbreak at school. It also means a generation of new parents may not appreciate just how dangerous measles is.

Before introduction of the measles vaccine and widespread vaccination, millions of people caught measles annually, meaning thousands were hospitalized, hundreds of people died, mostly children under 5 years old. But measles is not just deadly, it is also one of the world's most contagious diseases. It is easily transmitted through coughing and sneezing. It can linger in the air and on infected services for two hours. It is already contagious four days before an infected person develops a rash, and then another four days after. 9 out of 10 unvaccinated people exposed to measles catch it. That is why the measles vaccine is so important in providing protection. Experts say, in order to establish herd immunity against measles, in order to prevent an outbreak from occurring within a community, at least 95 percent of people should be vaccinated. Meeting that threshold is crucial to protect people who are unable to get vaccinated, infants, those with certain medical conditions.

Unfortunately, while the national vaccination rate remains high in communities across the country, we are falling behind. Vaccine coverage rates are declining in certain areas, contributing to the rise in preventable outbreaks like in Clark County, Washington, where public health officials continue to respond to a measles outbreak. The immunization rate among children in that community is less than 70 percent, far below what is needed to keep families safe. The result is a true public health emergency, over 70 confirmed cases and counting. And the majority of cases have affected children under 10 years old, who are unvaccinated. Each case is not just a concern for family members who are worried about their loved ones who are seriously sick, it is a threat to neighbors and communities left struggling to get an incredibly contagious disease under control. It is a terror for parents with newborns who cannot yet get vaccinated, and a strain on our public health system as hundreds of staff in Washington State are pulled from critical public health roles to respond to this crisis. And the Centers for Disease Control and Prevention stretches to support the response to outbreaks in Washington and several other states.

Measles is not the only disease that deserves our attention amidst slipping vaccination rates. Diseases like the Chairman mentioned, mumps, pertussis, or whooping cough are also cause for concern. These outbreaks are a clear sign we have to do more to address vaccine hesitancy, and make sure parents have the facts they need to understand the science. Vaccines are safe, and effective, and life-saving. Parents across the country want to do what is best for their families to keep them safe, which is why they need to be armed with knowledge about the importance of vaccination. And why we need research into vaccine communication tools and strategies to help us better educate people to address vaccine hesitancy and build vaccine confidence.

We also need to understand the roles social media and online misinformation play in spreading dangerous rumors and falsehoods, and we need to better prepare the full spectrum of health care providers, who are often the professionals people trust most, to counter vaccine hesitancy and promote vaccination. That is important not only for parents, but also for expectant parents who may already be deciding whether or not they plan to vaccinate, and for promoting adult vaccines and encouraging people to protect themselves and others throughout their lives.

I look forward today to hearing from Dr. Wiesman about how Washington State is working now to get parents reliable information about the importance of vaccination. And from all of our witnesses who are here today about how the Federal Government and other partners can promote vaccines and prevent the spread of misinformation. And while we are now fighting multiple measles outbreaks, it is important we also educate people on the HPV vaccine's role in preventing sexually transmitted diseases and lowering cancer risks. The flu vaccine, particularly on the heels of one of the most deadly flu seasons in years, the whooping cough vaccine specially for those around infants who are particularly susceptible to the disease, and the value of other recommended vaccines.

We also need to make sure we are approaching the public health challenges like this from a global perspective because we know dis-

eases are not stopped by borders or walls or bans. They are stopped by doctors, and nurses, and vaccines, and public health awareness. And are stopped by strong investments in public health systems here at home and abroad. They say an ounce of prevention is worth a pound of cure. That is certainly the case here. A dose of MMR vaccine covering measles, mumps, and rubella is about $20, meanwhile Washington State has spent over $1 million already addressing the current measles outbreak. Investing in prevention is not just more effective in keeping our families and communities healthy, it is also more affordable as well. The vaccines for children program is another great example of this. Over 25 years now, it has helped kids in low-income families get shots at no cost. It has saved $1.6 trillion, prevented 380 million illnesses, and saved 860,000 lives. That is more people than live in Seattle.

I hope we can work together in a bipartisan way to build on programs like this with strong steps to help address public health crisis, and better yet, to prevent them from happening in the first place. And I am glad to have this opportunity to learn more about how we can do that, and to consider how to make sure people across the country understand that vaccines are safe and effective to keep their families and their community healthy.

Mr. Chairman, I would ask that a letter from the National Association of County and City Health Officials be submitted for the record. It speaks to the important role of our local health departments across the country in responding to vaccine-preventable disease outbreaks and other emergency health threats.

The CHAIRMAN. So, ordered.

[The following information can be found on page 178 in Additional Material:]

The CHAIRMAN. Thank you, Senator Murray. We will now introduce our witnesses. Each one of you will have up to five minutes for questions and answers. I will ask the Senators, just try to keep questions and answers within the 5-minute period of time so everyone can have a chance to participate. Senator Murray will introduce the first witness.

Senator MURRAY. Well, thank you again Mr. Chairman. From my home State of Washington, I am very pleased to introduce Dr. John Wiesman. Dr. Wiesman was appointed as Washington State's Secretary of Health back in 2013, and his service there is just the latest in a 22-year career working to keep our families and communities healthy. Throughout his career, he has worked at four different health departments, including Clark County Public Health in Vancouver, which is the current frontline of our measles outbreak in our state.

Dr. Wiesman, I know some of my colleagues on the Committee will appreciate learning that before you came to my state to work in our public health system, you got your education in theirs, receiving your bachelor's degree in Wisconsin, your Masters in Connecticut, and your PhD in North Carolina. I am glad we have you now in Washington State, working to help keep our families safe and healthy, and respond to public health threats as we currently are. And I appreciate so much you coming all the way out here from our other Washington.

The CHAIRMAN. Thank you, Senator Murray. Senator Isakson, will you introduce our second witness.

Senator ISAKSON. Thank you very much, Chairman Alexander. I am very pleased to introduce to the Committee and everyone here today Dr. Saad Omer—and I believe that is the right pronunciation, is not?

Dr. OMER. Close enough.

Senator ISAKSON. Close enough, good. Well, mine is Isakson and I just want to make sure we got it right.

[Laughter.]

Senator ISAKSON. We are very delighted to have him here today as an expert on the subject we are discussing. Dr. Omer is a William H. Foege Professor of Global Health and Professor of Epidemiology and Pediatrics at Denver University School of Public Health and Medicine. Dr. Omer also works in the Emory Vaccine Center, making him a well-qualified witness for today's hearing.

His research includes studies in the United States and internationally, including clinical and P.O. trials to estimate the efficacy of influenza, polio, measles, and other vaccinations. Dr. Omer has published approximately 250 papers in peer-reviewed journals and has served on several respected advisory committees and panels, including U.S. National Vaccine Advisory Committee. He has also mentored over 100 junior faculty members, clinical and research postdoctoral fellows, and PhD and other graduate students, playing an important role in ensuring that the pipeline of qualified scientists is well stocked in the United States of America. Dr. Omer, welcome to the Committee today. We are here for your expertise. We appreciate your testimony, and "go Emory."

[Laughter.]

The CHAIRMAN. Thank you, Senator Isakson.

Third, we will hear from Dr. Jonathan McCullers. He is Chair of the Department of Pediatrics of the University of Tennessee Health Science Center. Services as Pediatrician and Chief at the remarkable Le Bonheur Children's Hospital in Memphis. Received his medical degree and completed his internship and residency at the University of Alabama at Birmingham. In 1999, he was named a St. Jude's scholar in the Physicians Scientist Development Program and joined the St. Jude's faculty in the Department of Infectious Diseases, where he spent 13 years managing a translational research lab studying influenza viruses and bacterial pneumonia. In 2012, he joined Le Bonheur. He has published more than 150 peer-reviewed articles.

Fourth, John Boyle. He is President and CEO of the Immune Deficiency Foundation in Towson, Maryland, which is focused on meeting the needs of people with primary immunodeficiency disease. Prior to joining the foundation, he worked for the Children's National Medical Center and the Platelet Disorder Support Association. He received his Bachelor of Science from Boston University. A Master in nonprofit management from Notre Dame of Maryland University.

Finally, we welcome Ethan Lindenberger. Mr. Lindenberger is currently a student at Norwalk High School in Norwalk, Ohio. He is here to share his experience seeking out information about vac-

cines and making decisions about whether or not to become vaccinated.

Welcome again to all our witnesses.

Dr. Wiesman, let us begin with you.

Dr. WIESMAN. Great.

The CHAIRMAN. Dr. Wiesman, excuse me.

STATEMENT OF JOHN WIESMAN, DRPH, MPH, SECRETARY OF HEALTH, WASHINGTON STATE DEPARTMENT OF HEALTH, OLYMPIA, WA

Dr. WIESMAN. Very good. That is good. Chairman Alexander, Ranking Member Murray, and distinguished Members of the Committee, thank you for the opportunity to discuss public health's work in protecting people from vaccine-preventable diseases.

Vaccines are safe, effective, and the best protection we have against serious preventable diseases like measles. Vaccinating children in the United States has saved millions of lives, increased expectancy, and saved our society trillions of dollars. My admission as Washington's Secretary of Health is to protect and promote the health of all its people and ensure our public policy is based on best available science. I want to speak directly to the parents who have children with serious health issues, and who have been attending our hearings in Washington State and are watching this hearing today. I see your pain and your desire for answers to your children's health issues. Your mission to protect and promote the health of your children is one we share.

While the science is clear that vaccines do not cause autism, we do need to better understand its causes. We need to develop together, affected families, scientists, and public health officials, research agendas to get the answers we need. State, territorial, and tribal, local public health agencies are on the front lines. In Washington State, we provide all recommended vaccines without charge to all children under the age of 19. We provide an electronic immunization information system for healthcare providers to track vaccine dose schedules, provide reminders when patients are overdue, and measure immunization rates. We help parents make informed decisions by sending them the information they need to keep children healthy and publish plain talk about childhood immunization. And we assist school nurses by giving them access to the electronic immunization records.

As of yesterday, Washington State's measles outbreak had 71 cases, plus 4 cases associated with our outbreak in Oregon and one in Georgia. Containing a measles outbreak takes a whole community response led by governmental public health. The moment a suspected case is reported, disease investigators interview that person to determine when they were infectious, who they were in close contact with, and what public spaces they visited. If still infectious, the health officer orders them to isolate themselves so they do not infect others, notifies the public—the community about the public places that they were in when they were infectious, and stands-up a call center to handle questions.

We also reached out to individuals who were in close contact with the patient. If they are unvaccinated and without symptoms, we ask them to quarantine themselves for up to 21 days. That is

how long it can take to develop symptoms, and we monitor them so that we quickly know if they develop measles. If they show symptoms, we get them to a healthcare provider and obtain samples to test for measles. And if they have measles, we start the investigation process all over again. This is a staff and time intensive activity, and it is highly disruptive to people's lives. Responding to this preventable outbreak has cost over $1,000,000 million and required the work of more than 200 individuals.

What do we need from the Federal Government? First, we need sustained, predictable, and increased Federal funding. Congress must prioritize public health and support the Prevention and Public Health Fund. We are constantly reacting to crisis rather than working to prevent them. The association of state and territorial health officials in over 80 organizations are asking you to raise the CDC budget by 22 percent by FY2022. This will immediately bolster prevention services, save lives, and reduce health care cost.

Second, our response to this outbreak has benefited greatly from the Pandemic and All-Hazards Preparedness Act, so thank you. The Public Health Emergency Preparedness Cooperative Agreement and the Hospital Preparedness Programs authorized by this law are currently funded $400 million below funding levels in the 2000s. More robust funding is needed, and I strongly urge you to quickly reauthorized PAHPA because many of the authorizations expired last year.

Third, the 317 Immunization Program has been flat funded for 10 years. Without increased funding, we cannot afford to develop new ways to reach parents with immunization information, nor maintain our electronic immunization systems. Fourth, we need Federal leadership for a national vaccine campaign spearheaded by CDC in partnership with states that counter the anti-vaccine messages similar to successful Truth Tobacco Prevention campaign. We have lost much ground. Urgent action is necessary. Everyone has a right to live in a community free of vaccine-preventable diseases. To make this a reality, we must continue to invest in and strengthen our public health system.

Thank you.

[The statement of Dr. Wiesman follows:]

PREPARED STATEMENT OF JOHN WIESMAN

Chairman Alexander, Ranking Member Murray, and distinguished Members of the Committee, thank you for the opportunity to appear before the Senate Committee on Health, Education, Labor and Pensions today to discuss an issue of significant importance to the lives of the American people—protecting people from vaccine-preventable diseases. State, territorial, tribal, and local public health agencies are on the front lines implementing vital public health programs, including immunization programs, and responding to a wide array of public health emergencies such as disease outbreaks.

One of our objectives in public health is to share accurate, science-based information. To that end, allow me to say at the onset, vaccines are safe, effective, and the best protection we have against serious preventable diseases like measles. Vaccinating children in the United States has saved millions of lives, increased life expectancy, and saved trillions of dollars in societal costs. [1] Yes, like any medication,

[1] Whitney, C. G., Zhou, F., Singleton, J., & Schuchat, A. (2014). Benefits from immunization during the vaccines for children program era—United States, 1994–2013. MMWR 2014;63(16): 352–355.

vaccines have some minor side effects and can have rare serious complications.[2] They can also eradicate diseases from our planet, like they did with smallpox and hopefully soon with polio.[3], [4] And in the United States, we have eliminated a number of vaccine preventable diseases. In 2000 we thought the United States had eliminated measles, but that is no longer the situation with the number of outbreaks we have had since then.[5]

As secretary of health for Washington State, my mission is to protect and promote the lives of all the people in our state and when making public policy to ensure that it is based on the best science available to us. To that point, I want to speak directly to the parents who have children with autism and other serious health issues and who have been attending our hearings in Washington State and who are watching this hearing today. I see you and your children. I see your pain, your desire for answers to your children's health issues, your skepticism of government and the pharmaceutical industry, your mission to give your children the best life they can have and your desire to prevent other parents from the pain and suffering you and your children experience. Your mission to protect and promote the health of your children is a mission I share. And I know on this point, some of you will strongly disagree with me: the science demonstrates that autism is not caused by vaccines. But while the science on that is clear, we do need to better understand the causes of autism and other diseases better than we do today. We need to develop together—scientists, public health officials and affected families—research agendas to get the answers we all need. We need to create an environment where we can respectfully listen to each other and engage.

Public health systems at every level are struggling due to chronic underfunding, increasing population size, and the emergence of new threats. We find ourselves constantly reacting to crises, rather than working to prevent them. It is therefore incumbent upon all of us at the federal, state, and local levels to provide the sustained, predictable, and increased resources necessary to focus on health promotion and disease prevention work as well as respond to emerging and reemerging diseases.

Measles Outbreak

Currently, there are six ongoing but completely preventable measles outbreaks in the U.S., including one in Washington, three in New York, one in Texas and one in Illinois.[6] Over the last 10 years, Washington State has had three measles outbreaks, one of which included the death of an immunocompromised person exposed to measles in a clinic waiting room.[7] The current outbreak is larger and infecting people faster than those in recent history. Between the end of December 2018 to March 1, 2019, Washington State has had 69 measles cases in our outbreak, plus four additional cases associated with our outbreak in Oregon and one in Georgia. Of the 69 Washington cases, 60 were unvaccinated, two had one dose of the measles vaccine and seven have an unverified immunization status. Two cases were hospitalized.

In a global society with increased air travel, a disease outbreak in one part of the world can easily be transmitted to another by travelers. Our best protection against these preventable diseases is quite simple—vaccination. Currently, many countries in Europe are experiencing significant measles outbreaks.[8] In this latest outbreak in Washington, we know that an individual traveled to Washington State from Europe who was already infected, but not yet symptomatic, with a wild strain of the measles virus circulating there.[9] Fighting disease outside the U.S., as well as inside, promotes health security for everyone. Research shows every dollar invested

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[2] McLean HQ, Fiebelkorn AP, Temte JL, Wallace GS. Prevention of Measles, Rubella, Congenital Rubella Syndrome, and Mumps, 2013: Summary Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2013; 62(RR04):1–34. Available at *https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6204a1.htm*

[3] *https://www.who.int/csr/disease/smallpox/en/* (accessed March 1, 2019)

[4] *https://www.who.int/features/factfiles/polio/en/* (accessed March 1, 2019)

[5] Papania, M. J., Wallace, G. S., Rota, P. A., Icenogle, J. P., Fiebelkorn, A. P., Armstrong, G. L., ... & Hao, L. (2014). Elimination of endemic measles, rubella, and congenital rubella syndrome from the Western hemisphere: the US experience. JAMA pediatrics, 168(2), 148–155.

[6] *https://www.cdc.gov/measles/ (accessed March 1, 2019)*

[7] *https://www.doh.wa.gov/Portals/1/Documents/5100/420–004–CDAnnualReport2015.pdf* (accessed March 1, 2019)

[8] *http://www.euro.who.int/en/media-centre/sections/press-releases/2018/measles-cases-hit-record-high-in-the-european-region* (accessed March 1, 2019)

[9] *https://www.clark.wa.gov/public-health/measles-investigation* (accessed March 1, 2019)

in global immunization programs in the world's poorest countries saves $16.[10] This is why we must fully fund the CDC and other health organizations to maintain disease-control activities globally.

According to the CDC, measles can be serious for all age groups. However, children younger than five years of age and adults over 20 years of age are more likely to suffer from measles complications. Common complications from the measles include ear infections, which can lead to permanent hearing loss, and diarrhea. However, some people may suffer from severe complications such as pneumonia and encephalitis. Finally, for every 1,000 people who get measles, one or two will die from it.[11] Measles is so contagious that if one person has it, 9 out of 10 people of all ages around him or her will also become infected if they are not protected.[12]

Even though there is an effective vaccine, measles still caused 110,000 measles deaths worldwide in 2017, mostly among children under five years of age.[13] In 1963, prior to the United States measles vaccination program, three to four million people a year were estimated to get measles, resulting in 48,000 hospitalizations and 450 to 500 measles deaths a year.[14] From 1989 to 1991, a resurgence of measles in the United States resulted in more than 55,000 cases and 120 deaths.[15] More than half of the children had not been vaccinated, even though they had seen a healthcare provider. In response, Congress created the Vaccine for Children program, which covers vaccines for those under 19 years of age on Medicaid, uninsured, underinsured, and American Indian/Alaskan Native.[16] In addition, the Advisory Committee on Immunization practices recommended the second dose of MMR.[17] We must continue the forward progress we have made protecting people from vaccine-preventable diseases.

Vaccine Effectiveness

The widespread use of measles vaccine led to a greater than 99 percent reduction in measles cases compared with the pre-vaccine era.[18] Two doses of the measles, mumps, and rubella (MMR) vaccination are 97 percent effective against measles.[19] And it is estimated worldwide that because of the measles vaccine, 20.5 million deaths were prevented between 2000 and 2016.[20]

It is important to note however, that some vaccines are not as effective as we would like. For example, according to the CDC the overall effectiveness of the 2017–2018 flu vaccine against both influenza A and B viruses was estimated to be 40 percent. This means the flu vaccine reduced a person's overall risk of having to seek medical care at a doctor's office for flu illness by 40 percent.[21] While the effectiveness of the flu vaccine can vary, it is still the best protection against this annual illness, and was estimated to prevent about 110,000 flu hospitalizations, and 8,000 flu deaths during the 2017–18 season.[22] A more effective vaccine would save even more lives. Similarly, protection from the current pertussis vaccine has been shown to wane during the five years after completion of the 5th childhood dose.[23] As a nation, we must continue to invest in critical research and vaccine technology to improve vaccine development.

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[10] Ozawa, S., Clark, S., Portnoy, A., Grewal, S., Brenzel, L., & Walker, D. G. (2016). Return on investment from childhood immunization in low-and middle-income countries, 2011–20. Health Affairs, 35(2), 199–207.

[11] *https://www.cdc.gov/measles/about/complications.html* (accessed March 1, 2019)

[12] *https://www.cdc.gov/measles/about/transmission.html* (accessed March 1, 2019)

[13] *https://www.who.int/news-room/fact-sheets/detail/measles* (accessed March 1, 2019).

[14] *https://www.cdc.gov/measles/downloads/measlesdataandstatsslideset.pdf* (accessed March 1, 2019)

[15] *https://www.cdc.gov/vaccines/pubs/pinkbook/meas.html* (accessed March 2, 2019)

[16] *https://www.cdc.gov/vaccines/programs/vfc/about/* (accessed March 2, 2019)

[17] CDC. Measles prevention: recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR 1989;38(No.S–9):1–18. Available at: *https://www.cdc.gov/Mmwr/preview/mmwrhtml/00041753.htm*

[18] *https://www.cdc.gov/measles/vaccination.html* (accessed March 1, 2019)

[19] *https://www.cdc.gov/measles/hcp/index.html*

[20] *https://www.cdc.gov/measles/downloads/measlesdataandstatsslideset.pdf* (accessed March 1, 2019)

[21] *https://www.cdc.gov/flu/about/season/flu-season-2017–2018.htm*

[22] *https://www.cdc.gov/flu/about/burden-averted/index.htm*

[23] Cherry JD. The 112-year odyssey of pertussis and pertussis vaccines—mistakes made and implications for the future. JPIDS. 2019; XX(XX):1–8.

Consequence of Vaccine Success

Due to the success of vaccines, fewer people have witnessed the complications and severity of vaccine preventable diseases. Unfortunately, this means that some parents may believe that vaccination is no longer necessary or that the minor or rarely severe complications from vaccines are somehow worse than getting the disease, resulting in some parents not vaccinating their children. Discredited and fraudulent research has been used as a basis to claim a link between MMR and autism.[24] Moreover, public health officials throughout the country are gravely concerned about the latest misinformation originating from a well-organized and orchestrated anti-vaccination movement.

In communities across Washington State and our nation, there are pockets of children who are not fully vaccinated or not vaccinated at all. This puts them at risk to contract measles and unintentionally spread it to others, especially since one is infectious with measles four days before the rash develops. It is absolutely paramount that public health and healthcare professionals across the nation join together to share the science about the safety and efficacy of vaccines with the public. And we must equip health care

providers to be able to effectively answer the questions their patients may have about vaccines, as we do want parents with questions to engage their trusted health care provider. The health concerns that parents have over the risks of vaccination must be addressed with compassion, care, and evidence-based practice so that informed decisions can be made, and so that people can protect themselves and their loved ones from dangerous, vaccine-preventable disease.

Communications Challenges

Public health and healthcare professionals face significant communications challenges with those who are uncertain about vaccinations because of fear, distrust, and/or misinformation. The increasing influence social media has over personal health decisions by promoting false information is alarming.

Admittedly, public health officials must be smarter in using media of all types to share factual, credible information. We must call on social media companies such as Twitter, Facebook, and Google to use whatever mechanism they have available to stop promoting pseudoscience. And the problem isn't limited to social media, traditional media can spread this false information as well. As public health officials, we often partner with traditional media outlets to spread critical life-saving information to the public. When traditional media invites and promotes celebrity spokespeople who question the validity of immunizations and remain blind to the body of scientific evidence, it makes our jobs all the more difficult, and frankly, puts the public's health at risk.

Civic discourse on vaccinations must be improved. Individuals opposed to vaccinations are extremely well organized across the country. In Washington, State lawmakers who proposed legislation to remove the personal exemption from vaccination have received death threats and been stalked. A health care professional who recently testified in support of removing philosophical exemptions for school entry vaccination has been vilified on their health practice website and in nasty social media posts.

For my part, I recently received an email from a parent who does not vaccinate their child concerning a social media post from my agency. Many of you have probably seen the post as it was going around many people's social media accounts during valentine's day. It's a cartoon of a school boy asking a school girl if she will be his valentine, and she asks if he has been vaccinated. While this social media post had one of our most shares ever and most likes, laughing faces, and angry faces, I have come to understand how this post just furthers the divide. I can do better, we all can do better. In fact, we must do better to focus on our mutual interest of keeping kids healthy.

I completely agree with CDC Director Robert Redfield who said we need to change the hearts and minds of people in this country to not leave science on the shelf.[25] Additional

federal funds should be provided to determine how best to communicate with vaccine hesitant parents and to counter the misinformation currently being spread.

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[24] Eggertson, L. (2010). Lancet retracts 12-year-old article linking autism to MMR vaccines. Canadian Medical Association. Journal, 182(4), E199.

[25] *https://www.seattletimes.com/seattle-news/health/cdc-director-federal-health-officials-stress-importance-of-measles-vaccinations/* (accessed March 1, 2019)

Washington State's Vaccine Program

Each year Washington State receives $105 million in federal funding and $66 million in state funding to support a comprehensive immunization system. Federal funding has a critical role in achieving national immunization coverage targets. It supports immunization system infrastructure and the purchase of vaccines for children who qualify and adults without health insurance. Our state supplements these federal funds to support health care providers and facilities, help parents make informed decisions, and partner with schools.

During my tenure we've worked hard to keep communities protected, ensure stable funding for vaccines and build public/private partnerships to strengthen the immunization infrastructure. For example, we have increased the number of 13 to 17 year olds who started human papillomavirus (HPV) vaccination series from 46 percent in 2015 to 61 percent 2018. This means that more youth in Washington are protected from the many cancers that HPV can cause.

One of the biggest challenges with childhood immunization in Washington is the percentage of students out-of-compliance with state law because the parents have not submitted immunization documentation or exemption paperwork with the school. In the 2017–2018 school year, 8.0 percent of kindergarten students lacked appropriate paperwork and were out-of-compliance. We believe this is largely because of the administrative burden on schools to staff this health work and track the paperwork from parents. To address this, we need to adequately fund school nurses. Our schools today are woefully understaffed with school nurses. This does not put our children first. Public health needs to partner with school nurses to ensure kids are vaccinated and keep our kids safe and healthy, especially during disease outbreaks. We are also working on health technology solutions to help school personnel easily access immunization records in our state immunization registry, which reduces duplicate data entry and allows for the easy use of report writing functions to track the immunization status of students.

In addition, Washington is one of 17 states that allow parents to send their children to school and child care unvaccinated for personal or philosophical reasons. Two state lawmakers from Clark County have each introduced legislation designed to protect more children from vaccine preventable disease and increase the safety of these environments. One bill would eliminate the philosophical exemption for the MMR vaccine. The other would eliminate that exemption for all vaccines required for school or child care entry. This approach honors the responsibility we all have to protect each other. This proposed policy change is a good step forward and one I support. Vaccines are the best protection we have: they are safe, readily available, given without charge to all kids under 19 years of age in Washington State and proven to be effective. And I believe that parents want safe schools and childcare centers for all kids and those

adults who serve them, including those who can't be vaccinated for medical reasons or who have lost their immunity due to serious medical conditions.

Public Health Response to a Measles Outbreak

In Washington, Governor Jay Inslee issued a Public Health Emergency Proclamation on January 25, 2019 to support the response efforts to our measles outbreak.[26] This proclamation allowed mutual aid assistance through the Emergency Management Assistance Compact enabling the state to request public health responders from other states to support the outbreak response. North Dakota, Idaho, and Oregon provided staff to assist with the outbreak response.

To date, this preventable outbreak has cost over $1 million and required the work of more than 200 individuals contributing over 10,000 hours of work. These estimates do not take into account the health care costs of those ill, the cost to schools and businesses as they responded to the event, the cost to student learning for those unvaccinated children excluded from school, and to the lost productivity of their workers. In comparison, the cost of an MMR vaccine dose is about 20 dollars.[27]

Importance of Federal Funding and Programs

Our response to this outbreak has benefited greatly from the Federal Government. The Pandemic and All Hazards Preparedness Act (PAHPA) authorities and

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[26] *https://www.governor.wa.gov/news-media/inslee-declares-local-public-health-emergency-after-identifying-outbreak-measles* (accessed March 1, 2019)

[27] *https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html* (accessed March 1, 2019)

funding over the years have allowed us to train, build, and maintain a strong Incident Management Team, which has ably led the response, and it has allowed us to develop strike teams to send into the response to carry out public health functions.

The public health system is often invisible to most Americans when it is working well. It is when an emergency or a disaster or an outbreak strikes where the fragility and chronic underfunding of the public health system is laid bare. As just one example, in Washington, Clark County repurposed their home visiting nurses to address this outbreak. The day to day job of the home visiting nurses is to assist expectant and new mothers, many in high-risk situations, to help improve birth outcomes and raise healthy children. By redirecting their work, families are going without this critical service and increasing the risk for bad health outcomes. [28]

In public health, we see the need to modernize. We do our best to make the most with the limited budgets we have. This is why federal funding is foundational for state, territorial, tribal and local health agencies to provide a comprehensive immunization system and emergency preparedness and response capability.

In this case, federal funds from Section 317 of the Public Service Act are used to support the immunization grant program and provide vital resources to support our comprehensive system. Section 317 funding provides support for our state to educate and inform the public, monitor vaccine effectiveness, account for the use of federal and state dollars, decrease ethnic and racial disparities, have strong outbreak investigation, improve tracking systems, and continue to provide the necessary support to health care professionals. Yet, the 317 immunization grant program has been flat funded since 2009. Without increased funding, we cannot afford to develop new and innovative ways to increase immunization rates especially in light of the anti-vaccine movement. Research shows every dollar spent on childhood vaccines saves 10 dollars, so this is a worthwhile investment. [29] Additional funding would help address growing gaps in immunization coverage and strengthen the scientific foundation for vaccine policy decision making.

The Pandemic and All Hazards Preparedness Act (PAHPA) provides a framework and resources to support our emergency preparedness and response. Funds from the Public Health Emergency Preparedness Cooperative Agreement Program allows state health departments to build and strengthen our ability to respond to public health emergencies. Without this funding, state and local public health agencies would have been significantly delayed in identifying and containing this measles outbreak. This program is currently funded $400 million below funding levels in the 2000s. More robust funding would allow public health agencies to not have to reallocate resources from other vital public health programs to respond to urgent public health emergencies like measles outbreaks or other disasters. Despite this Committee's action to reauthorize the law last year, it has now lapsed; I ask you to move quickly to reauthorize PAHPA.

The Prevention and Public Health Fund is the nation's first mandatory funding stream dedicated to improving our nation's public health system. The purpose of the fund was to supplement core public health programs with increased investment in disease prevention, yet it has primarily been used to backfill the funding of core public health programs. Currently 47 percent of the 317 immunization program is funded by the Prevention and Public Health Fund. Research shows every dollar invested in community-based prevention saves $5. [30]

I'm here to make clear the threat of these vaccine preventable illnesses, so we can respond together to restore health to the very part of our system responsible for prevention. One immediate response Congress can take is to raise the budget of the Centers for Disease Control and Prevention by 22 percent by 2022, as requested by the Association of State and Territorial Health Officials and over 80 other organizations. [31] Doing so will immediately begin to save lives, promote optimal health for all, bolster our prevention services and reduce healthcare costs.

Conclusion

Vaccines are a testament to human ingenuity to ward off morbidity and mortality. Vaccines activate the natural human immunity system. The science is clear that

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[28] *https://www.columbian.com/news/2019/feb/25/nurse-family-partnership-takes-on-intangible-costs-of-measles-outbreak/* (accessed March 2, 2019)

[29] Remy, Vanessa, York Zollner, and Ulrike Heckmann. "Vaccination: The cornerstone of an efficient healthcare system." Journal of market access & health policy 3.1 (2015): 27041.

[30] Prevention for a Healthier America: Investments in Disease Prevention Yield Significant Savings, Stronger Communities, Trust for America's Health, 2009.

[31] *http://www.astho.org/Advocacy-Materials/22-by-22/* (accessed March 1, 2019)

vaccines are safe and effective. Vaccines can eradicate diseases. Vaccine programs are one of public health's greatest accomplishments. They are under great threat and we need to reverse course.

I thank you for holding this hearing and increasing awareness about the importance of vaccines and public health. Everyone has a right to live in a community free of vaccine-preventable disease. We must continue to invest in and strengthen our public health system.

[SUMMARY STATEMENT OF JOHN WIESMAN]

Vaccines are safe, effective, and the best protection we have against serious preventable diseases like measles. Vaccinating children in the U.S. has saved millions of lives, increased life expectancy, and saved trillions of dollars in societal costs.[1] Yes, like any medication, vaccines have some minor side effects and can have rare serious complications, but they do not cause autism.[2,3] They can also eradicate diseases from our planet, like they did with smallpox and hopefully soon with polio.[4,5]

There are six ongoing but preventable measles outbreaks in the U.S., one in Washington, three in New York, one in Texas, and one in Illinois.[6] Washington's outbreak has cost over $1 million compared to the $20 cost of an MMR vaccine dose.[7]

Due to the success of vaccines, fewer people have witnessed the complications and severity of vaccine preventable diseases. Therefore, some parents may believe that vaccination is no longer necessary or that the minor or rarely severe complications from vaccines are somehow worse than getting the disease, resulting in some parents not vaccinating their children. Moreover, a well-organized and orchestrated anti-vaccination movement is a threat to the public's health.

Section 317 funding provides immunization program support for states and it has been flat funded since 2009, despite the threats noted above. We need increased funding to develop new ways to increase immunization rates. Currently 47 percent of the 317 immunization program is funded by the Prevention and Public Health Fund, a fund that was intended to add prevention capacity, not backfill.

The Pandemic and All Hazards Preparedness Act (PAHPA) provides essential support for response efforts, but it is currently funded $400 million below funding levels in the 2000s. More robust funding is needed to respond to urgent public health emergencies. And I ask you to quickly reauthorize PAHPA.

One immediate response Congress can take is to support public health is to raise the budget of the Centers for Disease Control and Prevention by 22 percent by 2022, as requested by the Association of State and Territorial Health Officials and over 80 other organizations.[8] Doing so will immediately begin to save lives, promote optimal health for all, bolster our prevention services, and reduce healthcare costs.

The CHAIRMAN. Thank you, Mr. Wiesman.
Dr. Omer.

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[1] Whitney, C. G., Zhou, F., Singleton, J., & Schuchat, A. (2014). Benefits from immunization during the vaccines for children program era—United States, 1994—2013. MMWR 2014;63(16): 352-355.

[2] McLean HQ, Fiebelkorn AP, Temte JL, Wallace GS. Prevention of Measles, Rubella, Congenital Rubella Syndrome, and Mumps, 2013: Summary Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2013; 62(RR04):1-34. Available at *https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6204a1.htm*

[3] Eggertson, L. (2010). Lancet retracts 12-year-old article linking autism to MMR vaccines. Canadian Medical Association. Journal, 182(4), E199.

[4] *https://www.who.int/csr/disease/smallpox/en/* (accessed March 1, 2019)

[5] *https://www.who.int/features/factfiles/polio/en/* (accessed March 1, 2019)

[6] *https://www.cdc.gov/measles/* (accessed March 1, 2019)

[7] *https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html* (accessed March 1, 2019)

[8] *http://www.astho.org/Advocacy-Materials/22-by-22/* (accessed March 1, 2019)

STATEMENT OF SAAD B. OMER, MBBS, MPH, PHD, WILLIAM H. FOEGE PROFESSOR OF GLOBAL HEALTH, PROFESSOR OF EPISTEMOLOGY AND PEDIATRICS, EMORY UNIVERSITY, ATLANTA, GA

Dr. OMER. Thanks for the opportunity for me to talk about vaccines in this forum.

Elimination of endemic measles transmission from the U.S. in 2000 is a significant public success. Since then, most of the cases have occurred through U.S. travelers going outside and bringing it back. While recent measles outbreaks have been contained, the frequency and size of these outbreaks have been particularly alarming for those of us who follow these trends. The rest of this testimony will be focused on answering some of the salient questions that have been coming up.

The first question is, why haven't we seen a national level outbreak in the U.S.? And we cannot take this for granted. Countries with similar development status like Germany, France, and Italy specifically more recently, have had national level outbreaks. And it is not a coincidence that we have not seen similar national outbreaks, and there are several reasons for it. First of all, our laws, school level mandates, work. And they work by changing the balance of convenience.

In most states, they work by changing the balance of convenience for vaccination compared to non-vaccination by having physician counseling, or by having parents go through a video that talks about vaccines and the benefits of vaccines, etc. And the third thing is, in our country, medical societies like the American Academy of Pediatrics and the Infectious Disease Society of America have been very prominent in vaccine advocacy, and it is important because it is based on the fact that physicians are the most trusted source of vaccine information.

We have talked about the role measles has played—vaccine refusal has played in these outbreaks, and I will just give a few numbers. For example, more than half of the cases since the elimination have been unvaccinated, and approximately 70 percent of them—of unvaccinated due to vaccine refusal are non-medical exemptions. So, there is a contribution of vaccine refusal in our epidemiology of measles. And vaccine mandates have been an effective tool in changing that balance of convenience that I was talking about. But that is a state level issue. I will focus on some of the things the Federal Government can do.

In my written testimony, I have provided a few more details on that specific issue and I would be happy to answer questions. So, there are a few things the Federal Government can do. First, consider making vaccine counseling reimbursable. And I have worked on vaccine research in multiple countries, in multiple states in the U.S. There are a lot of local factors that are specific, but there is one constant, vaccine providers—health care providers, specifically physicians, are the most trusted source of vaccine information even amongst those who are a little bit skeptical of vaccines. So, we need to use that tool more effectively.

On the practical side, physicians do not have the time to properly counsel patients using evidence-based approaches, and part of the reason, not all of the reason, is the fact that this is not reimburs-

able. So, physicians lose money on this kind of important public health education. We should as a country, the second point is, invest in high-quality vaccine acceptance and communications research. And I often say that if you do not accept half-baked vaccine development science—and we do not. The FDA goes through evaluation of the science from trials and basic sciences, etc. We should not be accepting of half-baked vaccine communication and behavioral science. And we have precedent in this country. For example, NIH's cancer prevention initiatives are a gold standard in these kinds of interventions and evidence-based communications strategy.

NIAID, national institute for immunology—I am sorry, national institute for infection and allergy, has—they have had very effective intervention development in the area of HIV, AIDS behavior. So, we have that precedent in this country, and we need to invest in actual research. And before we develop evidence, while we develop evidence, there is an existing blueprint of interventions that the National Vaccine Advisory committee put together, and unfortunately not all of its interventions and its recommendations have been implemented. So that is ready to be implemented.

CDC plays this important role in fighting these fires, working with state and local health departments, which is somewhat unique in the developed world and we need to support their mission. And we should continue to prioritize vaccine safety research, and I would want to thank you for bipartisan and consistent support for vaccines because that matters. And that shows that there is broad societal support for vaccines, and those of us who work to protect children from these infectious diseases really appreciate that.

[The statement of Dr. Omer follows:]

PREPARED STATEMENT OF SAAD B. OMER

I am Saad B. Omer, the William H. Foege Professor of Global Health and Professor of Epidemiology & Pediatrics at Emory University, Schools of Public Health and Medicine. I have served on several scientific and public health advisory committees including the National Vaccine Advisory Committee and the Public Health Committee of the Infectious Diseases Society of America. My research has focused on vaccines—including clinical/field trials, vaccine safety studies, and studies of interventions to increase vaccine acceptance.

I want to thank the Committee for the opportunity to share my perspective on vaccine preventable diseases, the current epidemiology of measles, and the importance of vaccines. In my testimony, I will attempt to answer a few salient questions on this topic. My statement substantially draws from my previous writings and research.

Should we be concerned about the recent measles outbreaks?

The elimination of endemic transmission of measles from the United States in 2000 is considered a significant public health success. Since then, measles has mostly occurred as outbreaks—either because of imported cases (mostly from U.S. travelers returning home with the infection) or among those who come in contact with these cases.

Are the recent cases and outbreaks sporadic, or are we on the verge of the return of widespread measles? While recent measles outbreaks have been contained, the frequency and size of these outbreaks is alarming. For example, according to a CDC study, the annual median number of cases and outbreaks more than doubled during 2009–2014 compared to the earlier post-elimination years *(Fiebelkorn et. al.; J Pediatric Infect Dis Soc.; 2017)*. This trend has continued since the publication of the CDC study. A return of widespread measles is not inevitable, but to ensure we pre-

vent it, we need to seriously address causes of non-vaccination including vaccine refusal.

Notably, each year there are children not vaccinated against measles. These non-immunized children join the ranks of all other susceptible children from years past, increasing the population of susceptible people. With the slow and steady accumulation of people who haven't been immunized, we may only be delaying a large measles outbreak. In fact, in an epidemiological study my research collaborators and I published in 2016, we estimated that 1 in 8 children younger than 18 are susceptible to measles (Bednarczyk, Orenstein, & Omer; American J. Epi, 2016).

Importantly, *we found that the rate of protection against measles is hovering dangerously close to the "herd immunity threshold"*—computed as the proportion of people who need to be immune to prevent outbreaks. Similar findings have been subsequently reported by other researchers, highlighting the need for interventions to improve measles vaccination rates. If vaccine refusal is left unchecked, more people will be susceptible to this disease, leading to larger outbreaks and possibly resumption of sustained transmission.

Why haven't we seen a national level measles outbreak in recent years?

A national outbreak, or an outright national-level measles resurgence, would not be out of the ordinary for a Western country. In recent years, there have been several large sustained outbreaks in Europe. In Italy, for example, approximately 5,000 measles cases were reported from February 2017 to January 2018. Similarly, large national-level outbreaks have occurred in Britain, Germany, and France. In 2008, the World Health Organization reported approximately 60,000 measles cases from countries included in its European region. While most European countries, including Britain, have been certified as having eliminated measles, the disease is still considered endemic in Italy, Germany, and France.

It's not just luck that the United States hasn't seen a similar resurgence. There are many things the United States does right in vaccine policy, compared to Europe. For example, the United States has a tapestry of school-entry vaccine requirements that work. These requirements, based in state laws, have contributed to maintaining high immunization rates and keeping rates of vaccine noncompliance low. In the U.S., the Centers for Disease Control and Prevention (CDC) aggressively monitors and responds to emerging outbreaks—an epidemiological firefighting function it performs with state and local health departments. In Europe, on the other hand, the effectiveness of public health agencies is uneven. The European Centre for Disease Prevention Control, a much smaller and newer agency compared to the American CDC, lacks the resources and mandate to perform a similar function. U.S. professional medical societies such as the American Academy of Pediatrics and the Infectious Diseases Society of America have been at the forefront of vaccine advocacy—leveraging the fact that physicians are the most trusted source of vaccine information.

But while a national measles resurgence in the United States has been so far kept at bay, we cannot be complacent. With the steady accumulation of susceptible individuals in our communities, efforts are required at the national, state, and local level to ensure that this dangerous disease does not return in full force.

What is the role of vaccine refusal in measles outbreaks?

In a 2016 paper, my colleagues and I evaluated the association between vaccine delay, refusal, or exemption and the epidemiology of measles in the United States (Phadke et al.; JAMA, 2016). We found that since the elimination of measles from the United States in 2000, more than half (56.8 percent) of measles cases had no history of measles vaccination. Among the unvaccinated, age-eligible measles cases for whom the reason for non-vaccination was available, 70.6 percent had a nonmedical exemption to vaccination.

One tool epidemiologists use to chart the temporal course of outbreaks is the epidemic curve in which the daily cases of a disease are plotted against time. In the 2016 paper, we created a cumulative epidemic curve comprising of all measles outbreaks since 2000 for which relevant data were available. According to this cumulative epidemic curve, unvaccinated individuals made up a greater proportion of measles cases in early parts of epidemics—meaning that unvaccinated people provided the tinder to start the fires of these epidemics.

In an earlier national study, the risk of measles among children with vaccine exemptions was 35 times that of the vaccinated population *(Salmon et.al; JAMA, 1999)*. Equally importantly, higher rates of vaccine exemption in a community are

associated with greater measles incidence in that community, among both the exempt and nonexempt population. One reason for ongoing outbreaks is the epidemiological phenomenon of clustering of susceptible individuals—which happens when a group of unvaccinated individuals in a specific area grows large enough to render protection from overall high immunization rates less effective.

Is vaccine refusal the only reason for recent outbreaks?

While vaccine refusal is an important risk factor for vaccine preventable disease outbreaks, it is not the only reason why these outbreaks occur. For example, CDC reported insurance status is an important factor in non-vaccination *(Hill et al.; MMWR; 2018)*. Similarly, while vaccine refusal plays a role, waning immunity is an important cause of decline in pertussis (whooping cough) vaccine effectiveness and subsequent outbreaks *(Klein et al.; NEJM; 2012)*.

Are vaccine mandates a useful policy option for controlling vaccine-preventable diseases?

State laws in the United States mandate that every child entering kindergarten either provide proof of being immunized or file for an exemption. All 50 states allow for medical exemptions from mandated vaccinations. Eighteen states allow religious and personal belief exemptions, 30 states permit religious exemptions only, and 3 states only allow medical exemptions. Mandates have played a key role in keeping disease rates low. Because vaccination and exemption laws are established at the state level, there is substantial variation in immunization requirements, types of nonmedical exemptions offered (i.e. personal belief exemption vs. only religious exemption), ease of obtaining an exemption, and enforcement of immunization legislation across the United States *(Omer et al.; NEJM; 2009)*.

The amount of administrative effort needed to complete the exemption process varies by state. Vaccine laws in the U.S. work by changing the balance of convenience in favor of vaccination and away from non-vaccination. Ease of obtaining a nonmedical exemption has been shown to be associated with state vaccine exemption rates—and, more importantly, higher rates of vaccine-preventable diseases. In a 2006 study published in The Journal of the American Medical Association, for example, we documented that states with easy procedures for granting nonmedical exemptions had higher rates of vaccine refusal and approximately 50 percent higher rates of whooping cough *(Omer et al.; JAMA; 2006)*. The association between ease of exemption and vaccine refusal rates has been consistent in our subsequent studies as well *Omer et al.; NEJM, 2012 & Omer et al.; Open Forum Infect Dis.; 2017)*.

The policy option of eliminating all nonmedical exemptions is being discussed in a few states. However, the evidence on the impact of this option is nuanced and evolving. Until recently, West Virginia and Mississippi were the only two states that did not allow any nonmedical exemptions. These states have traditionally had some of the highest immunization rates in the country. California recently eliminated nonmedical exemptions. The initial results from this policy change (through California law SB277) are nuanced. In addition to the implementation of this law, there was a state-level administrative initiative to correctly apply "conditional entrance" requirements—a category meant for children who had started but not completed their vaccine schedule or had temporary medical exemptions. Prior to the enforcement initiative, this category was inconsistently applied and, sometimes, misused. While there has been an increase in the percentage of California kindergartners entering school fully vaccinated, publicly available data suggest that this increase may by mostly due to the pre-SB277 education- and enforcement-based effort to correctly apply the conditional entrance requirements. Importantly, there is evidence of an emerging *replacement effect* as a result of increase in children being not up-to-date for vaccines due to other categories e.g. through increase in medical exemptions.

Irrespective of emerging evidence from California, states have other policy options short of eliminating all nonmedical exemptions. For example, states can tweak their rules to make sure parents are as informed as possible by adding a legally mandated physician counseling requirement for those seeking exemptions. This approach has been effective in reducing nonmedical exemptions *(Omer et al.; Pediatrics; 2018)*. Moreover, states can reconfigure their immunization requirements to tilt the balance of convenience in favor of vaccination *(Omer et al.; NEJM; 2019)*.

Vaccine mandates are implemented at the state level. Can the federal government do anything about vaccine acceptance and controlling outbreaks?

I believe the federal government has a substantial role to play in increasing vaccine acceptance. While vaccine mandates are a state-level issue, there are many policy options within the purview of the federal government. I will highlight a few of them:

1. *Consider making vaccine counseling reimbursable:*
Several factors associated with vaccine acceptance vary by location and demographics. But there is one constant: *healthcare providers, particularly physicians, are the most trusted source of vaccine information*—even among those who refuse vaccines *(e.g. Freed et al.; Pediatrics; 2011)*. A strong physician recommendation for vaccines is an extremely useful tool for immunization acceptance. However, having an effective conversation with vaccine hesitant parents requires time and effort. Unfortunately, the time spent on vaccine hesitant patients is not billable—further dis-incentivizing physicians from having this difficult but useful conversation.

2. *Invest in vaccine acceptance/communication research:*
While vaccine communication and acceptance interventions are an active area of research, a lot more needs to be done. In recent years, several promising leads have emerged—many from federally funded research. For example, research on "presumptive communication" leverages power of verbal defaults-based "nudges" for framing vaccine conversations *Opel & Omer; JAMA Pediatr.; 2015)*. Similarly, motivational interviewing—a well-established counseling technique that has been evaluated to increase vaccine acceptance—works through people's internal motivation for desirable health behavior *(Dempsey et al.; JAMA Pediatr.; 2018)*. In my research group, multi-tiered practice-provider-patient based interventions (the so called P3 model) have shown promise. However, current vaccine acceptance research is sporadic and a focused, high priority research program is needed. Fortunately, there are examples of similar high priority behavioral and communication research that can be emulated. These examples and potential templates include National Cancer Institute's Behavioral Research Program—a comprehensive program of research to increase the breadth, depth, and quality of behavioral research in cancer prevention and control. Given its role as the nation's premier biomedical and behavioral health research agency, it would be natural for NIH to have a leading role in guiding these investments.

3. *Implement the National Vaccine Advisory Committee's recommendations:*
While there is need for new research, there are existing approaches that can increase confidence in and acceptance of vaccines. Fortunately, an evidence-based blueprint exists in the form of recommendations published in 2015 by the National Vaccine Advisory Committee, an independent committee charged with the advising the Department of Health and Human Services *(NVAC; Public Health Rep.; 2015)*. These recommendations focus on evidence-based strategies for increasing confidence in vaccines. Unfortunately, these recommendations have not been fully implemented.

4. *Support CDC's mission of controlling measles outbreaks:*
As I mentioned earlier, CDC—in collaboration with state and local health departments—plays an important role in controlling outbreaks of vaccine preventable diseases such as measles. Responding to these outbreaks is costly and time and labor-intensive. Ensuring that CDC continues to have adequate resources will help with maintaining adequate outbreak response capabilities in the face of increasing outbreaks.

5. *Continue to prioritize vaccine safety research:*
Over the years, the U.S. has developed a robust vaccine safety research infrastructure. CDC's Vaccine Safety Datalink system utilizes data from 9 HMOs from across the country to conduct active epidemiologic surveillance for vaccine safety. The Vaccine Adverse Events Reporting System maintained by the CDC and the FDA captures spontaneous reports of potential vaccine side effects. The FDA's Sentinel is the largest system available in the U.S. for vaccines adverse event surveillance. Similarly, the FDA's prelicensure and post licensure safety review of vaccines is useful in ensuring vaccine safety. Continued support for these vaccine safety initiatives is not just useful for ensuring confidence in vaccines but, more importantly, it's

the right thing to do. However, it is important that assessment of vaccine safety continues to be science-based.

6. *Maintain bipartisan and vociferous support for vaccines:*
This committee has previously expressed strong support for vaccines—through statements supporting vaccines. Such statements matter. They indicate broad social support for vaccines and signal to the so-called fence sitters that vaccination is the social norm. As someone who has spent his professional life ensuring children and adults are protected from infectious diseases, I personally thank you for these statements.

We have a history of bipartisan action for vaccines

In the aftermath of the last measles resurgence in the United States in 1989–1991, there was a remarkably bipartisan effort to address the main cause of that resurgence: vaccine access. President Bill Clinton and congressional Republicans and Democrats came together to establish the Vaccines for Children program to remove affordability as a barrier to vaccination. This program was effective in addressing inequities in immunization coverage. Preventing the next potential resurgence of measles will require a similar broad-based response.

Acknowledgements and disclosures: I want to acknowledge the work by members of my research group and collaborators on some of the research and synthesis I shared. Part of the content in this testimony has previously appeared in peer-reviewed publications and op-eds (e.g. my February 11 Washington Post op-ed with my colleague Bob Bednarczyk). I have received funding for my research from federal agencies (e.g. NIH, CDC, AHRQ), international public health agencies (the World Health Organization, Gavi-the vaccine alliance), and philanthropic foundations (e.g. the Bill & Melinda Gates Foundation, Thrasher Research Fund). I do not receive funding from vaccine manufacturers.

[SUMMARY STATEMENT OF SAAD B. OMER]

Elimination of endemic transmission of measles from the United States in 2000 is a significant public health success. Since then, measles has mostly occurred either because of imported cases (mostly from U.S. travelers returning home) or among their contacts. While recent measles outbreaks have been contained, the frequency and size of these outbreaks is alarming. For example, according to a CDC study, the annual median number of cases and outbreaks more than doubled during 2009—2014 compared to 2000—2008.

Why haven't we seen a national level measles outbreak in recent years?

- Because school-entry vaccine requirements keep rates of vaccine non-compliance low.
- CDC aggressively responds to emerging outbreaks—an epidemiological firefighting function it performs with state and local health departments.
- Medical societies such as the American Academy of Pediatrics and the Infectious Diseases Society of America have been at the forefront of vaccine advocacy.

What is the role of vaccine refusal in measles outbreaks?

- Since the measles elimination, more than half of measles cases had no history of measles vaccination.
- Among the unvaccinated, age-eligible measles cases for whom a reason was available, 70.6 percent had a nonmedical exemption to vaccination.
- Unvaccinated individuals make up a greater proportion of measles cases in early parts of epidemics—indicating that unvaccinated people often provide the tinder to start the fires of these epidemics.
- Vaccine refusal is not the only reason for non-vaccination e.g. insurance status is an important factor.

Are vaccine mandates a useful policy option for controlling vaccine-preventable diseases?

- Most state-based vaccine mandates in the U.S. work by changing the balance of convenience in favor of vaccination and away from non-vaccination.

- Ease of obtaining a nonmedical exemption is associated with higher state-level vaccine exemption rates and higher rates of vaccine-preventable diseases.
- States have a range of policy options vis-&-vis mandates—ranging from eliminating nonmedical exemption to adding requirements such as legally mandated physician counseling.

Vaccine mandates are implemented at the state level. Can the federal government do anything about vaccine acceptance and controlling outbreaks?

There are many policy options within the purview of the federal government; these options include:

1. Consider making vaccine counseling reimbursable.
2. Invest in vaccine acceptance/communication research.
3. Implement recommendations from National Vaccine Advisory Committee's vaccine confidence report.
4. Support CDC's mission of controlling measles outbreaks.
5. Continue to prioritize vaccine safety research.
6. Maintain bipartisan and vociferous support for vaccines.

We have a history of bipartisan action for vaccines

In the aftermath of the last measles resurgence in the United States in 1989—1991, there was a remarkably bipartisan effort to address the main cause of that resurgence: vaccine access. Republicans and Democrats came together to establish the Vaccines for Children program to remove affordability as a barrier to vaccination. This program was effective in addressing many inequities in immunization coverage. Preventing the next potential resurgence of measles will require a similar broad-based response.

The CHAIRMAN. Thank you, Dr. Omer.

Dr. McCullers, welcome.

STATEMENT OF JONATHAN A. MCCULLERS, MD, PROFESSOR AND CHAIR, DEPARTMENT OF PEDIATRICS, UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER, PEDIATRICS–IN–CHIEF, LE BONHEUR CHILDREN'S HOSPITAL, MEMPHIS, TN

Dr. MCCULLERS. Thank you.

Good morning Chairman Alexander, Ranking Member Murray, other Members of the Committee. My name is John McCullers. I am the Chair of Pediatrics at the University of Tennessee and the Pediatrician-in-Chief at Le Bonheur Children's Hospital in Memphis. As someone who has devoted his career to the child health sphere, I truly believe there is no more precious resource than our children, and they should be protected by all means available to us. They really are the future of this Nation.

The Childhood Vaccination Program in the United States has proven to be one of the most powerful public health achievements in our history. In the first half of the 20th century there were more than 1 million infections and more than 10,000 deaths every year in this country from diseases which are now preventable by childhood vaccines. Measles alone costs more than a half-million illnesses every year. Measles is a highly contagious viral respiratory disease characterized by fever, cough, sore throat, and a rash. It is a very dangerous disease. About 1 in 1,000 infected persons develop encephalitis, an infection of the brain. 1 in 1,000 develop severe pneumonia, and about half of those with those severe complications die. There is no specific treatment for measles, so vaccination is the only means of preventing these outcomes.

With the introduction of a safe and effective vaccine for measles in 1963 and improved public health efforts to see that nearly every child received it, new cases of measles arising in the United States were entirely eliminated by the year 2000. Unfortunately, the issues of vaccine opposition and vaccine hesitancy are now impairing our ability to effectively ensure coverage aided by state laws that make it easier to avoid vaccination. The last decade has brought numerous outbreaks to the United States, including several that are ongoing at present. These outbreaks are strongly linked to vaccine refusal, and in particular, to clustering of unvaccinated individuals in specific communities or regions.

This problem is not limited to the United States, however. Countries worldwide are dealing with similar outbreaks. As a single example for the Committee, there was zero cases of measles in Brazil in 2017, but more than 10,000 cases occurred on a countrywide level in 2018, when infected travelers brought measles into that country. The vaccine against measles is very safe and very effective. One dose provides complete protection in about 93 percent of individuals, while a second dose raises that level of protection to 97 percent. Very few side effects occur. About 1 in 10 children experience fever for 1 to 2 days after vaccination. And about 1 in 3,000 to 1 in 4,000 have a simple seizure associated with fever with no lasting effects. Allergic reactions are very rare and typically very mild.

When compared to the outcomes of the disease itself, it is easy to see why doctors and public health officials universally recommend on time and complete vaccination. Unfortunately, vaccine refusal is high and getting worse in many states. This issue is complicated by the variety of state policies regarding exemption from vaccination and the methods of counseling about vaccines. The rate of parents claiming non-medical exemptions is about 2.5 times higher in states that allow both religious and philosophical objection. Evidence seeing that multiple pathways for exemption really worsens this problem. Social media is now driving a new phenomena somewhat distinct from vaccine opposition termed vaccine hesitancy. When parents get much of their information about health care issues such as vaccines from the internet or from social media platforms such as Twitter and Facebook, reading uninformed opinions in the absence of accurate information can lead to really understandable concern and confusion in these parents. They may be hesitant to get their children vaccinated without being provided with more information.

The role of the pediatrician is very important therefore with these families. We must do a better job of communicating at many levels, but particularly at the point of contact at the well-child visit when vaccination should take place. About half of the time when counseled appropriate, parents with vaccine hesitancy will agree to have their children vaccinated on time. And the other half, little seems to help at that stage. The solution must be earlier either in the form of policy or broader educational efforts.

In closing, I would like to thank the Committee for addressing this important issue. Vaccine refusal is one of the growing public health threats of our time. If we continue to allow non-medical exemptions to vaccination, the rates of vaccine will continue to fall,

more outbreaks will undoubtedly follow. As a leader at a children's hospital, I have a unique perspective on this. These children's hospitals are regional and sometimes national resources. Le Bonheur Children's Hospital sits in the corner of Tennessee next to Arkansas and Mississippi. These three states all have very different policies for granting exemptions to vaccines, which creates a tremendous problem for us and a threat to the children we serve, many of whom are too young to be vaccinated or immunocompromised, and more prone to severe diseases.

I urge the Committee to consider solutions that will both harmonize public health policy in this area and will also protect children as they grow up to become the next generation.

Thank you.

[The statement of Dr. McCullers follows:]

PREPARED STATEMENT OF JONATHAN A. MCCULLERS

Good Morning Chairman Alexander, Ranking Member Murray, other Members of the Committee, and interested parties. I am Dr. Jon McCullers, the Chair of the Department of Pediatrics at the University of Tennessee Health Science Center and the Pediatrician-in-Chief at Le Bonheur Children's Hospital in Memphis. As someone who has devoted his career to the child health sphere, I firmly believe that there is no more precious resource than our children, and that they should be protected by all means available to us. They truly are the future of this nation. As the lead pediatrician for one of our nation's top Children's Hospitals, I feel it is my duty and privilege to advocate on behalf of children everywhere. The declining rates of childhood vaccination in this nation and, indeed, worldwide, now prove to be a threat to this future.

The childhood vaccination program of the United States has proven to be one of the most powerful public health achievements in our history. In the first half of the 20th century, there were more than 1 million infections and more than 10,000 deaths every year from diseases which are now preventable by childhood vaccines. To put that into perspective in the current day, without childhood vaccines the States of Tennessee and Washington would be dealing with between 24,000 and 37,000 vaccine preventable diseases in an average year, and between 250 and 275 children would die, most of them under the age of 5. Measles alone caused more than a half million illnesses every year in the first half of the last century, and between 450 and 500 children died annually. Measles is a viral respiratory disease, characterized by fever, cough, sore throat, and a rash. It is a very dangerous disease—about 1 in a thousand infected persons develop encephalitis, an infection of the brain, 1 in a thousand develop severe pneumonia, and about half of those with these severe complications die. Measles is also highly contagious - while some individuals infected with some severe infectious agents like influenza only infect 1–2 other persons on average, a person infected with measles infects 20–30 other people on average if they are unvaccinated. There is no specific treatment for measles, so vaccination is the only means of preventing these outcomes. With the introduction of a safe and effective vaccine for measles in 1963 and improved public health efforts to see that nearly every child received it, new cases of measles arising in the United States were entirely eliminated by the year 2000. 2006 saw our lowest case number with only 55 illnesses, all imported from other countries, and no deaths.

Unfortunately, the issues of vaccine opposition and vaccine hesitancy are now impairing our ability to effectively insure appropriate vaccine coverage, aided by state laws that make it easier to avoid vaccination. The last decade has brought numerous outbreaks in the United States, including several that are ongoing at present. These outbreaks are strongly linked to vaccine refusal, and in particular to clustering of unvaccinated individuals in specific communities or regions. Cases are introduced from unvaccinated individuals traveling here from other countries, and spread rapidly through communities with vaccination rates under the level needed for herd immunity. 372 persons contracted measles during 17 different outbreaks in the United States in 2018, and 159 have been infected in the first 7 weeks of 2019. This problem is not limited to the US . . . many countries worldwide are dealing with similar outbreaks. As a single example, there were 0 cases of measles in Brazil in 2017, but more than 10,000 cases occurred in 2018 when infected travelers brought measles into that country.

The vaccine against measles is very safe and very effective. One dose provides complete protection in about 93 percent of individuals, while a second dose raises that level of protection to 97 percent. Very few side effects occur. About 1 in 10 children experience fever for 1–2 days, and about 1 in 3000 to 1 in 4000 have a simple seizure associated with fever with no lasting effects. Allergic reactions are very rare and typically very mild. No reactions or adverse effects of a more severe nature have been associated with the vaccine, despite extensive use, monitoring, and study for many decades. When compared to the outcomes of the disease itself, it is easy to see why doctors and public health officials universally recommend on time and complete vaccination.

Unfortunately, vaccine refusal is high and getting worse in many states. This issue is complicated by the variety of state based policies regarding exemption from vaccination and the methods of counseling about vaccines. Three states currently only allow medical exemptions from vaccination—California, Mississippi, and West Virginia. These states all have vaccination rates for measles at the age of school entry at 97 percent or better—above the 96 percent level needed for herd immunity. Thirty states allow for religious exemptions to vaccines, and 17 allow both religious and personal exemption. The rate of parents claiming non-medical exemptions to vaccines is 2.5 times higher in states that allow both religious and philosophical exemptions compared to religious exemptions alone—evidence that allowing multiple pathways to exemption worsens this problem. Of the 5 states that have less than 91 percent vaccination rates, Colorado, Idaho, Indiana, Kansas, and Washington, three allow both types of exemption. Although some states such as Tennessee have reasonable rates currently (97 percent) while allowing religious exemptions only, the rate of non-medical exemptions has nearly tripled under this policy in the past decade, and it can be predicted that this will continue to rise. California is an illustrative case . . . that state allowed both types of exemptions earlier in the decade, but non-medical exemptions rose to 3.3 percent in 2013, the overall level of vaccination dropped below the level needed for herd immunity, and the state experienced a large outbreak of measles in 2014–2015 with spread of the disease in Disneyland the park theme parks. California subsequently eliminated non-medical exemptions and the vaccination rate has returned to 97 percent. The American Academy of Pediatrics has suggested that the practice of delaying or spacing out childhood vaccines contributed to that outbreak.

Opposition to vaccines began in England in the early 19th century after introduction of Jenner's cowpox vaccine for the dangerous disease smallpox. People objected on religious grounds and due to the irrational fear of becoming a cow. Opposition in the United States became common in the 1850s, resulting in lawsuits against states that mandated vaccination, culminating in a Supreme Court opinion in 1905 that found in favor of states' right to enforce mandatory vaccination as a public health tool. Although the concept of vaccination opposition is not new, the rise in frequency and ease of rapid international travel has made it much more dangerous today than it was a century ago when vaccine refusers may have been isolated from others. The reasons for refusing vaccination have historically been very heterogenous. In 1998 the Wakefield Hoax unified many vaccine refusers by providing a single platform for them using a false narrative—that childhood vaccines caused unsuspected, long term medical problems that had been missed by scientists. In response, a great deal of scientific work was done to prove that there is no link between vaccines and conditions such as autism. The Institute of Medicine has now declared that the evidence is thorough and convincing on this point. The anti-vaccination movement at this time, therefore, no longer has a platform or any credibility and has returned to a more heterogeneous group of objections.

In the present day, however, social media and the amplification of minor theories through rapid and diffuse channels of communication, coupled with instant reinforcement in the absence of authoritative opinions, is now driving a new phenomenon somewhat distinct from vaccine opposition, termed vaccine hesitancy. When parents get much of their information from the internet or social media platforms such as twitter and Facebook, reading these fringe ideas in the absence of accurate information can lead to understandable concern and confusion. These parents may thus be hesitant to get their children vaccinated without more information. The role of the pediatrician is very important with these families—we must do a better job of communicating at many levels, but particularly at the point of contact in the well child visit when vaccination should take place. Half of the time when counseled appropriately, those with vaccine hesitancy will agree to have their children vaccinated on time. In the other half, little seems to help at that stage, so the solution must be earlier, in the form of policy or broader educational efforts.

In closing, I would like to thank the Committee for addressing this important issue. Vaccine refusal is one of the growing public health threats of our time. If we continue to allow non-medical exemptions to vaccination, rates of vaccination will continue to fall and more outbreaks will undoubtedly follow. As a leader at a Children's Hospital, I have a unique perspective on this, as Children's Hospitals are regional and sometime national resources. Le Bonheur Children's Hospital sits in the corner of Tennessee next to Arkansas and Mississippi, and serves a large number of children from 7 different states as well as providing high level specialty care for select diseases to children across the United States. Tennessee, Arkansas, and Mississippi all have different policies for granting exemptions to vaccines, which creates a tremendous problem to us and a threat to the children we serve, many of whom are too young to be vaccinated or are immunocompromised and more prone to severe diseases. I urge the Committee to consider solutions that will both harmonize public health policy in this area and will also protect children as they grow up to become the next generation.

[SUMMARY STATEMENT OF JONATHAN A. MCCULLERS]

Good Morning Chairman Alexander, Ranking Member Murray, and other Members of the Committee. I am Dr. Jon McCullers, the Chair of the Department of Pediatrics at the University of Tennessee Health Science Center and the Pediatrician-in-Chief at Le Bonheur Children's Hospital in Memphis. As someone who has devoted his career to the child health sphere, I firmly believe that there is no more precious resource than our children, and that they should be protected by all means available to us. They truly are the future of this nation. The declining rates of childhood vaccination in this nation and, indeed, worldwide, now prove to be a threat to this future.

The childhood vaccination program of the United States has proven to be one of the most powerful public health achievements in our history. In the first half of the 20th century, there were more than 1 million infections and more than 10,000 deaths every year from diseases which are now preventable by childhood vaccines. Measles alone caused more than a half million illnesses every year in the first half of the last century, and between 450 and 500 children died annually. Measles is a highly contagious viral respiratory disease, characterized by fever, cough, sore throat, and a rash. It is a very dangerous disease – about 1 in a thousand infected persons develop encephalitis, an infection of the brain, 1 in a thousand develop severe pneumonia, and about half of those with these severe complications die. There is no specific treatment for measles, so vaccination is the only means of preventing these outcomes. With the introduction of a safe and effective vaccine for measles in 1963 and improved public health efforts to see that nearly every child received it, new cases of measles arising in the United States were entirely eliminated by the year 2000.

Unfortunately, the issues of vaccine opposition and vaccine hesitancy are now impairing our ability to effectively insure appropriate vaccine coverage, aided by State laws that make it easier to avoid vaccination. The last decade has brought numerous outbreaks in the United States, including several that are ongoing at present. These outbreaks are strongly linked to vaccine refusal, and in particular to clustering of unvaccinated individuals in specific communities or regions. Cases are introduced from unvaccinated individuals traveling here from other countries, and spread rapidly through communities with vaccination rates under the level needed for herd immunity. This problem is not limited to the United States – countries worldwide are dealing with similar outbreaks. As a single example, there were 0 cases of measles in Brazil in 2017, but more than 10,000 cases occurred in 2018 when infected travelers brought measles into that country.

The vaccine against measles is very safe and very effective. One dose provides complete protection in about 93 percent of individuals, while a second dose raises that level of protection to 97 percent. Very few side effects occur. About 1 in 10 children experience fever for 1–2 days, and about 1 in 3000 to 1 in 4000 have a simple seizure associated with fever with no lasting effects. Allergic reactions are very rare and typically very mild. When compared to the outcomes of the disease itself, it is easy to see why doctors and public health officials universally recommend on time and complete vaccination.

Unfortunately, vaccine refusal is high and getting worse in many states. This issue is complicated by the variety of state based policies regarding exemption from vaccination and the methods of counseling about vaccines. Three states currently only allow medical exemptions from vaccination, while 30 states allow for religious

exemptions to vaccines, and 17 allow both religious and personal exemption. The rate of parents claiming non-medical exemptions to vaccines is 2.5 times higher in states that allow both religious and philosophical exemptions compared to religious exemptions alone – evidence that allowing multiple pathways to exemption worsens this problem. California is an illustrative case … that state allowed both types of exemptions earlier in the decade, but non-medical exemptions rose, the overall level of vaccination dropped below the level needed for herd immunity, and the state experienced a large outbreak of measles in 2014–2015 with spread of the disease in Disneyland the park theme parks. California subsequently eliminated non-medical exemptions and the vaccination rate has returned to 97 percent.

Social media is now driving a new phenomenon somewhat distinct from vaccine opposition, termed vaccine hesitancy. When parents get much of their information from the internet or social media platforms such as twitter and Facebook, reading fringe ideas in the absence of accurate information can lead to understandable concern and confusion. These parents may thus be hesitant to get their children vaccinated without more information. The role of the pediatrician is very important with these families – we must do a better job of communicating at many levels, but particularly at the point of contact in the well child visit when vaccination should take place. Half of the time when counseled appropriately, those with vaccine hesitancy will agree to have their children vaccinated on time. In the other half, little seems to help at that stage, so the solution must be earlier, in the form of policy or broader educational efforts.

In closing, I would like to thank the Committee for addressing this important issue. Vaccine refusal is one of the growing public health threats of our time. If we continue to allow non-medical exemptions to vaccination, rates of vaccination will continue to fall and more outbreaks will undoubtedly follow. As a leader at a Children's Hospital, I have a unique perspective on this, as Children's Hospitals are regional and sometime national resources. Le Bonheur Children's Hospital sits in the corner of Tennessee next to Arkansas and Mississippi. These three states all have very different policies for granting exemptions to vaccines, which creates a tremendous problem to us and a threat to the children we serve, many of whom are too young to be vaccinated or are immunocompromised and more prone to severe diseases. I urge the Committee to consider solutions that will both harmonize public health policy in this area and will also protect children as they grow up to become the next generation.

The CHAIRMAN. Thank you, Dr. McCullers.

Mr. Boyle, welcome.

STATEMENT OF JOHN G. BOYLE, PRESIDENT AND CEO, IMMUNE DEFICIENCY FOUNDATION, TOWSON, MD

Mr. BOYLE. Chairman Alexander, Ranking Member Murray, and Members of the Committee, thank you for inviting me here to testify in the importance of herd immunity, or community immunity as we like to say, for vaccine-preventable diseases.

My name is John Boyle and I am the President and CEO of Immune Deficiency Foundation, a not for profit patient organization that represents people with primary immunodeficiency disease or PI. Primary immunodeficiency diseases are a group of more than 350 rare and chronic disorders in which parts of the body's immune system are either missing or functioning improperly.

There is an estimated 250,000 people diagnosed PI in the U.S. alone. That is about 1 and 1,200 of your constituents. These disorders are caused by genetic defects and are not contagious. Now there is a variety between the different forms of PI, but one thing unites all of us, we are immunocompromised meaning that we are potentially vulnerable to even common viruses and bacteria. Now, I have a form of PI known as X-linked agammaglobulinemia or XLA. I was diagnosed with it when I was six months old, when a respiratory infection nearly killed me. In short, I do not produce

antibodies, but I am able to be here with you today because I receive weekly infusions of antibiotics from other people through a blood plasma product called immunoglobulin or IG. These infusions give me back some of what I am missing, but I am still susceptible to infections.

Now, because I was diagnosed early and I receive IG therapy, my health is better than most others with PI. However, a simple cold can wreak havoc with me or many other members of our community. We are incredibly vulnerable to communicable illnesses. Now for some members of our community, infections are truly a life-and-death matter. I think all of you probably remember David Vetter, affectionally known as the boy in the plastic bubble, who was born with severe combined immune deficiency or SCID. Children diagnosed with SCID, XLA, or any other form of PI face multiple challenges with simple everyday pathogens. Exposing these children to something as severe as measles could be life-threatening. Parents and communities where vaccine use is being questioned are afraid to send their children outside. They are afraid because they know the history, the science, and the math, and they know the stakes. If people stop vaccinating, the safety net of community immunity will fall, and their children will be among the first casualties.

Now, of course, this does not just affect children, it affects adults too. While there is now newborn screening for SCID, most members of our community go years or even decades with serious or recurrent infections without knowing that they have a compromised immune system. I am particularly concerned for the health of this segment of our community, the undiagnosed. If community immunity fails, they do not even know that they need to take precautions. Those of us who know that we have PI do what we can to avoid exposure to infections. But the undiagnosed lack this basic knowledge and are even more at risk. Now the reason that all of us are so dependent on community immunity in the PI community is that vaccines do not work with most of us who have forms of PI. Our systems either do not remember the pathogens, or we physically cannot create the antibodies.

A further complication is that there are some vaccines that are actually dangerous to us, live vaccines. As a result, those in the field of immunology have studied this issue thoroughly to produce evidence-based guidelines to best safeguard those of us with PI. An article that I shared with the Committee discusses the issue surrounding which vaccines are either indicated or not, but it also addresses the growing neglect of societal adherence to routine vaccinations, what we are here talking about today. It states how important it is for family members and then those around patients with immunodeficiencies to receive all available standard immunizations in order to protect the family member who has PI.

Now in closing let me say this, my life along with the lives of hundreds of thousands of others who are immunocompromised depend on community immunity. We depend on vaccines. I understand from the concern that some new parents have, particularly given the misinformation on social media. But that fear cannot override the facts.

History has shown us that vaccines work. Science has shown us that vaccines are necessary. And mathematics has shown us that

the odds of children having a healthy life are magnitudes greater if they have had their vaccines. The current decline in vaccine usage is literally bringing back plagues of the past. All those of us who are immunocompromised will suffer first and suffer more. The loss of community immunity is a threat to all of us.

We need to band together to dispel the myths, combat misinformation campaigns, and help ensure that measles and other vaccine-preventable diseases are once again put in their place, in history books and not in our communities.

Thank you.

[The statement of Mr. Boyle follows:]

PREPARED STATEMENT OF JOHN G. BOYLE

Chairman Alexander, Ranking Member Murray, and Members of the Committee:

Thank you for inviting me to testify on the importance of herd immunity for vaccine preventable diseases.

My name is John G. Boyle, and I am the President and CEO of the Immune Deficiency Foundation. IDF is a not-for-profit patient organization representing people with primary immunodeficiency diseases, or PI.

Primary immunodeficiency diseases are a group of more than 350 rare, chronic disorders in which part of the body's immune system is missing or does not function properly. There are an estimated 250,000 people diagnosed with a form of PI in the U.S. alone. That's approximately 1 in 1,200 of your constituents.

These disorders are caused by genetic defects and are not contagious. Many are first recognized shortly after birth or in early childhood, but many more are not diagnosed until much later in life.

There is some variety between the different forms of PI, but one thing unites all of us: we are immunocompromised, meaning that we are potentially vulnerable to even the most common viruses and bacteria. We all struggle, to varying degrees, with recurring infections and persistent illnesses even when treatments are available that lessen the impact of our diagnoses.

I have a form of PI known as X—Linked Agammaglobulinemia, or XLA. I was diagnosed with it when I was six months old after a respiratory infection nearly killed me. In short, I don't produce antibodies. I'm able to be with you today because I receive weekly infusions of antibodies from other people through a blood plasma product called immunoglobulin, or Ig.

These infusions give me back some of what I'm missing, but I'm still very susceptible to infections.

Because I was diagnosed early and receive Ig therapy, my day-to-day health is better than many others with PI. However, a simple cold can wreak havoc with the lives of many members of our community. Without a fully-functioning immune system, we're incredibly vulnerable to communicable illnesses.

For some members of our community, infections are unquestionably a life and death matter. I suspect that all of you recall David Vetter, affectionately known as the "boy in the bubble," who was born with Severe Combined Immunodeficiency or SCID, one of the most severe forms of PI. Infants born with SCID are missing vital portions of their immune system, and their survival is based on receiving a bone-marrow transplant or gene therapy in their first few months of life.

Children diagnosed with SCID, XLA, or any other form of PI face multiple challenges with simple, everyday pathogens. Children with PI regularly fall ill and miss school because of Rhinovirus and other diseases that are not that serious to most people. **Exposing these children to something as severe as measles could be life threatening**. Parents who live in communities where vaccine use is being questioned have shared that they are afraid to send their child to school—even when their child is not sick and should be able to participate.

They're afraid because they understand the science, the math, and the history. They know the stakes: **if people stop vaccinating and the safety net of "community immunity" fails, their children will be among the first casualties.**

As a father, I gravitate to talking about children first. But this issue affects adults too. While there is now newborn screening for SCID in all 50 states, most members of our community go years or even decades dealing with serious and recurrent infections without knowing they have a compromised immune system. Because of this,

we know there are many people living with PI who are undiagnosed. I am particularly concerned for the health of this segment of our community, the undiagnosed. If community immunity fails, they do not know that they need to take precautions. Those of us who know we have PI do what we can to avoid exposure to infections. But the undiagnosed lack this basic knowledge and are even more at-risk.

The reason that all of us, young and old, diagnosed or undiagnosed are so dependent on community immunity is that vaccines do not work for most of us with PI. The basic concept of a vaccine is to expose the body's immune system to an inert version of a pathogen so it can "remember" that pathogen and make antibodies when necessary. This does not work with us because our systems either don't remember the pathogens or we physically can't create the antibodies.

A further complication is that being immunocompromised as we are there are some vaccines that could actually be dangerous to us, particularly "live" vaccines. As a result, those in the field of immunology have studied this issue thoroughly to produce evidence-based guidelines to best safeguard those with PI.

In 2014, the IDF Medical Advisory Committee published an article in The Journal of Allergy and Clinical Immunology called "Recommendations for live viral and bacterial vaccines in immunodeficient patients and their close contacts," to help clarify which vaccines can be given to patients with PI. While the primary purpose of the article was to provide clarity about which vaccines were either indicated or contraindicated for people with various PI diagnoses, it also addressed the growing neglect of societal adherence to routine vaccinations, a topic particularly relevant to this morning's discussion. I would like to submit the full copy of this article for the committee report.

The authors clearly recommend, "Education about the critical need for maintenance of herd immunity (community immunity) in the population at large." In essence, community immunity offers valuable protection to patients with PI who are unable to mount protective antibody responses. It is particularly important for family members of patients with T and B cell immunodeficiencies, such as Common Variable Immune Deficiency (or CVID), SCID, and XLA to receive all of the available standard immunizations in order to protect their family member with these types of PI. I will note that any person with PI should consult a healthcare provider, particularly an immunologist, to discuss whether there should be any adjustments to the specifics of their vaccination care plan depending on their diagnosis. Of course, consulting a healthcare provider is what everyone should do when it comes to discussing vaccine-related questions. They can answer your questions, and—I hope—allay concerns and put things into perspective.

In closing, let me say this: my life, along with the lives of hundreds of thousands of others who are immunocompromised depend upon herd immunity. We depend on vaccines. I understand the concern that some new parents have particularly given the misinformation on social media, but that fear can't override facts. History has shown us that vaccines work. Science has shown us that vaccines are necessary. And mathematics has shown that the odds of children having a healthy life are magnitudes greater if they've had their vaccines.

The current decline in vaccine usage is literally bringing back plagues of the past. While those of us who are immunocompromised will suffer first and suffer more—the loss of community immunity is a threat to us all. We need to band together to dispel myths, combat misinformation campaigns, and help ensure that measles and other vaccine-preventable diseases are once again put in their place—in history books, not in our communities.

I thank you for inviting me to testify, and I look forward to any questions you may have.

[SUMMARY STATEMENT OF JOHN G. BOYLE]

For someone with any one of these disorders—particularly those who are untreated—what may be a modest cold or virus for most people could be a serious or even fatal condition. Severe infections, such as the measles, pose even more risk for immune compromised people, and community immunity represents the best way to effectively prevent what could be a life-threatening situation. People with PIs are unable to mount adequate protective antibody responses to infections so most people with these conditions cannot get vaccines themselves.

As outbreaks of vaccine-preventable diseases have increased over the years, the PI community has grown concerned. When the safety net of community immunity fails:

- Parents of children with PI are concerned about sending their children to school where they have no protection from contagious diseases, even when they are otherwise healthy enough to participate.
- Many people, including adults, who have not yet been diagnosed with a PI, are at high risk because they do not know to take precautions to avoid infections.

The lives of hundreds of thousands of individuals who are immunocompromised depend on herd immunity—they depend on their community being vaccinated. When people opt to not immunize—absent sound medical information or other compelling reasons—it creates a dangerous situation that is particularly harmful for individuals with primary immunodeficiency and to others with compromised immune systems.

The CHAIRMAN. Thank you, Mr. Boyle.

Mr. Lindenberger, welcome.

STATEMENT OF ETHAN LINDENBERGER, STUDENT, NORWALK HIGH SCHOOL, NORWALK, OH

Mr. LINDENBERGER. Thank you, Chairman Alexander, Senator Murray, and distinguished Committee Members for the opportunity to speak today.

Good morning everyone. As was stated, my is Ethan Lindenberger and I am a senior Norwalk High School, and my mother is an anti-vax advocate that believes vaccines cause autism, brain damage, and do not benefit the health and safety of society despite the fact such opinions have been debunked numerous times by the scientific community. I lived my entire life without numerous vaccines against diseases such as measles, chickenpox, or even polio. However, in December 2018, I began catching up on my missed immunizations, despite my mother's disapproval, eventually leading to this story and being able to speak here today. And I am very happy for that, so thank you.

Now, to understand why I have come here and what I really want to talk about, I have to talk about my home life and my upbringing. I grew up understanding my mother's believes that vaccines are dangerous, and she would speak openly about these views. Both online and in person, she would voice her concerns, and these beliefs were met with strong criticism.

Over the course of my life seeds of doubt were planted and questions arose because of the backlash my mother would receive, but over time that really did not lead anywhere. Now it is important to understand that as I approached high school and began to critically think for myself, I saw that the information in defense of vaccines outweighed the concerns heavily. I began leading debate clubs at my school and pursuing truth above all else, and I realized one certain quality to debates and to conversations in general when it comes to controversial discussions, which is that there seems to always be two sides to a discussion. There always seems to be a counterclaim or rebuttal and always something to strike back with in terms of debate. Though this may seem true in all instances, this is not true for the vaccine debate, and I approached my mother with this concern that she was incorrect.

I approached my mother numerous times trying to explain that vaccines are safe and that my family should be vaccinated. Approaching even with articles in the CDC explicitly claiming that ideas that vaccine cause autism and extremely dangerous consequences were incorrect. In one such instance where I approached

my mother with information from the CDC that claims vaccines do not cause autism, she responded with, that is what they want you to think. Skepticism and worry were taking the forefront in terms of information. Now, conversations like these reaffirmed that evidence in defense of vaccines was, at least on an anecdotal level, much greater than the deeply rooted misinformation my mother interacted with. And that is what I want to focus on today.

To combat preventable disease outbreaks, information is, in my mind, the forefront of this matter. My mother would turn to anti-vaccine groups online and on social media, looking for her evidence in defense, rather than health officials and through credible sources. This may seem to be in malice because of the dangers that not vaccinating imposes, but this is not the case. My mother came, in the sense of loving her children and being concerned. This misinformation spreads and that is not necessarily justifiable, but I carry this knowledge with me that it was with respect and love that I disagreed with my mother. And with the information she provided, I continued to try and explain that it was misinformed. Ideas that, again vaccine cause autism, brain damage, and also that the measles outbreak is of no concern to the society and to America, were ideas that were pushed by these sources that she would go to. And for certain individuals and organizations that spread this misinformation, they instill fear into the public for their own gain selfishly and do so knowing that their information is incorrect.

For my mother, her love, affection, and care as a parent was used to push an agenda to create a false distress. And these sources, which spread misinformation, should be the primary concern of the American people. Although change is already in place, more strides can be done. Almost 80 percent of people according to Pew Research Center, turn to the internet for health related questions. I further explained some more statistics and evidence in my written testimony. Now, in terms of what I would like to walkway with today and kind of finalize with, although my mother would turn to very illegitimate sources and sources that did not have peer-reviewed evidence or information, I quickly saw that the evidence and claims for myself were not accurate. And because of that and because of my health care professionals I was able to speak with and the information provided to me, I was able to make a clear, concise, and scientific decision.

Approaching this issue with the concern of education and addressing misinformation properly can cause change, as it did for me. Now, although the debate around vaccines is not necessarily centered on information and concerns for health and safety, this is why education is important, and also misinformation is so dangerous.

Thank you.

[The statement of Mr. Lindenberger follows:]

PREPARED STATEMENT OF ETHAN LINDENBERGER

Thank you Chairman Alexander, Senator Murray, and distinguished Committee Members for the opportunity to speak today.

Good morning, everyone. My name is Ethan Lindenberger and I am a senior at Norwalk High School. My mother is an anti-vaccine advocate that believes vaccines cause autism, brain damage, and do not benefit the health and safety of society de-

spite the fact such opinions have been debunked numerous times by the scientific community. I went my entire life without vaccinations against diseases such as measles, chicken pox, or even polio. However, in December of 2018, I began catching up on my missed immunizations despite my mother's disapproval, eventually leading to an international story centered around my decisions and public disagreement with my mother's views.

To understand why I am here and how I have come to this point, I first must share some details about my upbringing and household. I grew up understanding that my mother believed vaccines are dangerous, as she would speak openly about her views both online and in person. These beliefs were met with strong criticism, and over the course of my life seeds of doubt were planted and questions arose because of the backlash my mother received when sharing her views on vaccines.

These questions and doubts were minor and never led to a serious realization of how misinformed my mother was. As these thoughts grew, I continued to attend high school and remained undecided in my opinion of vaccinations for many years. At my high school, I ran a debate club and learned about the importance of finding credible information both through my own pursuits in leading this club and through the fantastic teachers at Norwalk.

This is important to understand, as learning to find credible research and information is fundamental to finding truth in a world of misleading facts and false views. Through leading my debate club, I saw there are almost universally two or more sides to every discussion. To every claim there is a counterclaim, and to every statement there was always a rebuttal. Though this may seem to be true in all instances, the scientific studies and evidence that analyze the benefits and risk of vaccinations are separate from this truth. In its essence, there is no debate. Vaccinations are proven to be a medical miracle, stopping the spread of numerous diseases and therefore saving countless lives.

I remember speaking with my mother about vaccines, and at one point in our discussion she claimed a link existed between vaccines and autism. In response, I presented evidence from the CDC which claimed directly in large bold letters, "There is no link between vaccines and autism." Within the same article from the CDC on their official website, extensive evidence and studies from the institute of medicine (IOM) were cited. Most would assume when confronted with such strong proof, there would be serious consideration that your views are incorrect. This was not the case for my mother, as her only response was, "that's what they want you to think."

This is only one example amongst a myriad of conversations where such evidence was disregarded and ignored. And this response is representative of the entire discussion around vaccines, where one side is based in scientific evidence and truth while the other is based in skepticism and falsities.

Conversations like these were what reaffirmed the evidence in defense of vaccinations and proved to me, at least on an anecdotal level, that anti-vaccine beliefs are deeply rooted in misinformation. Despite this, a necessary clarification must be made when discussing this misinformation: anti-vaccine individuals do not root their opinions in malice, but rather a true concern for themselves and other people. Although it may not seem to be true because of the serious implications of choosing not to vaccinate, the entire anti-vaccine movement has gained so much traction because of this fear and concern that vaccines are dangerous.

According to a study analyzing the views and beliefs of the dangers imposed by vaccinations by the Pew research center on February 5th, 2017, "About half (52 percent) of parents with children ages 0 to 4 say the risk of side effects is low, while 43 percent say it is medium or high. By contrast, seven-in-ten adults with no minor-age children (70 percent) rate the risk of side effects from the [MMR] vaccine as low." That means that nearly 20 percent of Americans which previously believed vaccines posed a low risk for children of a young age begin to raise concerns once they have a child. Such is the case for my mother.

This does not justify spreading misinformation, and I carried this knowledge with me as I pursued vaccinations without my mother's approval. Her beliefs were not true, and propagating these lies is dangerous. However, it is not necessarily ill-natured. This was the foundation for the respectful disagreement between us as I publicly expressed concerns for her misinformed beliefs.

I speak here today to first express this concept, that anti-vaccine parents and individuals are in no way evil. With that said, I will state that certain individuals and organizations which spread misinformation and instill fear into the public for their own gain selfishly put countless people at risk. If one agrees that vaccines are safe and substantially benefit the health and safety of the public, you'd see the anti-vaccine leaders and proponents of misinformation which knowingly lie to the Amer-

ican people are the real issue. Using the love, affection, and care of a parent for their children to push an agenda and create false distress is shameful. **The sources which spread misinformation should be the primary concern of the American people.**

Change is already taking place, as the largest source of misinformation comes from private social media platforms. In a 2011 study by the pew research center, 80 percent of Americans turn to the internet for health related questions. This is dangerous due to the sources which spread misinformation online, and the surprising influence they hold. *The Atlantic* examined vaccine related posts on the social media platform Facebook from 2016—2019. In their article, they found that "Just seven anti-vax pages *generated nearly 20 percent* of the top 10,000 vaccination posts in this time period." This echo-chamber that a handful of sources generate create the majority of anti-vaccine information on these platforms, and with my mother it continues to influence her views along with countless Americans.

My mother would turn to some of the cited sources in this article by The Atlantic, using their information as a basis for her views. This was problematic, as with a quick inspection of the claims and evidence of these sites their intentions are revealed. Information is not properly cited, and data is skewed to create false claims. In one video published by the website "*stopmandatoryvaccines.com*" (which was listed as one of the top contributors of anti-vaccine information by the Atlantic), the measles outbreak was made out to be a unfounded panic created by big pharmaceutical companies and meant to push legislative agendas. Del Bigtree, a celebrity in the anti-vaccine movement, spoke with "Dr. Bob Sears." My mom and I sat down, watching this video so she could prove her beliefs were not unfounded.

In this video, Dr. Bob Sears claims that in the past 15 years there hasn't been a single death to the measles. In contrast, 449 people have had fatal reactions to the MMR vaccine. This completely ignores that if the measles disease was left to its own devices, it could cause an incomparable amount of deaths. The World Health Organization (W.H.O) estimates that "During 2000–2017, measles vaccination prevented an estimated 21.1 million deaths making measles vaccine one of the best buys in public health." I bring this up to show how in my own personal life this misinformation reached my family. Not only that, it led to the people I care about being put at risk.

In school, I was pulled out of class every year and told that if I did not receive my shots, I wouldn't be able to attend my high school. But, every year, I was opted out of these immunizations and, because of current legislation, I was allowed to attend a public high school despite placing my classmates in danger of contracting multiple preventable diseases.

The debate around vaccinations is not centered around information, but instead concerns on the health and safety of society. We must distinguish the difference between a personal view and a medical concern, a safety concern, and the dangers of such rhetoric. The information leading people to fear for their children, for themselves, and for their families is causing outbreaks of preventable diseases. Therefore, combating this information while also working towards legislative changes may help protect our nation from needless deaths. My story highlights this misinformation and how it spreads. Between social media platforms, to using a parent's love as a tool, these lies cause people to distrust in vaccination, furthering the impact of a preventable disease outbreak and even contributing to the cause of diseases spreading. This needs to change and I only hope my story contributes to such advancements.

The CHAIRMAN. Thank you, Mr. Lindenberger. And thank you for coming from Ohio to let us hear what you have to say. Now we will begin 5-minute round of questions. I would—if many Senators interested, I would ask the Senators to keep the combination of questions and answers within five minutes. Dr. McCullers, you are a Pediatrician-in-Chief at one of our country's leading children's hospital, so your business is to talk every day during your career with lots of parents about their children. So, what do you say to parents, to a parent who comes to you in Memphis and said, I have heard on the internet or I have read that vaccines cause autism and I do not want my child to be vaccinated? What do you say to that parent?

Dr. MCCULLERS. Well, what we find when we look at this is that parents really have a very complex set of issues that they are concerned about. That is one of them but there is a lot of other things that they think about and that they bring to us. So, it is not one issue that we have to talk about, it is many, many issues.

The CHAIRMAN. But what—I want to focus on autism. What if they say that to you?

Dr. MCCULLERS. This was a concern that was raised about 20 years ago when there was a fraudulent paper published linking vaccines to autism.

The CHAIRMAN. That paper was published in the United Kingdom, correct?

Dr. MCCULLERS. It was published in the United Kingdom——

The CHAIRMAN. In a respected journal, is that correct?

Dr. MCCULLERS. It was a respected journal. It was a physician who published it, and he was, unfortunately, paid by a set of attorneys more than λ400,000 to falsify information because they were suing the government of England against vaccines. So, this was found to be wrong. It was retracted. He lost his medical license——

The CHAIRMAN. What did the journal do about it?

Dr. MCCULLERS. The journal retracted the paper and said it no longer is valid.

The CHAIRMAN. Have there been other papers or journals that agreed with that physician's——

Dr. MCCULLERS. There have not been that agreed with that position. There has been numerous scientific research done in the interim that have shown the opposite, that these vaccines are not linked. And the Institute of Medicine here in the United States, our highest authority on these sorts of issues, has declared that they are—it is a uniformly, basically, a closed issue now.

The CHAIRMAN. As you talk with parents, so is that persuasive with a mother who is concerned about her child and who has heard that vaccines cause autism?

Dr. MCCULLERS. I think if there is a rapport with the physician and a mutual respect, they are both for the opinion of the parent but then also for the position of the physician, you can say things like that and say the evidence is clear, I believe this, you should do this, and they will trust that information.

The CHAIRMAN. In your opinion, there is no evidence, reputable evidence, that vaccines cause autism?

Dr. MCCULLERS. There is absolutely no evidence at this time that vaccines cause autism.

The CHAIRMAN. Dr. Omer, do you agree with that?

Dr. OMER. Absolutely.

The CHAIRMAN. Dr. Wiesman, do you agree with that?

Dr. WIESMAN. I do.

The CHAIRMAN. Mr. Boyle, do you agree with that?

Mr. BOYLE. I do.

The CHAIRMAN. Mr. Lindenberger?

Mr. LINDENBERGER. I do.

The CHAIRMAN. Dr. Wiesman, what about state exemptions? You are a state public health officer and as a former Governor, I generally have a biased toward Washington not telling states what to do on many on——

[Laughter.]

The CHAIRMAN. With Washington, DC not telling states what to do. Senator Murray is correcting me here. So, what advice do you have about state exemptions and the effect on the concern we see today in pockets of measles across the country?

Dr. WIESMAN. I think as we heard earlier that the choice to sort of make exemptions more difficult to get, to be sort of as burdensome as sort of not getting the vaccine, is incredibly important. In Washington State, as you know, we have two bills right now that are looking to remove the personal exemptions from vaccine for school entry and for childcare entry. I think that is one of the tools that we have and that we should be using for this. I will also say in Washington State another problem we have is that about 8 percent of our kids are out of compliance with school records so that we do not even know if they are vaccinated or would like exemptions. And we have to tackle that problem as well, which really is a resource issue for schools and public health.

The CHAIRMAN. I am going to stay within my time. Senator Murray.

Senator MURRAY. Thank you very much. Dr. Wiesman, I really appreciate everything you and your state and local colleagues are doing on the frontlines of this measles outbreak in Washington State confirming and managing the cases, tracing potential contacts, identify exposures sights, crafting community messages. There is a lot going on, but it is really scary to imagine how much worse this outbreak would be if not for all the tireless work of so many public health officials on the ground. But we all hope we are able to not just respond to outbreaks, but also focus on preventing them in the first place. And I want to ask you, how have initiatives like the public-private partnership Vax Northwest and your department's proactive communication with parents of young children helped in building confidence?

Dr. WIESMAN. Great, thanks. Yes, we do believe that the child profile mailings that go out to parents, to kids up to age 6, they go out at points in time that are appropriate to the development of the child, are incredibly important. It is a trusted source of information, not just on vaccines, but on childhood development. And it is that relationship that we build with parents through that mailing that I think is incredibly important.

When I go out to the public and I see a new parent, I will often ask them, hey, do you get this little mailing from the health department? And they say, I do, we love, it is great information. So, I think that trusted source is really important. The public-private partnership that we have with Vax Northwest is actually a research initiative to try and best understand how we actually address vaccine hesitancy. There have been two studies done. One looking with health care providers on how to best train them around communication with their patients. Unfortunately, that work did not find that it made a difference in terms of addressing vaccine hesitancy nor necessarily health care providers efficacy around feeling confident in those conversations. The other piece was one with parents and parents who were interested in vaccine advocacy, training them on how to have conversations with parents, how to share information at PTA meetings, etc. And that did

find that it increased parents' knowledge of vaccines and reduced their hesitancy.

Senator MURRAY. Okay, thank you. And, Dr. Omer, as vaccination rates in some areas drop to low levels, we need to keep each other safe. Your research on vaccine hesitancy and likewise is really critical. And we know that some parents are making decisions about whether or not to vaccinate before they even have their child. I wanted to ask you, what are the implications of some of these early decisions and what have you learned about the key factors that lead some parents to hesitate to vaccinate?

Dr. OMER. Thank you for the question. And you rightly pointing out that a lot of this—that there is evidence to suggest that a lot of parents are making the decisions on vaccines before the baby is born. After the baby is born, it is like a fast moving train, and parents go through this extended jet-lag. And so, before that, there is a lot of discussion happening, etc. And there are several reasons for this. The first one is, the big picture reason is that vaccines are a victim of their own success, and as the rate of vaccine preventable diseases go down, because of vaccines, successive cohorts of parents see and hear about real or perceived adverse events and not the disease. And what happens is that mental calculus changes. And in that milieu, there are several that interact with several local factors, and in the U.S. for example, due to that sort of change in the disease rates, which is a good thing, we have less appreciation of vaccines susceptibility and severity and more questions about vaccine safety.

Senator MURRAY. Because we do not see it.

Dr. OMER. In that context, focusing on not just childhood but before the baby is born, we are working for example, our group is doing a randomized controlled trial in collaboration with University of Colorado and John's Hopkins, where we are—you now and this is due to an investment, due to funding from the National Institute for Allergy and Infectious Diseases, where we are looking at bringing together the best evidence and packaging it and seeing if that has an impact in not just maternal vaccination, but this intervention being performed in pregnancy, leading to childhood vaccination rates increase. And so, the initial results from them are promising, but to come back to the idea that we need to continue to invest in the best science for vaccine behavior and communication as we do for vaccine safety and vaccine efficacy.

Senator MURRAY. Okay, thank you very much.

The CHAIRMAN. Thank you, Senator Murray. Senator Isakson.

Senator ISAKSON. Thank you, Chairman Alexander. Thank you all for your testimony. Mr. Lindenberger, what year in school are you?

Mr. LINDENBERGER. I am a senior in high school.

Senator ISAKSON. When did you start doing the investigation and research on vaccination?

Mr. LINDENBERGER. From my mother specifically, I mean she would vocalize her views on vaccines throughout my entire life and it was a slow progression to start to see evidence as I would see people, I suppose, trying to counterclaim with her and argue online. I would see that she would have this backlash as she would share information. So, on Facebook, she shared a video and people

would be like that is incorrect, this is false. And so, as a child that intrigued me that people disagreed with my mom and I started to look into it over the course of multiple years.

Senator ISAKSON. That is the second time you have used online in your answer. I want to ask, does your mother get most of her information online?

Mr. LINDENBERGER. From what she has presented, yes. Either through Facebook or through sites that use the social media platforms, like Facebook—mainly Facebook, I mean.

Senator ISAKSON. Where do you get most of your information?

Mr. LINDENBERGER. From not Facebook. I mean, from CDC, the World Health Organization, scientific journals, and also cited information from those organizations like the Institute of Medicine. I try my best also to look at credited sources.

Senator ISAKSON. I would love to be guest at Thanksgiving dinner at your house. That would be——

[Laughter.]

Senator ISAKSON. It would be a heck of a discussion everybody would have. I know that. Dr. Omer, thank you for being here and thanks for the work that Emory does. Emory does a phenomenal job in infectious disease and all kinds of things like that. What currently—are there any things on the horizon that would join this group of people, that we might want to immunize for later on?

Dr. OMER. There are several exciting developments, and one of the big gaps in vaccine has been the fact that there is a gap of vulnerability between the baby is born and when we start vaccinating them. And that is due to immunological reasons. And one of the most exciting developments in this area is the area of maternal immunization where you vaccinate mom. And I had the privilege of being involved in some of those trials, etc. to protect not just the mother but the baby as well. So, there are vaccines against the respiratory syncytial virus, which is the biggest cause of viral pneumonia in the world on the horizon. So, there is a variety of vaccines being developed. There is a vaccine that is being developed against group B streptococcus, etc. So, there are several vaccines on the horizon. The field is expanding.

Senator ISAKSON. Now would those vaccinations take place in the mother before the baby is delivered?

Dr. OMER. Yes.

Senator ISAKSON. It transfers to the baby during the course of gestation?

Dr. OMER. Exactly. And our first trial had a name of "mother's gift" ages ago, and I think it is an appropriate name for this kind of first strategy where maternal antibodies protect the baby.

Senator ISAKSON. You know, I have been to Africa with CDC a number of times and seen your work, the work in the field that they do. I do not know of any organization that does more for health care in other countries that CDC does. How much do you use CDC as a resource in your work at Emory?

Dr. OMER. A lot. The CDC is a national treasure. And the firefighting function that I talked about they perform with the state and local health department is somewhat unique. For example, the European CDC is relatively new and has a very narrow mandate. And people who have looked at the effectiveness of national public

agencies in Europe, have clearly come out with the understanding that our CDC is very strong. And I am not trying to put down any other country's public agencies, because they are trying their best, but the kind of investments that have gone into building this cooperative framework of the CDC being the premier technical public agency but working closely with the state and local health department has served us really well, including in this area.

Senator ISAKSON. I do not think you are putting them down at all. In fact, to tell you the truth, it is the world's health care center, the CDC, and we are lucky to have it in the United States of America, but the world considers it their health center. And they are doing better job—CDC is doing a better job incubating CDCs in other countries now to replicate what they do in countries that are more developed and populated so——

Dr. OMER. Absolutely.

Senator ISAKSON. They are a great resource, great help, and a great service. And I thank all of you for being here today and Mr. Lindenberger, do not forgot that I will come to your Thanksgiving dinner one day and just meet you and your mom.

[Laughter.]

Senator ISAKSON. Thank you, Mr. Chairman, or Madam Chairman.

Senator MURRAY. [Presiding] Senator Baldwin.

Senator BALDWIN. Thank you. In 2015, this Committee held a similar hearing to discuss the resurgence of vaccine-preventable diseases in response to a multi-state measles outbreak. Our Nation's vaccination program has saved lives by preventing and reducing the outbreak of vaccine preventable diseases like measles, which has one of the most effective vaccines. So, I am troubled that we are here again facing another preventable outbreak in several states that has similarly been exacerbated by a surge of misinformation surrounding vaccine safety. I believe we must do a better job to prioritize investments in cutting edge science and public education surrounding vaccine safety. Younger children and those with compromised immune systems have a higher risk of measles complications. And with the breath of misinformation proliferating in the media and online about the science behind vaccines Dr. Wiesman,

Dr.—is it Omer?

Dr. OMER. Yes.

Senator BALDWIN. Dr. Omer, what role do state health departments play in our main community leaders like school officials and providers with accurate information and scientific resources on vaccine safety? And as a follow-on, what can Congress do to improve the public health education, so we do not see another preventable outbreak in the future?

Dr. WIESMAN. Thank you for that question. Yes, so states and local health departments really are the leaders in communities around these health strategies to engage their communities around vaccine information. They help provide the health education. They work with the school systems. They work with health care providers to make sure that health care providers have the information they need. It really takes a sort of coordinated effort.

Honestly, that system is crumbling. The sort of resources that are going into prevention in our state, local, tribal, and territorial health agencies has been decreasing. And we are really not up to the task. For example, I had a call with CDC a number of months ago. State health officials, we do this every two weeks, and CDC was on the call talking about a hepatitis A outbreak that is occurring throughout the country in many communities. They are encouraging us to do proactive vaccination campaigns with homeless and injection drug users, which is where this is being seen. I do not have the resources. I asked my staff, what would a plan look like? It would probably cost us $5 million. I do not have those resources. I do not have the staff that are there. That is very, very concerning to me. And, I forgot your second question, but——

Senator BALDWIN. How can Congress help? So, I am thinking——

Dr. WIESMAN. I sort of helped answer that right there.

Senator BALDWIN. That is right. That is right.

Dr. WIESMAN. Including, I think, in research around how do we—the social research around how is it we communicate with folks about vaccines, and then have a national campaign. We really need to get on this.

Dr. OMER. Just to add to that, in addition to research, investment in high quality research, I think Congress can work on making vaccine counseling reimbursable. So that is a specific tool that physicians can use at the periphery, at the frontlines of these conversations that are happening every day. Then sort of take the blueprint that I mentioned that is already there, that was developed by the National Vaccine Advisory committee, that has very specific science-based recommendations to have that kind of implementation out there.

To continue to support CDC's mission of this controlling outbreaks, etc. That should not be taken for granted. And the last thing in this stream of specific things is, continue to prioritize the vaccines safety research enterprise that we have, which is not just a template for this country, but everywhere else as well. So, having a robust vaccine safety system is not only a tool to maintain confidence in vaccines, but it is just the right thing to do. So, these are some of the specific things Congress and the Federal Government can do.

Senator BALDWIN. Thank you. I have only a few seconds left. I am going to ask a question. Maybe if we run out of time, you can submit information for the record. But I follow of course some of the advancements that happen in my state and some of the interesting things that are happening.

Since 2007, a company called FluGen in Madison, Wisconsin has been working to develop a more effective flu vaccine based on technology that was discovered and invented at the University of Wisconsin. As we have heard today, highly effective vaccines have played a critical role in advancing public health around the world, and I think there is more that we could do to support the development of better vaccines to protect individuals from an illness that results in literally thousands of deaths each year. Mr. Boyle, can you describe why it is important for Congress to continue to support this medical research that advances the development of more

effective vaccines for common illnesses like the flu, and specifically for vulnerable populations?

Mr. BOYLE. Sure, let me try. One of the challenges that I see when I even think about my colleagues and friends who sometimes struggle with whether to get the flu vaccine is basic issues of fears of things like needles. They do not want to get a shot. They are scared of that. For that reason, I know that things like the flu-mist and others are attractive, the problem is within our community a live virus, such as that has been used in the past, is a problem.

We are a little bit torn in that we want something to be easy and efficacious and something that is going to be widely adopted, but at the same time we have to be concerned about those who are especially undiagnosed. So, there is a little bit of a balance there and further investigation to help understand what new technologies could be made to reduce the burden of getting a vaccine, be it for the flu or anything more communicable, would be phenomenal. At the same time, we will have to work with the CDC and others in order to balance out the needs of those who are actually going to be affected by that negatively. But we are all in it together.

The continued conversation and exploration is important, and our community and other immunocompromised communities would I think be delighted to be part of these conversations.

Senator BALDWIN. Thank you.

Senator CASSIDY. [Presiding] Dr. Paul.

Senator PAUL. Thank you. Thank you for your testimony. For much of modern history, science and freedom have lived in relative harmony. Traditionally as medical discoveries came about like the smallpox, or polio vaccine, antisepsis or antibiotics, the results were so overwhelming that overtime the vast majority of the public accepted these advances voluntarily.

In fact, innovations like the smallpox vaccine had to overcome initially great public prejudice. Dr. Zabdiel Boylston learned about the Middle Eastern technique from his servant for the famous Pastor Cotton Mather. His first patient was actually his son, an incredibly brave choice. The consensus of the medical community though was entirely opposed to him at the time. The vaccine was a live vaccine, and as Dr. Boylston learned about 1 and 50 of those inoculated would die from the vaccine. And yet, the death rate from smallpox was approximately 50 percent. The Government did not mandate the vaccine though, but within two generations it was accepted enough that George Washington insisted that Martha be vaccinated with the smallpox vaccine before visiting him in the military camps.

Today though, instead of persuasion, many governments have taken to mandating a whole host of vaccines, including vaccines for non-lethal diseases. Sometimes these vaccine mandates have run amok, when the Government mandated a rotavirus vaccine that was later recalled because it was causing intestinal blockage in children. I am not a fan of Government coercion, yet given the choice, I do believe that the benefits of most vaccines vastly outweigh the risks. Yet, it is wrong to say that there are no risk to vaccines. Even the Government admits that children are sometimes injured by vaccines.

Since 1988, over $4 billion has been paid out from the Vaccine Injury Compensation Program. Despite the Government admitting to it in paying $4 billion for vaccine injuries, no informed consent is used or required when you vaccinate your child. This may be the only medical procedure in today's medical world where an informed consent is not required.

Now proponents of mandatory Government vaccination argue that parents who refuse to vaccinate their children risk spreading these disease to the immunocompromised community. There does not seem to be enough evidence of this happening to be recorded as a statistic, but it could happen. But if the fear of this is valid, are we to find that next we will be mandating flu vaccines? Between 12 and 56,000 people die from the flu or have been said to have died from the flu in America, and it is estimated to be a few hundred for measles. So, I would guess that those who want to mandate measles will be after us on the flu next. If the current science only allows for educated guessing when it comes to the flu vaccine, each year before that year's flu vaccine or strain is known, the scientist put their best guess into that year's vaccine. Some years it is completely wrong. We vaccinate for the wrong strand—the wrong strain of flu vaccine. Yet, five states already mandate flu vaccines. Is it really appropriate to mandate a vaccine that more often than not vaccinates for the wrong flu strain?

As we contemplate forcing parents to choose this or that vaccine, I think it is important to remember that force is not consistent with the American story, nor is force consistent with the liberty our forefathers sought when they came to America. I do not think you have to have one or the other though. I am not here to say, do not vaccinate your kids. If this appearing is for persuasion, I am all for the persuasion. I have vaccinated myself. I have vaccinated my kids. For myself and my children, I believe that the benefits of vaccines greatly outweigh the risks, but I still do not favor giving up on liberty for a false sense of security.

Thank you.

Senator CASSIDY. Do you yield back?

[Applause.]

Senator PAUL. I yield back.

Senator CASSIDY. Senator Warren.

Senator WARREN. Thank you, Mr. Chairman. So, we have heard today about how important vaccines are to preventing and controlling many diseases. And, I want to see, row in on one that we are battling right now in Massachusetts. Since last April, 318 outbreak associated cases of acute hepatitis A virus have been reported in the Commonwealth of Massachusetts. Hep A is a contagious virus that causes liver infection. Older children and adults who acquire the hepatitis A virus can experience a slew of incredibly unpleasant symptoms, fever, nausea. And in rare cases, the virus can even lead to death.

In Massachusetts, four people have already died since the outbreak began. Now, we did not use to have a hepatitis A vaccine at all, but in 1995 and '96 the Food and Drug Administration approved two hepatitis A vaccines, and soon after CDC recommended vaccination for certain populations, including routine vaccinations of children living in areas with elevated rates of the virus. Dr.

McCullers, you study infectious diseases, what impact did the introduction of the hepatitis A vaccine have on the national rates of the virus?

Dr. MCCULLERS. Well, thank you very much Senator Warren. Yes, hepatitis A can be a very sever disease in particular high risks groups. The vaccine that came out in the late 1990s is a very safe, very effective vaccine, and as we have increased vaccination rates, we have seen a tremendous decrease in the rate of the disease. We have seen more than a 50-fold decrease nationally over those years, primarily eliminating a lot of the disease in children as well as some of the food-borne outbreaks. But there is still a lot of public health work to do as it is illustrated by your current outbreak.

Senator WARREN. That is the question I want to ask. We have developed a vaccine, the rate goes way down, so we now have a vaccine-preventable virus here. Why are we seeing so many hepatitis A cases emerging now?

Dr. MCCULLERS. Well, what we are seeing is the vaccines administered in childhood. It has only been around for about 20 years so if you are 21 years or older, have not had it. Now it is recommended that high-risk groups such as recreational drug users as is part of the problem in Massachusetts, be vaccinated and we have not gotten all those groups yet. So, efforts to really find the high-risk individuals, which are well-defined, and to get them the vaccine would help prevent these outbreaks in the future.

Senator WARREN. Yes, and this is part of what is happening in Massachusetts. We have been battling the Opioid Crisis for years, and hepatitis A is just another place we need to fight on this. But we are learning from this. Just this past October, the same CDC committee whose recommendations in the 1990s helped the rates of the virus decline sharply, added persons experiencing homelessness to the list of those who are recommended to get hepatitis A vaccine. I see you are all nodding, right.

In Massachusetts, our public health workers, our community health centers, and our jails have sprung into action to try to get the vaccine to those who are most at risk. Dr. Wiesman, as Secretary of the Washington State Department of Health, you overseer your state's public health response. What can we be doing to ensure that local public health officials have the resources they need to be able to do their work?

Dr. WIESMAN. Yes, thank you. So, really part of this is making sure that the prevention public health fund is funded and that we look at funding the CDC. We have been asking ASTHO, the Association of state and Territorial Health officials and local public health for increasing the CDC budget 22 percent by FY2022.

Senator WARREN. Alright. So, we are talking money now.

Dr. WIESMAN. We are talking money.

Senator WARREN. We are talking money, and whether it is a situation like hepatitis A outbreak in Massachusetts or the measles outbreak in Washington State, how do the preventive costs of a vaccine program compare to the containment and treatment cost of an outbreak?

Dr. WIESMAN. Well in general we do know that for about every dollar spent on vaccines, you save about 10, so it is definitely a cost-effective intervention.

Senator WARREN. Good. So, the more we do on the front-end to ensure that everyone gets access to the vaccines, the less we will see individuals contracting hepatitis A, measles, whopping cough, all of the other vaccine-preventable diseases.

This Administration has repeatedly sought to cut the Prevention and Public Health Fund, which supports key immunization programs, and they have continued their efforts to weaken the Medicaid program, which covers all of the recommended vaccines for children and for many adults as well. I am glad that most of my colleagues are on the same page about the importance of vaccines.

Now let us make sure we are also on the same page about the importance of the public health funding, so people get access to those vaccines.

Thank you.

Senator CASSIDY. Senator Roberts.

Senator ROBERTS. Thank you, Mr. Chairman. I am going to go a little crosscurrent here, and I want to state that the importance of vaccine in infants and young people cannot be overstated. I understand that. But I want to talk about the seniors who are also at increased risk of experiencing serious and life-threatening effects of vaccine preventable diseases. We have quite a few octogenarians in the Senate that get vaccinated. More specially with flu. Mr. Boyle, you touched on this with your reference to this topic on the effect of a herd immunity syndrome, which I appreciate, particular settings in which adults and seniors are more susceptible to infectious diseases if they are not vaccinated.

But to figure out if we can look for ways that Federal programs can help by removing barriers to services like vaccines and providing the right incentives for people to use them. And, what procedural barriers exist to ensuring that seniors have proper access to vaccines? Do we need more education so seniors provide—overcome these challenges? I want to give you a personal illustration. A young lady, but she was in her 80s, but she was young.

[Laughter.]

Senator ROBERTS. She makes sure that all six of her children got flu shots, had in turn all of her grandchildren and that was a bunch of folks. And yet, she got the flu in Kansas this time around—bad just a very bad flu season. And for some reason, she did not get a flu shot. So here she is, a mother who has told her kids to get vaccinated and made sure it happened. And then, in her own situation, she did not get a flu shot along with her husband. We lost both. The sniffles became flu, the flu became serious, and we get into pneumonia, and we get into all sorts of other problems.

I am not going to go into what kind of treatment they received, but they were very important folks and they were pillars of their community, and they were still very active. I sometimes think that the octogenarian caucus in the, well in the Senate, we are known as potted plants.

[Laughter.]

Senator ROBERTS. We are also known as chairmen of the various committees around here.

Dr. Omer, you have written about vaccine confidence. And I am interested in how this applies to adults in recent years, who have seen outbreaks of vaccine preventable diseases in which

unvaccinated adults are an important factor. CDC also noted that a drop in the immunization rate contribute to rise in hospitalization and deaths during the last flu season. I do not get it. I do not understand why in a period of your life when you would be obviously saying I need a flu shot and then respond to why you did not do it, well we just did not get around to it. I do not know.

If any of you would like to offer any opinions. We are talking about young people all the time but there are people who still contribute to this society even though there is no bar graph after 80 for anything. We are just out there. Anybody want to comment? Dr. Omer.

Dr. OMER. Thank you Senator, and the story that you noted is not unique, unfortunately, in this country and throughout the world.

The elderly are one of the highest risk groups for count complications after influenza. The vaccines are slightly less effective in the elderly, but that is the reason we need more of them to be vaccinated. And this is one of the gaps that I was talking about, that we do not have evidence-based to communicate to several groups, including the elderly. And this is not a group that is actively opposed to vaccines. They have the concept of vaccines, and they have seen what infectious diseases can do. But the—at that time when a lot of the discussion has revolved around childhood vaccines, we need evidence-based strategies to communicate to not just the elderly, but also to their health systems. The providers, who deal with the elderly do not have, unfortunately, the muscle memory to talk about vaccines and to make it part of their routine clinical practices. There is a lot to be done and thank you for highlighting that issue.

Senator ROBERTS. Mr. Chairman, my time has expired. I want you to know that we did not plan this, Dr. Omer and myself before the Committee hearing, but he certainly hit the nail on the head. I think it is an issue that we overlook. Thank you.

Senator CASSIDY. Thank you.

Senator Kaine.

Senator KAINE. Thank you, Mr. Chair, and thank you to the witnesses. This has been a fascinating topic. Timely, I noticed yet another study has come out just in the last 24 hours, a study dealing with a very significant longitudinal study with a big chunk of children in Denmark that also, again, demonstrates no link between the MMR vaccine and autism, and so it is a timely date to have this hearing. I want to ask a question about—begin with a question about vaccination shortages, which as a former governor, worries me a lot. Problems in the supply chain that could lead to shortages of important medications.

In 2017, outbreaks of hepatitis A increased demand and lead to constraints supplies of that vaccine. Many constituents have contacted my office about their inability to access the shingles vaccine, shingrix. So, last year I joined the bipartisan group of Members of this Committee in a letter to commissioner Gottlieb of urging him to convene the drug shortage task force to develop a report on the root shortage of drug vaccines. I look forward to reading that report and I think it may be on the verge of being published. I think the Committee has completed the work and it is very close to publica-

tion. It might be worthy of some Committee consideration when it is done.

What more can we do, and I guess I will direct it specifically to Dr. Omer and Dr. Wiesman, what more could we do at the Federal level to make sure there is an adequate supply of vaccines?

Dr. WIESMAN. Well, just to start out and then turn it to my colleague. So, one, we would need to continue investing in vaccine research figuring out new technologies for producing vaccines. We use sort of egg technology and it is a very long, laborious process in many of these. So, we have to move towards new technologies, I think, around cell-based or recombinant vaccines, so that we can produce them more quickly and assure the safety. And it is a problem with the vaccine shortages.

Dr. OMER. Yes, so one of my mentors has said a few times that it is not—vaccine is in a vial, that remains in a vial, is 100 percent safe, but 0 percent effective. And so, inventing a vaccine or developing a vaccine or licensing a vaccine is not sufficient. We need to have a stable supply of vaccines. And that requires A. a Federal-wide thinking and response from regulation to working with our research entities to say that there is a robust pipeline of new vaccines, and there are multiple approaches.

Infectious diseases attack our bodies through multiple mechanisms, therefore there are multiple vulnerabilities. What it does is that it creates an intellectual marketplace of ideas so that if there is more than one strategy that we are focusing on at the science level, we have more likelihood of having multiple products that compete with each other and have a—sort of give us more options as a country. Then working with manufacturers. Sort of ensuring that we understand that there is a stable manufacturing pipeline.

The third thing is sometimes in certain specially pandemics, etc., one policy intervention is BARDA, which invest in preparedness related interventions. And for example, some flu vaccines that would be required in a pandemic, there it is in our interest to ensure a stable seasonal flu pipeline. And so, there are interventions and investments which are a little bit more direct that sort of straddle that divide between emerging and routine vaccination, etc. So, it will require a nationwide—a national response, not just a Federal response in this sense, that sort of bringing in states and other partners as well.

Senator KAINE. Thank you for that. Yes, Dr. McCullers. You need to be quick because I have one more question.

Dr. MCCULLERS. Alright, very quickly then. Three quick issues, one is that these are for-profit companies generally that create the vaccines, so having a Federal buy that gives them some surety will make them produce more, which will help the vaccine shortages. The second is, we really have a problem not so much with shortage but with maldistribution, so it becomes a logistics effort and we can do better at that at the local level, being able to make sure every physician, practice, or hospital has that. And the third is to reinforce the importance of the strategic national stockpile, which again keeps these vaccines in reserve when we might need them. Thank you.

Senator KAINE. Thank you. I just in my last minute Mr. Lindenberger, I just want to compliment you. We revere Jefferson

in Virginia and one of the things that he said that still is so powerful is, "progress and Government and all else depends upon the broadest possible diffusion of knowledge to the general population." He believed that the diffusion of knowledge and giving people knowledge would enable them to make the right decisions. Now, fake knowledge, misinformation, intentionally misleading information can also be disseminated.

In this social media age with the internet, the competition between the true and the valid, and the fake and the dangerous, even the manipulated by people who want to do us harm is very difficult, but I think it is interesting probably both your mother and you reached your conclusions because you had an internet and tools to do your own research. And so, the different between, your mom and you, you are using some of the same tools and reaching different conclusions, but I applaud your critical thinking skills and your willingness to share your story.

Mr. LINDENBERGER. Thank you. I do not want to go overtime, but just to comment on that very quickly, I think part of the issue is being able to inform people about how to find good information because with my mother it was not that she did not have the information, but she was manipulated into disbelieving it. And that is part of the attack, which is that the CDC was made out to be a fraudulent group that was pushing vaccines for its own demand and—but that is not the case and the evidence proposed is genuine. And so, I just want to comment on that.

Senator KAINE. Thank you, Mr. Chairman.

Senator CASSIDY. My turn. Let me give some color to what Senator Paul said. You may or may not know I am a physician, and I have seen people who have not been vaccinated. Who have required liver transplantation because they were not, and or who ended up with terrible diseases because of no other reason, they just for whatever reason did not understand that vaccination was important. It is important to point out that even a flu shots are not completely effective, they do mitigate.

There is a cross benefit that will decrease the severity, number one. Number two, hospitals commonly require their employees to be immunized because they understand that herd immunity is important, and if the nurse's aide is not immunized, she can be a typhoid Mary, if you will, bringing disease to many who are immunocompromised, as Mr. Boyle points out. And as regards to the Federal Government requiring, there is a Federal statute requiring that vaccine information statements should be given, that is a Federal requirement. And in the name of liberty we should rely therefore upon states and localities to make a further requirement, but they typically do require informed consent.

That is important to note, not to be misled by—not to be misled regarding that. Secondly, I think our next—I think we should point out that in terms of requirement, the requirement is just that you cannot enter school unless you are vaccinated. Now, if you are such a believer of liberty, that you do not wish to be vaccinated, then there should be a consequence, and that is that you cannot infect other people.

Mr. Boyle, if your child is born with immunodeficiency, and someone comes to your school who is not vaccinated, and the lack

of herd immunity means that your child, who no fault of their own, cannot be immune, is it a victimless crime that somebody does not get vaccinated and your child dies? I mean, my gosh, you are the guy who is representing those people, who for whatever reason the vaccine does not work, and they are particularly susceptible. Now, Dr. Wiesman, I seem to remember a particularly tragic case in Washington State from about six years ago of a child who was immunocompromised on steroids chemotherapy for cancer, and someone brought measles to the school and I think I remember that child died. Do I remember that correctly?

Dr. WIESMAN. If we are talking about the same child, yes, he dies a number of years later from a follow-up reaction.

Senator CASSIDY. Now, so the parent has had the child vaccinated, but now she is on cancer chemotherapy and she is immunocompromised, and she is in school thinking that she can be a normal child, even though she is on cancer chemotherapy, but because someone else has made a decision not to vaccinate their child, her child dies. Now, do you believe in liberty? That is fine. Do not get immunized, but I do not think you need to necessarily expose others to disease. Dr. McCullers, tell me, you are in a state—you mentioned a practice where you have people from three different states, and hats off to Mississippi, they always have the highest immunization rate. You did not elaborate. What are the differences between the patients from these three different states in terms of, okay, Mississippi is always immunized, do you imply that maybe Tennessee and Arkansas are not?

Dr. MCCULLERS. Alright, so Mississippi does not allow any non-medical exemptions and they have nearly a 100 percent rate of immunization at school entry. They pay a lot of attention to it. Tennessee is in the middle. They allow religious exemptions but not philosophical exemptions. In Tennessee we have about a 97 percent vaccination rate at kindergarten entry, but we have seen the rate of non-medical exemptions under religious exemption triple in the last 10 years, so you can predict where that is going. Arkansas on the other hand allows both religious and philosophical exemptions and has a rate that is around 93 to 94 percent, below the level for community immunity.

Senator CASSIDY. In what state do you see the most vaccine-preventable diseases, nonetheless, presenting themselves?

Dr. MCCULLERS. Well, all of these are rare, and we see them from all—we see things from all the states. Tennessee, we get about one a year measles case, always imported from outside the United States.

Senator CASSIDY. We have adequate herd immunity that would still protect even if people are coming in and bringing another disease?

Dr. MCCULLERS. To this point the problem is as you have seen in California, in Oregon, and Washington, is that there are pockets where it low and it could happen easily in Tennessee next week. Even though we are 97 percent, there is plenty of communities that are below that level, and we might see the outbreak in that community.

Senator CASSIDY. Now, Mr. Lindenberger, so obviously we have a bunch of Docs or people who I cannot help but notice that your beard is not as heavy as the other peoples'.

[Laughter.]

Senator CASSIDY. This was not total—you do not have to be an MD or PhD, or a Master of Public Health to understand these issues, correct?

Mr. LINDENBERGER. Correct.

Senator CASSIDY. You just need to bring your critical faculty to it, and look at it, and understand it is not just the individual who is affected but it is the individual whom the person goes to school with, correct?

Mr. LINDENBERGER. As I have stated before, my decision to get vaccinated was based on the health and safety of myself and other people. And I approached my family physician. I spoke to her. She encouraged me to get vaccinated. Even at school, I was told I would not be able to attend if I did not get my vaccines but was opted-out. And so, my school viewed me as a health threat. And so that for me also pushed me to getting my vaccines despite my mother's beliefs because I saw the threat that was being imposed.

Senator CASSIDY. I am out of time, although I am the Chair. I will nonetheless defer to myself.

[Laughter.]

Senator CASSIDY. But I thank you very much. And Mr. Lindenberger thank you for caring for the people you went to school with, as much as you cared for yourself.

Mr. LINDENBERGER. Thank you.

Senator CASSIDY. I yield my time. Senator Hassan.

Senator HASSAN. Well, thank you Mr. Chair and Ranking Member Murray for having this hearing. Thank you all for being here. I had the great good fortune of having a grandfather who was a pediatrician, and he practiced medicine from 1921 to about 1985. And my childhood was filled with his accounts on the changes that he saw on the medical landscape over the course of his career. I still remember him describing what it was like to see somebody suffer from lockjaw, which is tetanus. The jaw locks, the swallowing stops, the breathing stops, the muscles spasm, and he was talking about what a difference it made when the tetanus vaccine became available.

I remember my mother who had three children, youngest one born in 1960, remarking during my childhood that now that there was a vaccine against rubella, German measles, pregnant women did not have to worry nearly as much about going out of their house during pregnancy, accidentally contracting German measles which could be so damaging to the fetus.

I think it is incumbent on all of us to remember these stories because a number of you have made the point that without this experience of what these diseases actually do and mean, we have gotten less vigilant as a society about the importance of this, the importance of vaccinations. Dr. Omer, I wanted to follow-up with you. You talked about the importance of work you are doing on helping pregnant women get vaccinated. We know that in the United States, almost all vaccines are administered to infants once they are at least 2 months old. So, for the first two months of their lives,

infants rely on the antibodies of their mothers. The antibodies that moms transfer during pregnancy to protect them from preventable diseases or viruses such as the flu.

We now that vaccines like the flu vaccine currently available, not necessarily the new ones you are working on, are critical for pregnant women and their babies. And we know that these populations face a greater risk of complications due to the flu, including premature birth delivery, hospitalization, or in severe cases, death. But astonishingly, only about half of women receive the flu vaccine during pregnancy. With infant and mortality rates reaching startling numbers in the United States in recent years, it is absolutely critical that we take basic steps to help protect women and babies during pregnancies and childbirth.

Dr. Omer, what do you think is the leading cause for the lone number of vaccinated pregnant women, and what can we do moving forward to help improve these numbers and keep mothers and babies save?

Dr. OMER. There are several causes, and there are only few women who are outright opposed to vaccines. And there is this huge gap, this huge groove, which is the fenceter groove. And so that is an opportunity to persuade, to educate, to have these meaningful conversations. So, in terms of how to intervene, we proposed a model called the P3 model. It is practice, provider, and patient. We changed it at the third P to pregnant women because pregnancy is not a pathology. It is a very physiological state to be in and we advocate for and evaluating strategies.

There is emerging evidence that there is promise to this strategy to work with the practice, for example, things like standing orders, which use behavioral economic studies concepts to notch a practice into vaccinating, working on the supply side issues, working on physicians communications, and persuading pregnant women. In terms of the specific reasons, there is this focus on the baby. And so, we have found this is one of the other universal things, that mothers are both motivated to protect the baby, and scared to harm the baby. And as we generate safety evidence, which is very robust for influenza vaccine, we need to find better ways and evidence-based ways, as I alluded to, to communicate to pregnant women as well.

Senator HASSAN. Okay. Well, thank you. And maybe what I will do then just with my limited time is also as, Dr. McCullers, as a practitioner, I am curious about how you go about communicating with parents who are having vaccination hesitancy? Among parents who choose not to vaccinate their children, what is their most common reason? And moving forward, what can we do to really help ensure that parents are educated about the importance of vaccinations?

Dr. MCCULLERS. Yes. It is interesting. 10 years ago there was one common reason and that was the fear of autism and these bad things. Right now, there is really a polyglot of reasons. They have all sorts of different minor concerns that come up. And so, the most important thing for a pediatrician to do, or a family practitioner, or an OB, is listen, understand, respect what those concerns are because they are different for every person.

Senator HASSAN. Right.

Dr. MCCULLERS. Then really individualize how you are going to approach that and what education you are going to give because there are a lot of concerns that are floating around out there, and we need to have an individualized message. So it is that rapport between the patient and the physician.

Senator HASSAN. The sharing of best practices, I would expect, among professionals about how to do this.

Dr. MCCULLERS. Absolutely. Directed at what their particular concern is, what that best practice is.

Senator HASSAN. Right. Thank you very much, and thank you, Mr. Chair.

Senator CASSIDY. Senator Smith.

Senator SMITH. Thank you, Mr. Chair and Ranking Member Murray, and thanks all of you for being here. I really appreciate it. So, in 2017, my home State of Minnesota experienced the largest measles outbreak that we had seen since 1990, and between March and August of that year, we had 75 cases of measles and 21 related hospitalizations.

Of course, our State Department of Health, which is really a model for great Departments of Health, stepped in and did a really remarkable job working with children's hospitals and Hennepin County, and a whole range of other partners. So, Dr. Wiesman, I know you have been dealing with this in Washington, and some of my colleagues have gotten at this, but could you just tell us, summarize for us, like how best the Federal Government can be a good partner as State Departments of Health are dealing with these outbreaks?

Dr. WIESMAN. Great. Well, first of all I would say that the Centers for Disease Control and Prevention is amazing. They have lent us their technical experts around measles, and have actually sent people out to our state, in part based on our request. So that is incredibly important. I think again we need to be looking at how is it we get to the, as the CDC Director said in my state last week, how do we get to the hearts and minds of people around vaccines and to not put science on the shelf. We need to have this national conversation and national campaigns that is based on evidence and that we develop the evidence on how to best communicate. It is a response effort and it happens at the local level. I think we need to remember that, which means we have got to fund our local health departments adequately, so they have the staff resources to be able to respond. But actually, frankly, also to prevent these. Work with communities in advanced, these pockets of communities that have these unvaccinated folks.

Senator SMITH. This gets to another question related which is that in Minnesota when we saw this measles outbreak, we saw some communities that were disproportionately affected, and there was—in order to communicate and hear well the concerns and issues in these communities, it was important that we had culturally competent specific kinds of outreach. Can you talk a little bit about what you have seen that are good models in that area?

Dr. WIESMAN. Right. Well, I think the good model is having folks on your staff who are actually culturally diverse. Who know these communities inside and out as being really important. So, we have to have employees who reflect the face of the community, and that

is a challenge for a lot of us and we are not there. And then I think it is really this community development outreach work, building the relationships with informal leaders in communities, whether they be church leaders, whether they be elders in tribal communities, whatever, those trusted folks there that people listen to, and engage them in health promotion work.

Senator SMITH. Thank you. Thank you. Would anybody else like to comment on that specific question of how we can have culturally connected outreach in this area?

Dr. OMER. If I may add——

Senator SMITH. Yes, please.

Dr. OMER. That that specific example stood out for many of us because that community was targeted for misinformation. And there were several visits by folks who were not particularly enthusiastic about vaccines, and so the response is also an example of to engage communities. So, the children's hospital, not just the health department, but other partners came together and worked with the community itself, to bring up the rates of vaccination. They have the tools which are evidence-based, and one of the evidence-based tool is that you have a disease salient based approach. And you do not just talk about the vaccine, which you talked about, but the disease itself, because that is what it is what is all about.

Senator SMITH. Mr. Lindenberger, did you want to say—add to this?

Mr. LINDENBERGER. I would also add that when you were talking about a diverse group of people also addressing specific communities, one thing I would address in a biased level at least, is that for young people, specially moving into adulthood with their decisions on a medical level, is extremely important because once you become of age, at least for me, most of my friends did not even understand that they could get vaccinated despite their parents' wishes. And once you move into living on your own and starting your career, still that push of explaining to young people that vaccines are important is especially important. So, I would just add that.

Senator SMITH. Thank you.

Mr. Boyle.

Mr. BOYLE. If I may, just to add on to that as we are talking about the cultural issues here. One of the things that I found, while I love most of what the CDC and others provide, one of the pieces of the communication that I find missing are stories. There is precious little that really connects the person, if they are not swayed by facts, to the needs. And so, if someone's tia or aunty is receiving chemotherapy and is immunocompromised, tying it back to the personal in their community, I think is a piece that I have not seen much. And I think that as we talk about these sort of campaigns and needed next steps, that is another layer to add in to everything else that needs to happen.

Senator SMITH. Thank you.

Senator CASSIDY. Senator Casey.

Senator CASEY. Thank you, Mr. Chairman. I want to thank you, Dr. Cassidy, and Ranking Member Murray for presiding over this hearing. It is an important set of issues. I want to start with Mr. Lindenberger. I would like to be able to think that or believe that when I was—you are a senior in high school now? I would like to

be able to believe that at that age, that I could do what you have done today. I think the answer to that is probably no. There may be some Members of the Committee that could have, but I am not one of them. Second, I wanted to say I know how difficult this would be no matter what age you are, what station in life, because it is a difficult topic and you also have a personal story to tell, which is difficult to even tell in private and let alone in a public setting.

Thirdly, you have done something that we do not often do in Washington. This is a town where people are pretty good at demonizing and dividing, and we are really experts at being categorical that someone who disagrees with us is always bad. You have been able to be very clear about where you stand and what you believe, and bear witness to the truth without being categorical and without demonizing. So that is not only helpful for this topic, but it is instructive for the rest of us here in both parties in both Houses. I hope people are listening.

I wanted to ask if you could share additional ideas about that you have developed over because of the experience you have had, as to how to effectively reach out to parents and address their concerns so that they are confident in the advice that their doctors—advice of their doctors—and do not hesitate to have their children immunized. You have spoken of this a little bit already.

Mr. LINDENBERGER. Yes, thank you for that question actually because there is a really important distinction that needs to be made between the information provided as we discussed earlier, were people do not resonate well with information and data numbers, and they resonate better with stories. You see that with a lot of the anti-vaccine community, that a large portion of the foundation that they build to communicate with parents is on a very anecdotal level, sharing stories and experiences.

That speaks volumes to people because, at least for even my family, my mom would reaffirm that her position was correct because she knows people and she has seen stories. But correlation does not equal causation and we do not know a lot of factors involved. And even though I could say that, that still does not resonate. And so, I have seen that a large portion of what we have missed, and to address your question even more accurately, just the stories of people suffering from preventable diseases. The stories of preventable diseases ravaging countries and nations is extremely important, and the side effects and complications that these diseases impose. Even when talking about measles, there is a huge misinformed belief that measles is not a dangerous disease that spreads around the anti-vaccine community. But measles is one of the biggest killers of young infants because of the dangers it imposes to young children. You see the upwards of an 80 percent of measles death in certain statistics are from children five and under.

When convince parents that not that information is incorrect, but that their children are at risk, that is a much more substantial way to cause people to change their minds.

Senator CASEY. Thank you. That is helpful and I appreciate your testimony. I know we are a little low in time. I will just ask one more. Dr. McCullers, I want to get to the issue of prevention which we repeat over and over again is the best cure. We know that vac-

cines provide the best type of prevention not only for the individual, but for the population by way of herd immunity, as we have heard so often today. I guess my question for you though is, can you describe based upon your own experience, your own work, your own research, both in terms of your experience and research and in patient care, what are some of the both symptoms and the outcomes of typical vaccine-preventable diseases for children and adults?

Dr. MCCULLERS. There is a wide spectrum depending on which disease you are talking about. Obviously, these are diseases that cause severe disease and death, or they would not have been targeted 50 years ago for and longer ago for elimination. I think one of the things that as physicians and as providers that we do not realize really how bad it was. You know, I trained at a time where haemopholis B, meningitis was a scourge. Or varicella, every kid got varicella and came in with chickenpox, and I can remember working in the emergency department and seeing three or four kids a night coming in almost comatose and with brain damage and some dying. That vaccine came in while I was in my pediatric residency, and the disease disappeared overnight. And so, trainees now do not see that and do not understand just how bad these vaccine preventable disease are because they have never experienced them.

Senator CASEY. Maybe because of the advancements.

Dr. MCCULLERS. Absolutely. I think that education piece and the ability to really spread that message that these really were terrible things and it is good that they were eliminated, and we have these vaccines, is important.

Senator CASEY. Thanks, and I have more questions for the panel, and we want to thank everyone for being here.

Senator CASSIDY. I thank everyone for participating. Ranking Member Murray, thank you. The hearing record will remain open for 10 days. Members may submit additional information for the record within that time if they would like.

Senator CASSIDY. Thanks for being here. The Committee stands adjourned.

ADDITIONAL MATERIALS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Assistant Secretary
for Health
Washington DC 20201

MAY 4 1988

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EC3224

The Honorable George Bush
President of the Senate
Washington, D.C. 20510

Dear Mr. President:

The enclosed report is submitted to you in accordance with Subtitle 1 of Title XXI of the Public Health Service Act, as amended by Title III of P.L. 99-660, the National Childhood Vaccine Injury Act of 1986.

Although no funds have been appropriated for operation of the National Vaccine Program, the Secretary decided to establish the Program with available resources. This report provides information on the implementation of the National Vaccine Program, and discusses the activities planned for Fiscal Year 1988 that are related to the long-term goals of the National Vaccine Plan.

This first report was prepared without input from the National Vaccine Advisory Committee. The Committee has been chartered and letters soliciting nominees have been sent out, and members are being appointed.

Sincerely,

Robert E. Windom, M.D.
Assistant Secretary for Health,
and Director, National Vaccine
Program

Enclosure

NATIONAL VACCINE PLAN

FIRST REPORT TO THE CONGRESS

APRIL 1988

Prepared by The National Vaccine Program
U.S. Public Health Service
Department of Health and Human Services

TABLE OF CONTENTS

EXECUTIVE SUMMARY

P.L. 99-660 establishes a National Vaccine Program (NVP) and calls for the development of a National Vaccine Plan, which is to be submitted to Congress and subsequently updated annually (see Subtitle 1 of Title XXI, Public Health Service Act). To implement the NVP, an independent staff office was created in the Office of the Assistant Secretary for Health, staff were selected, and a NVP Interagency Group was created. In addition, the National Vaccine Advisory Committee called for by the legislation was chartered and is being formed.

This document represents the first step toward development of a long-term comprehensive National Vaccine Plan. It indicates the eight major areas to be addressed during Fiscal Year 1988 by the National Vaccine Program and describes the major activities planned for Fiscal Year 1988 within each of these areas. Subtitle 2 of Title XXI, which has recently gone into effect, calls for a variety of specific activities relating to patient/parent notification, reporting of adverse events associated with vaccination, and special studies to be carried out. Implementation of Subtitle 2 will substantially alter the sections of this Plan dealing with these three issues. The magnitude of the changes is not yet clear.

Many of these activities are currently underway, and therefore, do not require additional resources. Should additional resources become available, these activities will be expanded as necessary. The report does not attempt to assess the appropriate mix of private and public sector involvement required to achieve National vaccine goals.

This report does not deal specifically with development of a vaccine for AIDS, although a summary of AIDS vaccine development is appended.

OUTLINE OF REPORT

I. IMPROVING COORDINATION OF VACCINE RESEARCH, DEVELOPMENT, USE, AND EVALUATION.

1. Formation and functioning of the National Vaccine Advisory Committee.
2. Develop a comprehensive long-term National Vaccine Plan.
3. Continue functioning of the NVP Interagency Group.
4. Continue liaison with private sector advisory groups.
5. Continue promotion of dialogue on vaccine policies.
6. Meet with individual manufacturers, researchers, public health agencies, etc.
7. Complete a survey to inventory current vaccine research.

II. ASSURING AN ADEQUATE SUPPLY OF VACCINES.

1. Purchase additional vaccines for stockpile.

2. Determine what other vaccines should be included in the stockpile.

3. Develop approaches to ensure supply of vaccines of limited use.

4. Consider longer-term approaches to assuring adequate supplies.

III. ASSESSING BENEFITS AND RISKS OF VACCINES AND ASSURING PUBLIC AND PRACTITIONER AWARENESS OF THE BENEFITS AND RISKS.

1. Continue Assessing the benefits and risks of immunization.

   - Maintain and improve national surveillance systems for major vaccine-preventable diseases.
   - Maintain, improve, and establish sentinel and/or pilot surveillance systems for other diseases.
   - Maintain, improve, and establish surveillance systems for adverse events following immunization.
   - Maintain, improve, and establish surveillance systems for specific events following the administration of certain vaccines.
   - Identify other data bases which may be useful in estimating the incidence and severity of vaccine-preventable diseases in the U.S. and abroad.
   - Conduct basic, applied, and operational research in the U.S. and elsewhere.

2. Improve practitioner awareness.

   - Publish information and surveillance summaries in Morbidity and Mortality Weekly Reports and the FDA Drug Bulletin and elsewhere.
   - Update manufacturer's package inserts when indicated.
   - Present surveillance and other data at scientific meetings.
   - Continue to work with various advisory groups.
   - Prepare, update, and distribute "Important Information Statements."

- Coordinate with private and public organizations various vaccine-preventable disease-related educational programs.
- Conduct knowledge, attitudes, and practices survey of health care providers and of the public.
- Prepare prototype educational materials for primary-care physicians and other providers.
- Prepare prototype manuals for vaccination programs in hospitals, HMOs, and other outpatient settings.

3. Improve public awareness.
   - Prepare and distribute lay publications.
   - Promote the use of patient education materials and attempt simplification of the "Important Information Statements".
   - Prepare and distribute public information materials such as radio and TV public service announcements.
   - Prepare prototype public educational materials such as videotapes and slide sets.

IV. ASSURING ADEQUATE REGULATORY CAPACITY TO EVALUATE VACCINES.

1. Continue to review existing INDs and license applications, perform control tests, inspect, perform research, prepare regulations, and monitor adverse reactions.
2. Assure prompt evaluation of new vaccines.
3. Assure continuation of the necessary research base.
4. Complete the reorganization of the Center for Biologics Evaluation and Research.
5. Continue discussions through appropriate channels for new laboratory facilities as requested in the President's Fiscal Year 1989 budget request.

V. IMPROVING SURVEILLANCE OF ADVERSE EVENTS.

1. Improve reporting of adverse events.
2. Improve adverse events surveillance systems.
3. Implement the National Childhood Vaccine Injury Act.
4. Investigate additional approaches for adverse event surveillance.
5. Examine specific research questions.
   - CDC/Vanderbilt cooperative studies.
   - Study of Neurologic Illness in Childhood (SONIC)

VI. ESTABLISHING RESEARCH PRIORITIES.

1. Reevaluate or reassess the Institute of Medicine priorities for vaccine research.
2. Continue emphasis on the development of improved, acellular pertussis vaccines.
3. Continue emphasis on the development of improved vaccines to prevent disease caused by Haemophilus influenzae type B.
4. Stimulate basic and clinical research on targeted vaccines.
5. Stimulate basic and clinical research on other important vaccines.
6. Establish liaison with members of the pharmaceutical industry.
7. Complete a survey to inventory current vaccine research.

VII. PROMOTING RAPID DEVELOPMENT AND INTRODUCTION OF IMPROVED PERTUSSIS VACCINES.

1. Analyze and present the clinical results from the Swedish trial.
2. Test blood specimens from Sweden and correlate results with clinical findings.
3. Continue IND reviews and license application evaluations on new candidate vaccines.

4. Carry out clinical studies of candidate vaccines in NIAID Vaccine Evaluation Centers.

5. Assess feasibility of a large scale safety and efficacy trial in the U.S.

6. Standardize serologic tests for pertussis.

7. Complete evaluation of new diagnostic tests for pertussis.

8. Complete pilot Study Of Neurologic Illness in Children.

9. Continue intramural research on pertussis at FDA, NIH, and CDC.

VIII ASSURING OPTIMAL IMMUNIZATION LEVELS IN ALL HIGH RISK AND TARGET GROUPS.

1. Assess appropriate mix of private and public sector involvement to achieve optimal immunization levels in high risk and target groups.

2. Revise adult immunization action plan.

3. Form an ad hoc Committee to promote information and education on the need for adult immunization.

4. Implement cooperative agreement for studying Health Maintenance Organizations.

5. Distribute and promote use of adult immunization materials.

6. Monitor activities outlined in program grant guidelines.

7. Conduct surveys to establish baseline data.

8. Develop and implement appropriate strategies to improve immunization levels in high risk groups.

9. Distribute automated patient recall systems.

10. Review effectiveness of preschool efforts.

11. Convene a National immunization conference.

FIRST NATIONAL VACCINE PLAN

INTRODUCTION

Subtitle 1 of Title XXI of the Public Health Service Act, enacted by P.L. 99-660 (Appendix 1) establishes a National Vaccine Program and calls for the development of a National Vaccine Plan, which is to be submitted to Congress and subsequently updated annually. The Assistant Secretary for Health (ASH) was appointed as the Director of the NVP. To implement the NVP, an independent staff office was created in the Office of the Assistant Secretary for Health, staff were selected, and a NVP Interagency Group was created. In addition, the National Vaccine Advisory Committee called for by the legislation was chartered and is being formed.

This document represents the first step toward development of a long-term comprehensive National Vaccine Plan. It is clear from the legislation as well as statements of congressional staff that wide input was intended in development of the Plan, particularly from the National Vaccine Advisory Committee. Since that Committee had not been appointed by the end of Fiscal Year 1987 it was not possible to develop a definitive Plan. Consequently, this Report should be read as indicating the major items to be addressed during Fiscal Year 1988 by the National Vaccine Program, one of which is to develop a definitive National Vaccine Plan.

It must also be recognized that Subtitle 2 of Title XXI, establishing a National Childhood Vaccine Injury Compensation Program, mandates a variety of specific activities relating to patient/parent notification, reporting of adverse events associated with vaccination, and special studies to be carried out. At the time this document was prepared, Subtitle 2 had just gone into effect. Implementation of Subtitle 2 will alter the sections of this Plan dealing with these three issues. The magnitude of the changes is not yet clear.

During Fiscal Year 1988, activities will be directed towards achieving eight long-term goals: improving coordination of vaccine research, development, use and evaluation; assuring an adequate supply of vaccines; assessing benefits and risks of vaccines and assuring public and practitioner awareness of the benefits and risks; assuring adequate regulatory capacity to evaluate vaccines; improving surveillance of adverse events; establishing research priorities; promoting rapid development and introduction of improved pertussis vaccines; and assuring optimal immunization levels in all target and high risk groups. For each of these areas there will be a brief description of the current situation as well as a discussion of the activities planned for Fiscal Year 1988.

Many of these activities are currently underway, and therefore, do not require additional resources. Should additional resources become available, these activities will be expanded as necessary. The report does not attempt to assess the appropriate mix of private and public sector involvement required to achieve National vaccine goals.

AIDS vaccine development is being coordinated by the AIDS Vaccine Research and Development subgroup of the PHS Executive Task Force on AIDS. The National Vaccine Program collaborates with this subgroup but primarily directs its efforts at non-AIDS vaccines. A brief summary of AIDS vaccine development is included as Appendix 2.

I. IMPROVING COORDINATION OF VACCINE RESEARCH, DEVELOPMENT, USE, AND EVALUATION

A. CURRENT SITUATION

In the last ten years, several different reviews of vaccine-related activities and policies have been carried out. These include a National Conference held in two parts in 1976 and 1977, two reviews by the Government Accounting Office (GAO), two reviews by the Congressional Office of Technology Assessment (OTA), and a series of studies and meetings carried out by the Institute of Medicine (IOM) of the National Academy of Sciences (NAS). The IOM carried out 3 separate studies, 2 of them primarily funded by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) and the Agency for International Development (AID), addressing the establishment of priorities for vaccine research and development for the United States (1985) and the developing world (1986), respectively (see Section VI of this Report). The third study, on the topic of Vaccine Supply and Innovation, was completed in 1985. Finally, the IOM convened another Workshop on Vaccine Innovation and Supply in 1986.

In general, these reviews concluded that existing advisory bodies (see below), although quite useful, tended to dwell on relatively narrow issues and they recommended formation of an independent Committee or Commission to consider all aspects of vaccine issues, including research, development, production, distribution, supply, utilization, liability, and compensation.

There are currently three Public Health Service (PHS) Advisory Committees dealing directly with vaccines. These are (1) the NIAID Microbiology and Infectious Diseases Research Committee, (2) the Food and Drug Administration (FDA) Vaccine and Related Biologic Products Advisory Committee (VRBPAC), and the Centers for Disease Control (CDC) Immunization Practices Advisory Committee (ACIP). The first of these Committees reviews and makes recommendations on research grants, cooperative agreements, and contracts. In addition, it provides review and recommendation on research directions in infectious diseases (including vaccines) to the NIAID. The second reviews and evaluates data relating to safety and effectiveness of vaccines and related biological products and makes recommendations, including those related to licensure. It also considers the quality and relevance of FDA's research program. The third advises on the most appropriate use of vaccines for disease control in the civilian population, particularly those served by the public sector (approximately 50% of the childhood population); reviews and reports on immunization practices; and recommends improvements in national immunization efforts.

For the Department of Defense (DOD), the Armed Forces Epidemiological Board (AFEB) reviews a variety of issues, including vaccine use, and makes recommendations for the Armed Forces. In addition, the American Public Health Association (APHA) covers many vaccines in its handbook "Control of Communicable Diseases in Man", which is revised every 5 years. Finally, the World Health Organization (WHO) has a Global Advisory Group (GAG) for its Expanded Programme on Immunization (EPI) which also makes recommendations regarding vaccine use.

In addition to these external Advisory Committees, since 1980 the Department has had an Interagency Group to Monitor Vaccine Development, Production, and Usage composed of representatives of NIH, FDA, and CDC, with liaison representation from the military. The purpose of this group is to monitor production and distribution of vaccine and resolve problems relating thereto, monitor development and stimulate research on new vaccines, plan for continuing availability of vaccines of limited use, and consider options as to when the Federal Government should manufacture vaccines. This Group has played an important coordinating role, particularly with regard to the evaluation of new types of pertussis vaccines (see Section VII of this Report). These efforts included sponsoring a visit to Japan by a group of PHS scientists; sponsoring a workshop on acellular pertussis vaccines; and being intimately involved in the design, funding, and monitoring of the Swedish acellular pertussis vaccine field trial.

In the private sector, three groups currently make recommendations on vaccine use. These are the Committee on Infectious Diseases (the "Red Book" Committee) of the American Academy of Pediatrics (AAP), the Committee on Immunization of the American College of Physicians (ACP), and the Scientific Activities Division of the American Academy of Family Physicians (AAFP), each of which publishes its own set of recommendations. PHS agencies have maintained formal liaison with each of these groups, as well as with international advisory bodies such as the GAG of WHO and the National Advisory Committee on Immunizations (NACI) of the Canadian Ministry of Health and Welfare. Because of this liaison, vaccine recommendations in the public and private sectors (and internationally) are generally concordant. However, occasional issues arise that would benefit from even wider input (e.g., the preferred vaccine for prevention of poliomyelitis and the balance between benefits and risks of Haemophilus B polysaccharide vaccine [HBPV] and pertussis vaccines).

During FY 1987, several activities were undertaken to implement the National Vaccine Program and improve coordination. These included designation of the Assistant Secretary for Health as the Director of the NVP (in January) and formation of an Interagency Work Group chaired by the Deputy Assistant Secretary for Health (Planning and Evaluation) to consider the most appropriate means of implementing the Program. This group submitted its report in May. Subsequently, the NVP was formally established (Appendix 3), a coordinator was selected, and further staff were obtained.

In addition, an expanded NVP Interagency Group was formed (Appendix 4), including representatives of the Department of Defense (DOD) and the Agency for International Development (AID).

The National Vaccine Advisory Committee (VAC) was chartered (Appendix 5) and is being formed. This Committee will provide one of the most important mechanisms for coordination between governmental and non-governmental vaccine activities, just as the NVP Interagency Group provides the mechanism for intra-governmental coordination. The VAC also will play a major role in developing the comprehensive National Vaccine Plan.

B. ACTIVITIES FOR FISCAL YEAR 1988

1. Formation and Functioning of the National Vaccine Advisory Committee.

It is anticipated that the appointment of Committee members will be completed early in calendar year 1988 and that the first meeting of the Committee can occur during the second quarter of that year, with quarterly meetings thereafter. Although the Committee will clearly set its own priorities, it is intended that all of the topics mentioned in the law as well as in this Report will be discussed with the Committee. In addition, the Committee will be heavily involved in preparation of the National Vaccine Plan (see below) and consideration of the resource requirements to implement the Plan.

2. Develop a Comprehensive Long-Term National Vaccine Plan.

Following initial discussions with the National Vaccine Advisory Committee, NVP staff and the NVP Interagency Group will draft a comprehensive long-term National Vaccine Plan for review by the Committee. After needed modifications, this Plan will be submitted to Congress and will serve as the basis for development of Government agency budget requests as well as outlining the activities projected by non-governmental organizations.

3. Continue Functioning of the NVP Interagency Group.

As the primary means of implementing the National Vaccine Program, continued functioning of the NVP Interagency Group is critical. It is anticipated that the Group will probably meet at least on a monthly basis during 1988. In addition to working with the VAC to draft the National Vaccine Plan, this Group will be responsible for assuring that the other activities called for in this Report are accomplished as well as dealing with other issues that may arise.

4. Continue Liaison With Other Advisory Groups.

To assure continued concordance between recommendations in the public and private sectors, representatives of the PHS agencies will continue formal liaison with other governmental, private sector, and international advisory bodies.

5. Continue Promotion of Dialogue on Vaccine Policies.

At the request of the PHS, the Institute of Medicine held a workshop to review all aspects of poliomyelitis prevention on January 21-22, 1988. The IOM expert panel will make recommendations for consideration by the Immunization Practices Advisory Committee (ACIP) which will then make its recommendations to the PHS. Public meetings have previously been held on the benefits and risks of pertussis vaccines and HBPV. At this point it is not clear what other topics might merit such an approach but this matter will be brought to the VAC for its consideration.

6. Meet With Individual Manufacturers, Researchers, Public Health Agencies, etc.

To assure the fullest communication with involved parties, individual staff members of the NVP Office and NVP Interagency Group will meet with manufacturers, researchers, public health agencies, etc., for in-depth consideration of a range of vaccine issues.

7. Complete a Survey to Inventory Current Vaccine Research.

This survey is attempting to catalog current vaccine research activities in the private and public sectors.

II. ASSURING AN ADEQUATE SUPPLY OF VACCINES.

A. CURRENT SITUATION

In recent years, the continuity of supply of essential vaccines has been threatened by a number of factors, including the limited number of manufacturers, production problems, strikes of manufacturers' employees, and liability issues. For example, there are currently only one licensed manufacturer in the U.S. of oral poliovirus vaccine (OPV) and one manufacturer of measles, mumps, and rubella vaccines (MMR). Two manufacturers currently distribute diphtheria and tetanus toxoids and pertussis vaccine (DTP) and three distribute Haemophilus B polysaccharide vaccine (HBPV). For some vaccines (e.g., rabies), the sole manufacturer is a foreign firm. On several occasions, production problems have resulted in temporary shortages of vaccines although these have been resolved by redistribution of existing supplies or temporary alteration in immunization schedules. Strikes have posed threats to continuing supply but fortunately have been resolved before actual shortages occurred. Concerns about liability issues have been a major factor in recent dramatic increases in vaccine prices (most notably with DTP) and apparently are also important factors as manufacturers consider whether to enter (or remain in) the marketplace.

To forestall the impact of interruptions of supply, in 1983 CDC began to establish a six month stockpile of childhood vaccines, which were felt to represent the most pressing need. This stockpile is to be continually rotated so vaccines would have adequate shelf life. A six month stockpile was selected as representing the most reasonable compromise between the limited shelf life of vaccines, the likely duration of an interruption, and the likely time required to license an alternative manufacturer. The status of the stockpile as of the end of Fiscal Year 1987 is shown below, expressed as the number of weeks the stockpile could supply the total national demand (both public and private).

Vaccine	Amount
DTP	13.8 weeks
MMR	20.8 weeks
OPV	20.5 weeks
IPV	8.0 weeks
DT	20.8 weeks
Td	20.8 weeks

B. ACTIVITIES FOR FISCAL YEAR 1988

1. Purchase Additional Vaccines for Stockpile.

Insofar as resources are available, additional vaccines will be purchased toward the desired goal of a 6 month supply. In addition, discussions will be held with the VAC regarding the appropriate size of the stockpile.

2. Determine What Other Vaccines Should be Included in the Stockpile.

The stockpile currently includes only vaccines used in childhood or very widely in adults (Td). Other vaccines of quite wide use which might be included are pneumococcal polysaccharide vaccine and hepatitis B vaccine. Although influenza vaccine is also widely used, since its composition changes each year the stockpile approach does not seem appropriate. The NVP Interagency Group will bring this issue to the VAC for consideration.

3. Develop Approaches to Ensure Supply of Vaccines of Limited Use.

Certain licensed vaccines are in limited use but nonetheless quite important for use in either civilian or military populations (e.g., meningococcal polysaccharide vaccine, yellow fever vaccine). In addition, other important vaccines are not currently licensed in this country but have been available under Investigational New Drug (IND) permits (e.g., Japanese B encephalitis [JE] vaccine). The supply of JE vaccine in this country is currently in serious jeopardy. Although these vaccines are in limited use, they may play an essential role in preventing or controlling certain infections. Continued availability of these vaccines must be assured. The NVP Interagency Group will discuss the supply of limited use vaccines with the VAC.

4. Consider Longer-Term Approaches to Assuring Adequate Supplies.

Other approaches to assuring adequate supplies of vaccines will also be brought to the VAC, including the possibilities of stimulating the entry into the marketplace of new manufacturers, increasing competition, changing the liability climate, direct government manufacture, government subsidy of manufacture or guarantee of purchase, etc.

III. ASSESSING BENEFITS AND RISKS OF VACCINES AND ASSURING PUBLIC AND PRACTITIONER AWARENESS OF THE BENEFITS AND RISKS.

A. CURRENT SITUATION

Assessing Benefits and Risks of Immunization

The Food and Drug Administration (FDA), the Centers for Disease Control (CDC), and the National Institutes of Health (NIH) have been the principal Federal agencies involved in evaluating the benefits and risks of immunization for both children and adults. Initially, FDA, often in conjunction with its VRBPAC, reviews preclinical and clinical data prior to licensing a product. Various pre and post marketing studies may be conducted. For example, data collected from a number of sources are analyzed periodically to: 1) obtain current estimates of morbidity, complications, and mortality attributable to various vaccine preventable diseases (VPD) in the U.S.; 2) identify groups at high risk of severe morbidity and/or mortality from each VPD; 3) obtain estimates of the efficacy in field experience of vaccines recommended for use; 4) obtain estimates of the frequency of adverse events associated with each vaccine in field experience; and 5) project the overall benefits and risks for vaccines using techniques such as mathematical modeling and decision analysis. The results of these and other assessments are disseminated to the general public and practitioners in both the public and private sectors. Since the balance of benefits and risks may change over time and varying epidemiological circumstances, the assessment is a continual process.

The Public Health Service established the Immunization Practices Advisory Committee (ACIP) to routinely review critical issues regarding immunization practices and surveillance data. This committee, composed of leading authorities in vaccine-preventable diseases from academia, public health agencies and national medical organizations meets three or four times a year at CDC. The ACIP assesses the risks and benefits of vaccination and makes recommendations for use of vaccines and other selected interventions. These recommendations are published in Morbidity and Mortality Weekly Reports (MMWR).

Practitioner Awareness

The recommendations of the ACIP as well as surveillance summaries reach practitioners through publication in the MMWR, FDA Drug Bulletin, and subsequent reprinting in other medical and scientific journals. Package inserts accompanying each container of product provide relevant information for each manufacturer's product. In addition, articles regarding other aspects of vaccine-preventable diseases are periodically published in the leading medical and scientific journals. Surveillance and epidemiologic data are presented at professional and scientific symposia, conferences, and other appropriate forums. CDC has established formal liaison with other national and international advisory groups including the Committee on Infectious Diseases of the AAP, the Committee on Immunization of the ACP, and the Scientific Activities Division of the AAFP, each of which publishes its own set of recommendations.

Public Awareness

The PHS has created a variety of publications, pamphlets, posters and other educational materials for the general public. The pamphlet "A Parent's Guide to Immunization" was created and distributed (primarily in the public sector) to assist parents in knowing what immunizations were advised for their children and when they should be administered. Disease-specific pamphlets such as "Questions and Answers Regarding Pertussis and Pertussis Vaccine" have been developed and distributed to assist parents in evaluating the risks and benefits of immunization. CDC has developed a complete series of "Important Information Statements" for use with Federally purchased vaccines used in public clinics to aid in informing parents regarding the vaccines their children may need. The "Important Information Statements" (IIS) describe the specific disease, the risk of infection, and the risks of severe complications. In addition, they describe the indications and contraindications to vaccination, the possible side effects associated with the vaccine, and the benefits of vaccination.

B. ACTIVITIES FOR FISCAL YEAR 1988

The activities described below may change as the National Vaccine Injury Compensation Program (Subtitle 2 of Title XXI of the PHS Act) is implemented.

1. Continue Assessing the Benefits and Risks of Immunization.

- Continue the review of preclinical and clinical data submitted as part of investigational new drug (IND) or license applications;

- Maintain and improve national surveillance systems for measles, mumps, rubella (including congenital rubella syndrome), pertussis, tetanus, diphtheria, paralytic poliomyelitis, and influenza;

- Maintain, improve, and establish sentinel and/or pilot surveillance systems at local and/or regional levels for hepatitis B, meningococcal and pneumococcal disease, and Haemophilus influenzae type B disease;

- Develop and use tools which may facilitate diagnosis of illnesses such as pertussis, pneumococcal pneumonia, etc.

- Maintain, improve, and expand surveillance systems for identifying a wide range of adverse events following administration of vaccines (see Section V of this Report);

- Maintain, improve, and expand surveillance systems for specific events following the administration of certain vaccines (e.g., fetal outcome following rubella vaccination in the first trimester of pregnancy; development of residual paralysis following the administration of oral polio vaccine, etc.);

- Identify other data bases which may be useful in estimating the incidence and severity of VPD;

- Investigate outbreaks of VPD in the U.S. and elsewhere;

- Conduct basic, applied, and operational research related to VPD in the U.S. and elsewhere; and

- Examine surveillance and other pertinent data reported from other nations.

2. Improve Practitioner Awareness.

- Publish surveillance summaries in the Morbidity and Mortality Weekly Report (and/or other medical and scientific journals), which are often publicized simultaneously in the lay press;

- Publish information in the FDA Drug Bulletin relevant to vaccine use or adverse events when indicated.

- Update manufacturer's package inserts when indicated.

- Publish and update ancillary documents such as "Health Information for International Travel" and special advisory memoranda;

- Present surveillance data and other relevant epidemiologic data at scientific meetings, symposia, public meetings, seminars, and other forums;

- Continue to work with the ACIP, whose recommendations are published in the MMWR and reprinted in the Journal of the American Medical Association, Annals of Internal Medicine, and other medical journals with a wide circulation;

- Continue formal liaison with other national and international advisory groups, including the Committee on Infectious Diseases of the AAP, the Committee on Immunization of the ACP, and the AFEB to assure timely exchange of information;

- Prepare, update, and distribute "Important Information Statements" for use with federally purchased vaccines given in public health clinics and make available camera-ready copy for use in the private sector;

- Contact private and public sources to identify the type and content of VPD-related educational programs initiated outside the Federal Government; assist in the coordination of these activities as needed to avoid unnecessary duplication of effort (see Section I of this Report);

- Continue to encourage professional organizations to urge their members to become actively involved in immunization activities, through becoming more knowledgeable personally and by developing systems to ensure identification and vaccination of high risk persons;

3. Improve Public Awareness.

- Prepare, update, and distribute lay publications such as "A Parent's Guide to Immunizations" and "Questions and Answers Regarding Pertussis and Pertussis Vaccine" and expand to include other vaccines as necessary;

- Promote the use of patient education materials such as the "Important Information Statements" in the private sector;

- Attempt simplification of the "Important Information Statements". These statements are currently assessed as requiring a reading skills level equivalent to 12-13 years of education;

IV. ASSURING ADEQUATE REGULATORY CAPACITY TO EVALUATE VACCINES

A. CURRENT SITUATION

The FDA has the primary responsibility for the regulation of vaccines through its Center for Biologics Evaluation and Research (CBER). The CBER (formerly the Office of Biologics Research and Review [OBRR] of the National Center for Drugs and Biologics [NCDB]) has been recently formed as a separate entity. It will continue to reflect FDA's commitment to assuring that high quality vaccine regulation and the related research programs continue as well as the agency's increased efforts in its activities related to AIDS.

The research and laboratory activities of the scientists of the Center are an integral part of its regulatory activities as the research is aimed at understanding disease pathogenesis and immunity. The laboratory investigator brings state-of-the-art methods and knowledge to the review and regulatory process. The scientists play a major role in evaluating specific products and use their laboratory skills to develop and evaluate quality control procedures and to evaluate methods of manufacture.

CBER staff reviews Investigational New Drug (IND) applications and the supplements to these applications for vaccines and other biologics; meets with manufacturers for pre-IND and IND discussions; reviews license applications and amendments for biologics and issues licenses for biologics and establishments; reviews and approves labeling (including package inserts); performs selected analytical, potency and other quality control assays; and performs inspections of production establishments before and after licensing. In addition, other parts of CBER address issues of compliance, preparation of regulations (e.g., Notices of Proposed Rule Making and preparation of guidelines and regulations) and address issues related to post-marketing surveillance (e.g., release of product lots submitted by manufacturers, adverse reaction reports, and epidemiologic issues).

The Center works closely with the scientific and industrial communities to identify problems in vaccine development and manufacture. FDA's investigators present their findings at scientific meetings and in the scientific literature. The Center holds workshops to focus on the scientific issues related to product development, as well as frequent meetings of the advisory committee, to involve outside experts in the decision making process.

B. ACTIVITIES FOR FISCAL YEAR 1988

1. Continue to Review Existing INDs and License Applications, Perform Control Tests, Inspect, Perform Research, Prepare Regulations, and Monitor Adverse Reactions.

2. Assure Prompt Evaluation of New Vaccines.

New types of vaccines can be expected in 1988 and ensuing years which will result in many new IND's. The preparation of these products will likely involve many new technological methods. In addition, many new license applications will be submitted for review. FDA will review the allocation of its staffing resources to review these documents, continue review of existing applications, perform control tests, and inspect manufacturers' facilities.

3. Assure Continuation of the Necessary Research Base.

Basic and applied research programs will be continued and expanded in order to meet the increasing number of product applications and differing types of products being developed. Adequate numbers of highly qualified scientific personnel are needed to address specific issues and to evaluate or develop appropriate methods to be used for control of vaccines, including the establishment of vaccine standards, i.e., methods of antibody assay and physicochemical criteria. Appropriate reference reagents will need to be identified, evaluated, and collaborative studies conducted to assure the appropriate standardization and testing of vaccines by manufacturers and other involved parties. Emphasis in recruiting scientists knowledgeable in the new technologies, such as molecular biology, genetics, biochemistry, cell physiology, immunology, and pharmacology will be necessary to enhance CBER's regulatory capabilities.

4. Complete the Reorganization of the Center for Biologics Evaluation and Research.

This reorganization is expected to assist in the provision of resources which will allow an expansion of the regulatory and research programs needed to meet the increasing number of products and to assure that appropriate resources are available to evaluate the currently licensed products.

5. Continue Discussions Through Appropriate Channels for Adequate Laboratory Facilities.

Adequate facilities are required for the activities associated with the regulation of other vaccines and biologics, including the rapidly expanding AIDS program. The Fiscal Year 1989 President's budget includes a request for $25 million to expand FDA laboratory facilities for vaccines and biologics review and research, particularly in the area of AIDS.

V. IMPROVING SURVEILLANCE OF ADVERSE EVENTS

A. CURRENT SITUATION

There are two complementary national systems in the United States for the surveillance of adverse events after immunization: the Spontaneous Reporting System (SRS) of the FDA, and the Monitoring System for Adverse Events Following Immunization (MSAEFI) of the CDC. The SRS is a physician- and manufacturer-based, passive system primarily designed for the detection of new, previously undescribed, serious adverse reactions and for some frequency measurements for serious known reactions. SRS has collected reports of biologics adverse reaction data from the private sector since 1984 when biologics reaction reporting was integrated into a pre-existing drug reaction reporting system. Prior to that time, biologics adverse event information was collected and stored in a computerized catalog not designed for this type of epidemiologic analysis.

MSAEFI is a stimulated passive surveillance system in operation since 1979 for events temporally related to vaccination with public sector vaccines. "Public sector vaccines" are all vaccines purchased with Federal, State, or local government funds, and account for approximately one-half of all childhood immunizations in the United States. Events severe enough to require a health care provider visit which occur within 28 days after immunization are to be reported to MSAEFI.

A major problem with passive reporting systems is underreporting, i.e., lack of sensitivity. Also, a nonrandom sample of all adverse events is reported to FDA and CDC. The actual reporting fraction is unknown and is likely to differ between systems and among States. In addition, although adverse events reported to SRS and MSAEFI are temporally related to vaccination, vaccine causation can not be inferred. Also, adequate data are not available on the expected background rate of occurrence of events such as convulsions or encephalitis, making it difficult to assess risk for these adverse events after immunization.

One additional approach to adverse event surveillance is the use of population-based data bases. A current project funded by CDC in Tennessee involves the linkage of immunization clinic records to Medicaid records. This linkage defines a cohort of children in whom adverse events following immunization can be followed. Such population-based systems offer the potential of universal reporting of serious events whether or not immunizations were received. Comparison of rates of event occurrence with and without vaccination allows determination of whether vaccine causes a particular type of event as well as calculation of the actual risk attributable to vaccination.

FDA has established contracts with five States to explore means of informing health care professionals about FDA's SRS and providing ready access to the system. These contracts have resulted in increased reporting to FDA from these States. In addition, FDA may require a post marketing study for safety of a newly licensed vaccine and may target possible adverse events of particular concern for specific post-marketing surveillance studies as part of requests made of manufacturers prior to licensure of new biological products.

Furthermore, FDA has access to several extramural data bases through cooperative agreements to investigate biologic or drug events. These data bases include the Boston Collaborative Drug Surveillance Program (based on automated data from a large Health Maintenance Organization); Medicaid data from several states through Health Information Design (based on Medicaid billing data); and the Drug Epidemiology Unit (based on various national data bases). Existing databases may be expanded and others initiated to design and perform particular epidemiologic studies on vaccine-associated adverse events.

FDA and CDC share data on at least a quarterly basis, including the provisional numbers of deaths, convulsions and selected other events (encephalopathies or anaphylaxis) reported to each agency after immunization with HBPV, DTP, and MMR vaccine. Informal collaboration is frequent between the two agencies on individual vaccines or specific adverse events being monitored. Dialogue is maintained on specific issues and has included studies on the efficacy of HBPV and on adverse events reported after hepatitis B vaccine.

Subtitle 2, Sec. 2125(b), of the PHS Act mandates reporting from each health care provider and vaccine manufacturer of the occurrence of any event in the Vaccine Injury Table or any event which is a contraindication to further doses of vaccine. When implemented, Subtitle 2 will necessitate significant changes in adverse events surveillance systems of both CDC and FDA which will substantially modify present and future planned activities.

B. ACTIVITIES FOR FISCAL YEAR 1988

1. Improve Reporting of Adverse Events.

Evaluation of methods to stimulate reporting of adverse events will be a priority during Fiscal Year 1988. These methods could include increasing routine availability of surveillance results, increasing access to the system by individual reporters, and mandating reporting by manufacturers and providers. Providing information to health care providers and others involved in monitoring systems is a positive reinforcement to reporting of adverse events. A summary of MSAEFI results for the years 1985-86 will be published and distributed during the year. In addition, feedback letters to MSAEFI coordinators and State Vaccine Program managers will be produced periodically.

FDA will continue to evaluate methods to increase reporting through contracts with individual States to increase health care provider awareness of the SRS and to improve access to the SRS by reporters. CDC will evaluate methods of electronic data transfer from reporting States to CDC. The FDA is developing proposed regulations to require manufacturer reporting of vaccine adverse events similar to that required for drugs under 21 CFR 314.80. Currently, reports received by manufacturers are submitted to FDA voluntarily following this same system.

2. Improve Adverse Events Surveillance Systems.

The quality of surveillance systems can be improved by continuing to coordinate approaches to adverse events monitoring among the FDA, CDC and large vaccine providers, and by focusing on the evaluation of serious adverse events. Dialogue and sharing of data between CDC and FDA will continue.

3. Implement the National Childhood Vaccine Injury Act.

PHS will develop approaches for implementation of the mandatory reporting requirements of Subtitle 2 of Title XXI of the PHS Act.

4. Investigate Additional Approaches for Adverse Event Surveillance.

Population-based data bases, such as Medicaid or Health Maintenance Organizations, may provide an additional method to monitor vaccine safety. In addition to the Tennessee Medicaid study, CDC will establish and evaluate an additional population-based data set in at least one other location. FDA has cooperative agreements with such data bases which may be used depending on the questions to be studied. FDA will continue to include post-marketing surveillance and reporting requirements in new vaccine licensures, and will explore additional types of studies to monitor potential adverse events in prelicensure negotiations with manufacturers.

5. Examine Specific Research Questions.

A. CDC/Vanderbilt cooperative studies

The final report of the Tennessee Medicaid study on the relation of Sudden Infant Death Syndrome (SIDS) and DTP vaccination will be prepared and submitted for publication. Continued progress on a study of neurologic illness after DTP will be monitored. An additional study on the relationship of vaccination to subsequent serious infection after immunization is being planned.

B. Study of Neurologic Illness in Childhood (SONIC)

A pilot study of the risk factors associated with neurologic illness in children was begun in 1987 in Washington and Oregon. This pilot is expected to demonstrate whether or not a full scale study of this question is feasible. An objective for Fiscal Year 1988 is to complete the pilot study and arrive at a decision about undertaking a larger, more definitive project.

VI. ESTABLISHING RESEARCH PRIORITIES

A. CURRENT SITUATION

Five Institutes of the National Institutes of Health and its Division of Research Resources support vaccine research and development. The lead Institute is the National Institute of Allergy and Infectious Diseases (NIAID). Other PHS agencies involved are FDA and CDC. In addition, the Department of Defense (DOD) and the Agency for International Development (AID) provide support for vaccine research and development. In the fall of 1981, NIAID began a program for the "Accelerated Development of New Vaccines." The purpose of the new initiative was to develop within DHHS a clearly-defined and coordinated approach to the further conquest of vaccine-preventable diseases. The incentive for this expanded effort lay in new knowledge and processes emerging from recombinant DNA and hybridoma technology, and in the better understanding of the workings of the immune system. In December 1979 the Secretary of Health and Human Services accepted the recommendation of the HHS Steering Committee for the Development of a Health Research Strategy that the NIAID proposal for the "Accelerated Development of New Vaccines" be added as one of four new initiatives to 11 priority initiatives identified.

The goal of the initiative on Accelerated Development of New Vaccines was to expedite the availability of needed vaccines by selecting a few candidate vaccines for extra research and development efforts. It was anticipated that with the assistance of existing advisory committees and "state-of-the-art" reviews by workshops, and in coordination with the PHS Interagency Group to Monitor Vaccine Development, Production, and Usage, and with enhanced collaboration with industry, selected high priority candidate vaccines could be brought into use several years earlier than otherwise might be the case.

To assist in planning, NIAID and AID commissioned the Institute of Medicine (IOM) of the National Academy of Sciences to develop a model decision process that could be used for establishing priorities among candidate vaccines. The IOM study, which began in September 1982, was divided into two major phases; first, development of a model decision system for the examination of vaccines for domestic use, and second, development of a model decision system for international vaccines. The IOM developed a model based on comparisons of expected health benefits and expected net costs (or savings) calculated for candidate vaccines. This quantitative approach combines elements of decision analysis and cost-effectiveness analysis.

The IOM Committee considered 14 disease pathogens for analysis by the domestic model, the criterion for consideration being whether or not a vaccine was foreseeable within the next decade. The analysis assigned the highest priority to the following five vaccines in the order listed:

Hepatitis B virus (HBV, recombinant DNA-derived)
Respiratory Syncytial virus (RSV, live-attenuated)
Haemophilus influenzae, type b
Influenza (live attenuated)
Varicella (immunocompromised children)

An improved pertussis vaccine had already been assigned high priority by NIAID, so pertussis was not ranked by the IOM. Acquired Immunodeficiency Syndrome (AIDS) had just been recognized and the HIV retrovirus had not yet been isolated when the IOM began its deliberations. A vaccine for AIDS has now been assigned special priority apart from this program.

The IOM Committee considered 19 disease pathogens for analysis by the international model, including six previously reviewed for domestic use, since developing countries have all the infectious diseases of developed countries as well as others peculiar to or magnified in the tropics. The analysis assigned the highest priority to the following five vaccines in the order listed:

Streptococcus pneumoniae (protein-polysaccharide conjugates)
Rotavirus
Plasmodium species (sporozoite)
Salmonella typhi
Shizella species

NIAID and AID had previously assigned priority to ten agents or agent pairs, five for use in the U.S., and five for use in developing countries. Concordance between the NIAID and IOM rankings was excellent. The NIAID and IOM lists have been combined to provide the following list of vaccines targeted for priority development.

	U.S.		International
1.	Bordetella pertusssis (improved)	1.	Streptococcus pneumoniae (conjugate)
2.	Hepatitis B virus (rDNA)	2.	Rotavirus
3.	Haemophilus influenzae type b	3.	Plasmodium species (sporozoite)
4.	Respiratory syncytial virus	4.	Salmonella typhi (typhoid)
5.	Influenza viruses A & B (live, attenuated)	5.	Shigella species (dysentery)
6.	Herpesvirus varicellae	6.	Vibrio cholerae
7.	Neisseria gonorrhoeae	7.	Mycobacterium leprae

The fact that vaccines for other diseases do not appear on the priority lists does not mean that the disease is not important or that no work is being done on development of a vaccine for it. Indeed, considerable progress has been made in fashioning new or improved vaccines for many of the 13 other agents reviewed by the IOM.

Total NIAID expenditures for vaccine research and development in Fiscal Year 1987 are estimated to have been $31.16 million, exclusive of AIDS. Within the NIH, the next largest expenditure, $2.1 million, was by the National Institute of Child Health and Human Development (NICHD). Other estimated Fiscal Year 1987 Federal expenditures for vaccine research and development include $25 million from the Department of Defense, $17.0 million from the Agency for International Development, $9.3 million from FDA, and $3.2 million from CDC.

Considerable progress has been made toward developing and evaluating vaccines for high priority diseases. A synopsis of progress for each is presented in Appendix 6. Much of this effort was supported by NIH as well as other government agencies, including the World Health Organization. Individual vaccine manufacturers have also been quite active.

B. ACTIVITIES FOR FISCAL YEAR 1988 (Excluding AIDS)

1. Reevaluate or Reassess the Institute of Medicine (IOM) Priorities for Vaccine Research.

This activity will determine if the domestic and international priorities established earlier still apply. This is particularly important in view of the significant progress achieved to date in the development of vaccines identified on the IOM list of priorities.

2. Continue Emphasis on the Development of Improved, Acellular Pertussis Vaccines.

The results of the Swedish clinical trial will serve as an important guide to future directions with these vaccines (see Section VII of this Report).

3. Continue Emphasis on the Development of Improved Vaccines to Prevent Disease Caused by Haemophilus Influenzae type B.

The clinical trial of one vaccine in native Alaskan infants continues for at least another winter season of observation. The results of studies in Finnish infants will be evaluated for their applicability to any license applications for this type of product.

4. Stimulate Basic and Clinical Research on Targeted Vaccines.

This effort will be directed particularly to vaccines to prevent disease caused by Respiratory Syncytial Virus, rotavirus, Streptococcus pneumoniae, Plasmodium species, varicella, and vaccines to prevent sexually transmitted diseases.

5. Stimulate Basic and Clinical Research on Other Important Vaccines.

Several diseases of importance in developing countries did not rank high enough to make the targeted vaccines list, in part because of the amount of basic research required (e.g. Chagas' disease, schistosomiasis, filariasis). Other vaccines of interest in the U.S. also to be addressed are parainfluenza viruses and Herpes simplex viruses. Efforts will be made to stimulate needed research in these areas.

6. Establish Liaison With Members of the Pharmaceutical Industry.

This will enable the NVP to keep abreast of individual companies' research activities for vaccines of U.S. and international interest.

7. Complete a Survey to Inventory Current Vaccine Research.

This survey is attempting to catalog current vaccine research activities in the private and public sectors.

VII. PROMOTING RAPID DEVELOPMENT AND INTRODUCTION OF IMPROVED PERTUSSIS VACCINES

A. CURRENT SITUATION

The development of a safer pertussis vaccine has been a longstanding goal. Recently, progress has been made in understanding the pathogenesis of pertussis and in isolating antigens which could be protective in a vaccine. Much of the pioneering work in this area was carried out in the Laboratory of Pertussis, Center for Biologic Evaluation and Research, FDA. Two antigens which have received the most attention in this regard are pertussis toxin (PT) or Lymphocytosis Promoting Factor (LPF) and Filamentous Hemagglutinin (FHA).

Acellular pertussis vaccines containing principally PT and FHA have been developed and used in Japan since 1981. Their use has been almost exclusively in children 2 years of age and older. Available data suggest that these vaccines cause fewer immediate reactions than whole cell vaccines and protect against pertussis.

A clinical trial of two Japanese vaccines containing PT alone and in combination with FHA sponsored in part by the U.S. has been underway in Sweden since 1986. This trial is expected to define the clinical efficacy of these vaccines in 6-10 month old infants and possibly provide a serologic means by which other candidate vaccines could be evaluated without the need for other field efficacy studies. This trial will provide information about the safety of these vaccines with regard to commonly seen reactions but is not large enough to address the incidence of rare adverse events.

Currently, three manufacturers with an interest in marketing in the U.S. have either imported vaccine from Japan or have developed their own acellular pertussis vaccines. All of these products are currently undergoing clinical evaluation in NIAID sponsored Vaccine Evaluation Centers or at clinical sites sponsored by the manufacturers. Lederle is also working in collaboration with investigators in Japan to evaluate their vaccine in infants. In addition, a vaccine containing exclusively PT has been developed at NIH laboratories and has undergone limited clinical evaluation in U.S. adults and children.

Other U.S. researchers, such as those at the Michigan Department of Health are working on the development of acellular pertussis vaccines containing antigens similar to those previously described. Likewise, investigators at the NIAID Rocky Mountain Laboratory are working on the use of recombinant DNA techniques to produce PT, however this research is still in its early stages and is expected to produce second rather than first generation acellular pertussis vaccines.

Investigators in Britain have also developed an acellular pertussis vaccine which they expect to evaluate in young children during the fall of 1987. This vaccine contains PT and FHA as well as agglutinogens which British scientists believe will be important for protection against pertussis. Of interest to the United States is that British researchers may include Lederle and Merieux vaccines in their comparative trial in 1987 and plan to conduct an efficacy trial beginning in 1988 which will furnish a direct comparison of the efficacy of acellular and whole cell vaccines. Other manufacturers currently have or are developing vaccines which may eventually be proposed for licensure in the U.S. There reportedly is some hesitation to seek entry to the U.S. market because of concerns about liability.

In addition to these vaccine development activities, other studies have been underway at the FDA and CDC which are expected to facilitate the eventual licensure of improved pertussis vaccines in the United States. FDA scientists have purified and evaluated several of the virulence factors which have been considered important antigens for inclusion in acellular pertussis vaccines. These scientists have developed methods for evaluating the structure, function, and inactivation of pertussis toxin. These studies served as the basis for the preparation, review, and evaluation of acellular pertussis vaccines described above. In addition, they are evaluating the role of other pertussis antigens in inducing protection (e.g., agglutinogens, adenylate cyclase, etc.). In addition, FDA scientists have developed serologic assays to evaluate antibody responses to pertussis antigens, the preparation of purified reagents, and the establishment of serological reference standards for international use. At CDC, studies have focused on the development of improved diagnostic tests for pertussis, and on a large case-control study to assess the association between whole cell pertussis vaccine and neurological events in children. These data may eventually be useful in assessing the risk of rare neurological illnesses after whole cell compared to acellular pertussis vaccines.

B. ACTIVITIES FOR FISCAL YEAR 1988

The major focus of efforts in the coming year will be to help collect the additional information necessary to support licensure of one or more acellular pertussis vaccines. This priority assumes that the trial in Sweden will demonstrate the efficacy of acellular pertussis vaccines containing PT alone or in combination with FHA, and that an acceptable serologic correlate of protection is derived from the same trial.

1. Analyze and Present the Clinical Results From the Swedish Trial.

Data collection for the trial has been completed and plans for analysis of the results have been made. An objective for Fiscal Year 1988 is to help insure adequate and appropriate analysis of the clinical results of the trial and timely presentation of the findings to the international community.

2. Test Blood Specimens From Sweden and Correlate Results with Clinical Findings.

The blood specimens collected in the Swedish trial are expected to provide data on the relationship between antibody response to vaccination and protection from disease. If a correlation can be established, it may be possible to assess other candidate vaccines in terms of the antibody responses they evoke in lieu of clinical trials to evaluate prevention of disease. Blood specimens from the trial will be analyzed both in Sweden and, if available, at the laboratories of the FDA. An objective for Fiscal Year 1988 is to accomplish this serologic evaluation of the specimens from the trial and to present the results in a timely manner. In addition, sera from trials of other candidate vaccines are expected to be submitted to the FDA laboratories and these will be assessed in light of the findings on the Swedish sera tested in the same labs.

3. Continue IND Reviews and License Application Evaluations on New Candidate Vaccines.

The FDA reviews all new products submitted for Investigational New Drug (IND) applications and examines proposed protocols. Since additional new vaccines are expected to be ready for clinical evaluation in the coming year, an objective for Fiscal Year 1988 is to review IND submissions and evaluate license applications as expeditiously as possible on all products submitted.

FDA laboratories have tested several candidate vaccines to evaluate the characteristics of the vaccines including selected toxic activities and immunogenicity in animals. All new vaccine candidates will be tested expeditiously to ensure that clinical evaluation is not delayed.

4. Carry out Clinical Studies of Candidate Vaccines in NIAID Vaccine Evaluation Centers.

Presently, NIAID supports four Vaccine Evaluation Centers at Marshall, Vanderbilt, Baylor, and Rochester Universities. These Centers are currently evaluating products from Connaught and Merieux. During Fiscal Year 1988, other products from these manufacturers and from different producers are expected to be made available. An objective for the coming year is to accommodate any vaccine producer who obtains an IND and who requests assistance in clinical evaluation. It is anticipated that at least four separate producers will have their products evaluated in NIAID Centers in Fiscal Year 1988.

5. Assess Feasibility of a Large Scale Safety and Efficacy Trial in the U.S.

Preliminary discussions have been held with NIH vaccine developers and Massachusetts investigators about the desirability and feasibility of conducting a safety and efficacy trial in the U.S. using the vaccine developed at NIH or some other equally suitable vaccine. More detailed discussion about this large scale project in the U.S. will be carried out in Fiscal Year 1988 to define the objectives and design of any proposed trial and to assist in obtaining support for it if indicated.

6. Standardize Serologic Tests for Pertussis.

Serologic tests to measure the antibody responses to pertussis and to pertussis vaccines have been developed in different laboratories. These tests have not yet been standardized to permit accurate comparison of the results from different laboratories. An objective for Fiscal Year 1988 is to standardize procedures and prepare and distribute reference sera which will facilitate comparison of results between manufacturer, government, and university laboratories.

7. Complete Evaluation of New Diagnostic Tests for Pertussis.

At present, other than culture of Bordetella pertussis organisms, there is no agreed upon test which can reliably diagnose pertussis. A rapid diagnostic test would facilitate clinical and epidemiologic studies. FDA and CDC have used enzyme-linked immunosorbent assays (ELISA) for an experimental assay which appears very promising in identifying pertussis infection. CDC has funded contracts in the U.S. and abroad which have shown promising results. An objective for Fiscal Year 1988 is to consolidate the information obtained to date, to select the most practical test, and to finalize test evaluation so that it can be made available to a wider group of researchers.

8. Complete Pilot Study Of Neurologic Illness in Children.

A pilot study of the association between risk factors (including pertussis vaccination) and neurologic illness in children was begun in 1987 in Washington and Oregon. This pilot is expected to demonstrate whether or not a full scale study of this question is feasible. An objective for Fiscal Year 1988 is to complete the pilot study and arrive at a decision about undertaking the larger, more definitive, project.

9. Continue Intramural Research on Pertussis at FDA, NIH, and CDC.

The Laboratory of Pertussis of CBER, FDA, has been an international leader in identifying and characterizing pertussis antigens as well as developing techniques for measuring antibodies and assessing virulence factors. Laboratories at NIH and CDC are heavily involved in developing candidate vaccines and diagnostic tests, respectively. These efforts will be continued.

VIII. ASSURING OPTIMAL IMMUNIZATION LEVELS IN ALL HIGH RISK AND TARGET GROUPS

A. CURRENT SITUATION

High immunization levels have been best achieved in school age children. Continued efforts have resulted in the adoption of state laws requiring certain immunizations for attendance in kindergarten through grade 12 in most states, and kindergarten entrants in all states. As a result of this, immunization levels greater than 95% have been achieved in school age children. Continued support will maintain these gains. Activities dealing with infants, preschoolers, and adults are not proceeding as well. For example, immunization levels for 2-year old children are estimated to be approximately 80% nationwide, with levels in some inner cities substantially lower than that.

Age appropriate immunization in preschoolers can be assured in settings such as day care facilities where appropriate monitoring is possible. However, the majority of preschool age children do not enter such programs. Additionally, opportunities for immunization may be missed when children (or adults) seek medical care for another reason and do not receive indicated vaccines or when indicated vaccines are withheld for inappropriate reasons. Such missed opportunities for immunization play an important part in the underimmunization of both preschool and adult populations. Moreover, many persons in need of vaccination fail to interact with the health care system at all. Although vaccines are safe and effective in preventing disease, there is need to increase awareness on the part of the general population about the need to immunize preschoolers at recommended ages and to maintain protection against vaccine preventable diseases throughout their adult life.

Increasingly, vaccine prices in recent years have made it more difficult for public sector agencies to obtain adequate quantities of vaccines and have also raised concerns about possible shifts from private to public sector. Federal immunization grant funds have provided a stable quantity of childhood vaccine but State and local resources have not always been able to purchase other vaccines for public sector use. To date there is no evidence of a significant shift from the private to the public sector.

The occurrence of vaccine-preventable diseases in adult and preschool groups is unacceptably high because of the low vaccine coverage in these groups. Reliable baseline data to measure progress or determine current status are unavailable at this time. Activities to increase the acceptance of vaccine in a timely manner are increasingly necessary. Immunization levels in other high risk groups (e.g., hepatitis B vaccine in health care workers, homosexual males, and injectable drug users) are also quite low and require increased attention.

The Federal government currently provides Medicare reimbursement for pneumococcal polysaccharide vaccine and hepatitis B vaccine. In 1988 a Medicare demonstration project will support influenza vaccination. It is not proposed to use Federal immunization grant funds to purchase adult vaccines. In addition to the Medicare reimbursement mentioned above, Federal efforts will concentrate on making adults aware of the need for immunizations.

B. ACTIVITIES FOR FISCAL YEAR 1988

The major focus will include program activities to increase awareness of the need for vaccines in the adult population and other high risk groups and to continue programs to locate and immunize children outside controlled settings such as schools and day care centers.

1. Assess Appropriate Mix of Private and Public Sector Involvement to Achieve Optimal Immunization Levels in High Risk and Target Groups.

2. Revise Adult Immunization Action Plan.

An adult immunization action plan was developed by CDC in 1985. The plan is in need of revision to reflect current activities and future needs. These revisions will be made and the revised plan will be distributed to immunization projects and other health organizations.

3. Form an Ad hoc Committee to Promote Information and Education on the Need for Adult Immunization.

CDC will provide direction to a campaign aimed at increasing awareness of vaccine needs of the general public and among health professionals by calling on organizations and manufacturers to promote a unified theme for the nation. The Committee would develop a plan directed toward raising immunization awareness among adult populations.

4. Implement Cooperative Agreement for Studying Health Maintenance Organizations (HMOs).

CDC will assist the American Medical Care and Review Association (AMCRA) in assessing policies, procedures and coverage levels among representative types of Health Maintenance Organizations (HMOs) and to design and implement interventions to increase immunization levels in adult populations. The cooperative study will assess the coverage levels for pneumococcal, influenza, adult tetanus and diphtheria toxoids, and other appropriate vaccines.

5. Distribute and Promote Use of Adult Immunization Materials.

CDC has a contract to develop materials and methods appropriate for increasing levels of awareness in the general public and among health professionals about the need for immunizing adults. CDC will distribute the materials and assess their use and effectiveness in promoting adult immunization program activities.

6. Monitor Activities Outlined in Program Grant Guidelines.

A recent change in program guidelines allows immunization project grantees to expand their role to include promotion of adult and additional childhood immunizations through education as a part of grant supported activities. Many areas have approaches that could be used by other immunization programs around the nation to assist in the promotion of adult and childhood immunization.

These new programs and activities will be summarized on a quarterly basis and shared with other state and local projects. The elimination of indigenous rubella in the United States was also added as an overall program goal and efforts to achieve this and monitor progress will be continued.

7. Conduct Surveys to Establish Baseline Data.

Appropriate methods to establish baseline data in certain areas including size of target population, immunization coverage, and vaccine usage in public and private sectors, will be necessary. Studies will be designed that will measure knowledge, attitudes, and practices in nursing homes, hospitals and selected physicians' practices.

The hospital study may include the use of such activities as home health programs to determine levels of coverage for influenza, pneumococcal and other appropriate vaccines. The nursing home survey would be conducted on a nationwide basis and would be designed to determine usage and coverage with influenza, pneumococcal, and Td vaccines in residents. The survey would assist in evaluating the distribution and use of the manual "Managing an Influenza Vaccination Program in the Nursing Home" and provide information regarding vaccine coverage. Preschool baseline data collection techniques will be evaluated in Chicago during 1988.

8. Develop and Implement Appropriate Strategies to Improve Immunization Levels in High Risk Groups.

Based on the results of the studies enumerated above, new approaches will be undertaken to improve immunization coverage in defined high risk groups.

9. Distribute Automated Patient Recall System.

An automated data system has been developed under contract to assist clinics in patient recall and program management. This Immunization Control and Evaluation (ICE) system will be made available to project grantees during 1988. It should allow programs to assess levels of coverage in preschool populations and assist them in tracking and follow-up of those shown to be delinquent in immunizations.

10. Review Effectiveness of Preschool Efforts.

During Fiscal Year 1988, data obtained from studies in St. Louis on immunization education systems directed at mothers of newborns and in Los Angeles on an active recall system in public clinics will be reviewed to evaluate their effectiveness.

PHS will also review a new reporting format for vaccine administered in the public and private sectors. This new format will allow better determination of vaccine coverage and age, appropriate administration of vaccine, and estimates of coverage levels in specific age groups. These evaluations will be shared with State projects.

11. Convene a National Immunization Conference.

CDC will hold a National Immunization Conference in San Antonio, Texas, June 20-24, 1988. This conference will feature programs and activities emphasizing the needs of the preschool and adult populations. Conference proceedings will be published and distributed.

LIST OF ACRONYMS/ABBREVIATIONS

AAFP - American Academy of Family Physicians
AAP - American Academy of Pediatrics
ACIP - Immunization Practices Advisory Committee
ACP - American College of Physicians
AFEB - Armed Forces Epidemiological Board
AID - Agency for International Development
AIDS - Acquired Immunodeficiency Syndrome
AMCRA - American Medical Care and Review Association
APHA - American Public Health Association
ASH - Assistant Secretary for Health
CBER - Center for Biologics Evaluation and Research
CDC - Centers for Disease Control
CMI - Cell-Mediated Immunity
DHHS - Department of Health and Human Services
DOD - Department of Defense
DT - Diphtheria and tetanus toxoids (pediatric formulation)
DTP - Diphtheria and tetanus toxoids and pertussis vaccine
EPI - Expanded Programme on Immunization
FDA - Food and Drug Administration
FHA - Filamentous hemagglutinin
GAG - Global Advisory Group
GAO - Government Accounting Office
HBPV - Haemophilus B polysaccharide vaccine
HMO - Health Maintenance Organization
IIS - Important Information Statements
IND - Investigational New Drug
IOM - Institute of Medicine
IPV - Inactivated poliovirus vaccine
JE - Japanese B encephalitis
LPF - Lymphocytosis promoting factor
MMR - Measles, mumps, and rubella virus vaccines (combined)
MMWR - Morbidity and Mortality Weekly Reports
MSAEFI - Monitoring System for Adverse Events Following Immunization
NACI - Canadian National Advisory Committee on Immunization
NAS - National Academy of Sciences
NCDB - National Center for Drugs and Biologics
NIAID - National Institute of Allergy and Infectious Diseases
NICHD - National Institute of Child Health and Human Development
NIH - National Institutes of Health
NVP - National Vaccine Program
OBRR - Office of Biologics Research and Review
OPV - Oral poliovirus vaccine
OTA - Office of Technology Assessment
PHS - Public Health Service
PRP - Polyribosylphosphate
PT - Pertussis toxin
PTA - Parent Teacher Association
rDNA - Recombinant DNA (desoxyribonucleic acid)
RSV - Respiratory Syncitial Virus

SIDS	- Sudden Infant Death Syndrome
SONIC	- Study of Neurologic Illness in Childhood
SRS	- Spontaneous Reporting System
Td	- Tetanus and diphtheria toxoids (adult formulation)
VAC	- National Vaccine Advisory Committee
VPD	- Vaccine-preventable diseases
VRBPAC	- Vaccines and Related Biologic Products Advisory Committee
WHO	- World Health Organization

TITLE III—VACCINE COMPENSATION

National Childhood Vaccine Injury Act of 1986. 42 USC 201.

SEC. 301. SHORT TITLE.

This title may be cited as the "National Childhood Vaccine Injury Act of 1986".

PART A—VACCINES

SEC. 311. AMENDMENT TO PUBLIC HEALTH SERVICE ACT.

42 USC 300aa *et seq.*, 300cc *et seq.*

(a) NEW TITLE.—The Public Health Service Act is amended by redesignating title XXI as title XXIII, by redesignating sections 2101 through 2116 as sections 2301 through 2316, respectively, and by inserting after title XX the following new title:

"TITLE XXI—VACCINES

"Subtitle 1—National Vaccine Program

"ESTABLISHMENT

42 USC 300aa-1. "SEC. 2101. The Secretary shall establish in the Department of Health and Human Services a National Vaccine Program to achieve optimal prevention of human infectious diseases through immunization and to achieve optimal prevention against adverse reactions to vaccines. The Program shall be administered by a Director selected by the Secretary.

"PROGRAM RESPONSIBILITIES

42 USC 300aa-2. "SEC. 2102. (a) The Director of the Program shall have the following responsibilities:

"(1) VACCINE RESEARCH.—The Director of the Program shall, through the plan issued under section 2103, coordinate and provide direction for research carried out in or through the National Institutes of Health, the Centers for Disease Control, the Office of Biologics Research and Review of the Food and Drug Administration, the Department of Defense, and the Agency for International Development on means to induce human immunity against naturally occurring infectious diseases and to prevent adverse reactions to vaccines.

"(2) VACCINE DEVELOPMENT.—The Director of the Program shall, through the plan issued under section 2103, coordinate and provide direction for activities carried out in or through the National Institutes of Health, the Office of Biologics Research and Review of the Food and Drug Administration, the Department of Defense, and the Agency for International Development to develop the techniques needed to produce safe and effective vaccines.

"(3) SAFETY AND EFFICACY TESTING OF VACCINES.—The Director of the Program shall, through the plan issued under section 2103, coordinate and provide direction for safety and efficacy testing of vaccines carried out in or through the National Institutes of Health, the Centers for Disease Control, the Office of Biologics Research and Review of the Food and Drug Administration, the Department of Defense, and the Agency for International Development.

"(4) LICENSING OF VACCINE MANUFACTURERS AND VACCINES.—The Director of the Program shall, through the plan issued under section 2103, coordinate and provide direction for the allocation of resources in the implementation of the licensing program under section 353.

42 USC 263a.

"(5) PRODUCTION AND PROCUREMENT OF VACCINES.—The Director of the Program shall, through the plan issued under section 2103, ensure that the governmental and non-governmental production and procurement of safe and effective vaccines by the Public Health Service, the Department of Defense, and the Agency for International Development meet the needs of the United States population and fulfill commitments of the United States to prevent human infectious diseases in other countries.

"(6) DISTRIBUTION AND USE OF VACCINES.—The Director of the Program shall, through the plan issued under section 2103, coordinate and provide direction to the Centers for Disease

Control and assistance to States, localities, and health practitioners in the distribution and use of vaccines, including efforts to encourage public acceptance of immunizations and to make health practitioners and the public aware of potential adverse reactions and contraindications to vaccines.

"(7) EVALUATING THE NEED FOR AND THE EFFECTIVENESS AND ADVERSE EFFECTS OF VACCINES AND IMMUNIZATION ACTIVITIES.—The Director of the Program shall, through the plan issued under section 2103, coordinate and provide direction to the National Institutes of Health, the Centers for Disease Control, the Office of Biologics Research and Review of the Food and Drug Administration, the National Center for Health Statistics, the National Center for Health Services Research and Health Care Technology Assessment, and the Health Care Financing Administration in monitoring the need for and the effectiveness and adverse effects of vaccines and immunization activities.

"(8) COORDINATING GOVERNMENTAL AND NON-GOVERNMENTAL ACTIVITIES.—The Director of the Program shall, through the plan issued under section 2103, provide for the exchange of information between Federal agencies involved in the implementation of the Program and non-governmental entities engaged in the development and production of vaccines and in vaccine research and encourage the investment of non-governmental resources complementary to the governmental activities under the Program.

"(9) FUNDING OF FEDERAL AGENCIES.—The Director of the Program shall make available to Federal agencies involved in the implementation of the plan issued under section 2103 funds appropriated under section 2106 to supplement the funds otherwise available to such agencies for activities under the plan.

"(b) In carrying out subsection (a) and in preparing the plan under section 2103, the Director shall consult with all Federal agencies involved in research on and development, testing, licensing, production, procurement, distribution, and use of vaccines.

"PLAN

"SEC. 2103. The Director of the Program shall prepare and issue a plan for the implementation of the responsibilities of the Director under section 2102. The plan shall establish priorities in research and the development, testing, licensing, production, procurement, distribution, and effective use of vaccines, describe an optimal use of resources to carry out such priorities, and describe how each of the various departments and agencies will carry out their vaccine functions in consultation and coordination with the Program and in conformity with such priorities. The first plan under this section shall be prepared not later than January 1, 1987, and shall be revised not later than January 1 of each succeeding year. 42 USC 300aa-3.

"REPORT

"SEC. 2104. The Director shall report to the Committee on Energy and Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate not later than January 1, 1988, and annually thereafter on the implementation of the Program and the plan prepared under section 2103. 42 USC 300aa-4.

"NATIONAL VACCINE ADVISORY COMMITTEE

42 USC 300aa-5.

"SEC. 2105. (a) There is established the National Vaccine Advisory Committee. The members of the Committee shall be appointed by the Director of the Program, in consultation with the National Academy of Sciences, from among individuals who are engaged in vaccine research or the manufacture of vaccines or who are physicians, members of parent organizations concerned with immunizations, or representatives of State or local health agencies or public health organizations.

"(b) The Committee shall—

"(1) study and recommend ways to encourage the availability of an adequate supply of safe and effective vaccination products in the States,

"(2) recommend research priorities and other measures the Director of the Program should take to enhance the safety and efficacy of vaccines,

"(3) advise the Director of the Program in the implementation of sections 2102, 2103, and 2104, and

"(4) identify annually for the Director of the Program the most important areas of government and non-government cooperation that should be considered in implementing sections 2102, 2103, and 2104.

"AUTHORIZATIONS

42 USC 300aa-6.

"SEC. 2106. (a) To carry out this subtitle other than section 2102(9) there are authorized to be appropriated $2,000,000 for fiscal year 1987, $2,500,000 for fiscal year 1988, $3,000,000 for fiscal year 1989, $3,500,000 for fiscal year 1990, $4,000,000 for fiscal year 1991.

"(b) To carry out section 2102(9) there are authorized to be appropriated $20,000,000 for fiscal year 1987, $22,500,000 for fiscal year 1988, $25,000,000 for fiscal year 1989, $27,500,000 for fiscal year 1990, $30,000,000 for fiscal year 1991.

NIH PLAN FOR AIDS VACCINE DEVELOPMENT AND EVALUATION

EXECUTIVE SUMMARY

Development of a safe and effective vaccine to prevent human immunodeficiency virus (HIV) infection and AIDS presents a wide range of scientific and public policy challenges. The continual growth of the AIDS pandemic, coupled with epidemiological estimates of the numbers of persons currently infected with HIV and capable of spreading the virus, has placed vaccine development into a prominent role among the strategies for prevention and control of AIDS. The National Institutes of Health (NIH) is the agency of the United States Public Health Service (PHS) with the lead responsibility for AIDS vaccine research and development efforts. Recognizing that AIDS vaccine development will require a coordinated effort and active participation by government, industry, and academia, the NIH has generated a comprehensive plan to assure the expedited preclinical and clinical development of a safe and effective AIDS vaccine.

BACKGROUND

Historically, vaccine research and development has relied on an interactive system between federally funded academic and government laboratories and commercial manufacturers of vaccines. In a broad sense, this process can be divided into three major steps: basic research; preclinical development; and clinical development. In addition, an infrastructure of research resources serves to complement the major steps in vaccine development by providing the resources necessary to expedite the stepwise progression from basic research through clinical testing.

The basic research necessary to define the pathogenesis of the disease, mechanisms of immunity, genetic and immunologic variation, animal models and other factors which precede preclinical development of experimental vaccines can often be time-consuming and expensive. Because of this large investment of time and other economic costs, basic research studies have generally been carried out by government and academic research scientists funded by the federal government.

Preclinical development of vaccines includes all of the steps from immunogen identification through manufacture, scale-up and testing of vaccine lots in suitable animal model systems, to the filing of an Investigational New Drug (IND) application with the Food and Drug Administration (FDA) for permission to conduct safety, immunogenicity and efficacy studies in humans. These preclinical development steps have generally been undertaken by commercial vaccine manufacturers. The manufacture of vaccines requires a long-term commitment in biotechnology, a major capital investment in technologically advanced scale-up production facilities for biological products, and the willingness of the manufacturer to undertake risks and commitments in the face of several economic disincentives such as an uncertain market and

apprehension over liability issues. These risks have led to a decreasing number of commercial manufacturers remaining in the vaccine industry over the past twenty years. As a result, the U.S. has become dependent on single suppliers for many vaccines, and the vaccine industry has become dominated by a few large commercial firms. The urgency of the AIDS problem, coupled with the recent advances in molecular biology and recombinant DNA technology has led to an explosion of interest by small biotechnology companies in AIDS vaccine development. However, many of these companies do not have the resources to undertake several of the preclinical development steps. Thus, these lack of resources may serve as obstacles to the development of a safe an effective AIDS vaccine and novel approaches to public-private sector interactions may be required to accelerate AIDS vaccine development.

The clinical development of vaccines includes the human safety, immunogenicity, and efficacy trials, the license application process, and the mechanisms for distribution of AIDS vaccines to the general public. Clinical testing of candidate vaccines has been carried out by both commercial vaccine manufacturers and by federally sponsored vaccine evaluation efforts. AIDS vaccine testing is associated with complex recruiting, seroconversion, ethical, and liability issues, and highlights the necessity for establishing mechanisms to assure that collaborative efforts at the interagency, public-private sector, and international levels are promoted. The license application process includes a review of the sponsor's vaccine production and clinical trials data by the FDA, often following consultation with the Vaccines and Related Biological Products Advisory Committee. A series of advisory groups from the PHS, American Academy of Pediatrics, and American College of Physicians are involved in recommendation process for vaccine utilization within the United States.

As discussed below, the NIH Plan for AIDS Vaccine Development represents a multidisciplinary framework for a government-industry-academia cooperative effort to expedite AIDS vaccine development. This Plan will utilize a coordinated program of innovative strategies aimed at maximizing the interaction of public and private sector components through resource allocation, reagent distribution, technology transfer, and information exchange.

AIDS VACCINE RESEARCH AND DEVELOPMENT SURVEILLANCE

The advances in understanding the molecular biology of HIV which have occurred since the virus was first isolated have been remarkable. The molecular biology and genome organization of HIV is more clearly delineated than for any other retrovirus. However, the basic information on the pathogenesis of infection and mechanisms of immunity which are necessary to predict whether immunization against HIV is possible and what types of host responses must be induced to elicit resistance against HIV infection and AIDS have not been defined. As a result, the state-of-the-art in basic research related to AIDS vaccine development is constantly being surveyed in order to identify areas of research which require greater emphasis. These surveys are conducted by both formal and informal mechanisms. Major conferences and smaller workshops sponsored by NIH, other agencies of the PHS, professional societies, the World Health Organization (WHO), commercial manufacturers, and other interested parties serve as forums for information

exchange regarding the identification of gaps in research. Within the PHS Executive Task Force on AIDS, NIH chairs the Vaccine Research and Development Subgroup which also focuses on plans for future research initiatives, and coordinates efforts between other PHS agencies and the Department of Defense. Similarly, surveillance of research gaps is provided within the NIH by a series of committees including the NIH AIDS Advisory Committee, the NIH AIDS Executive Committee, and the NIH Scientific AIDS Vaccine Advisory Committee. This continual review of the basic research related to AIDS vaccine development is a critical exercise which facilitates the process of resource allocation on AIDS vaccine studies to scientists within the academic and commercial sectors of the extramural community and within the intramural structure at NIH.

BASIC RESEARCH INITIATIVES

Basic research serves as the seed and soil from which advances toward AIDS vaccine development are cultivated. NIH has dedicated significant resources to the major research disciplines of virology, immunology, structural biology, and molecular biology which continue to yield a wealth of information accelerating the vaccine development process. Several Institutes of the NIH, coordinated by the NIH AIDS Executive Committee, participate in the support of scientists of the extramural community and intramural NIH laboratories to address the major gaps in the knowledge base required for AIDS vaccine development. The basic research challenges remain formidable, yet the current rate of progress coupled with expanded efforts in coordination and information exchange offer promise for future success. Among the major unanswered questions still impeding AIDS vaccine development are: What are the immune mechanisms responsible for protection against HIV infection and development of AIDS? What is the extent of genetic variation in HIV, and how does this variation affect AIDS vaccine development? Can a standardized animal model-challenge system be established to evaluate the efficacy of candidate AIDS vaccines? What approaches can be developed to interfere with cell-free and cell-associated transmission of HIV?

Investigator initiated research grants continue to serve as the major avenue for basic research studies. However, given the urgency of the AIDS problem, NIH has taken active measures to stimulate studies on basic research problems which impact AIDS vaccine development. Programs of Excellence in Basic Research on AIDS (PEBRA) will soon be awarded to encourage multidisciplinary efforts at academic research settings. Similarly, the National Cooperative Vaccine Development Groups are scheduled to be awarded in February, 1988. These groups are composed of government-industry-academic participants interacting in a formalized framework with the capacity to move rapidly from the basic research setting through the preclinical development process for candidate AIDS vaccines. These groups represent the first of what is anticipated to be an expanding network of scientists linking resources, reagents, and technology with the common goal of expediting AIDS vaccine development. In addition, several other grants, cooperative agreements, and contracts serve as a basic research core for future applied research initiatives. They address issues such as pathogenesis of HIV infections, animal models for HIV, sequencing and cloning of HIV strains, correlates and markers of immunity in AIDS, structural biology of HIV proteins, studies on vaccine adjuvants, and

methods to quantitate HIV.

Similarly, the intramural research programs at NIH have established major efforts in basic research studies on AIDS which have resulted in several important research breakthroughs directly related to AIDS vaccine research. NIH intramural scientists, working in the fields of retrovirology, immunology, and structural and molecular biology, have been major players in the progress towards understanding the molecular and cellular mechanisms of HIV infections. Through a series of subcontracts and collaborative agreements, the intramural programs have linked up with commercial firms in efforts to accelerate these basic research efforts.

Information exchange efforts on basic research studies on AIDS related to vaccine development continue to be carried out through workshops and ad-hoc advisory group meetings. In efforts to enhance reagent distribution, NIH is instituting an HIV Reagent Repository where HIV reagents will be deposited and made available to the entire research community. Similarly, contracts to support virus production and viral component production will soon be in place to feed into the repository, thereby expanding the potential volume of reagents available to the research community. In total, these efforts are aimed at establishing an interactive atmosphere for government, industrial, and academic scientists to engage in basic research studies with the goal of closing the gaps in the knowledge base required to expedite the preclinical development of AIDS vaccines.

PRECLINICAL AIDS VACCINE DEVELOPMENT

Commercial manufacturers of vaccines are presently faced with a series of economic disincentives to vaccine innovation and production, which has caused the number of manufacturers to dwindle over recent years. These disincentives include the long term nature of vaccine development, production and quality control; the costs of research and development in relation to anticipated sales; concerns over liability; patent concerns relating to the perception that vaccines have less patent protection than drugs. Recognizing these concerns, the NIH Plan for AIDS Vaccine Development provides for a network of national resources to facilitate all steps in AIDS vaccine development. This network of resources will assist commercial vaccine manufacturers by providing mechanisms to insure that no gaps exist in the AIDS vaccine development process.

The NIH is committed to encouraging active participation by industrial, academic, and government scientists in the preclinical development of AIDS vaccines. As already mentioned, one of the mechanisms to coordinate multidisciplinary approaches to AIDS vaccine development will be through the National Cooperative Vaccine Development Groups. In addition, the NIH will establish biocontainment facilities at institutions involved in AIDS vaccine development thereby allowing for an increased effort in virus production and genetic manipulation studies. Primate breeding and testing facilities will be established. The breeding facilities will expand the numbers of rhesus macaques available for the simian immunodeficiency virus (SIV) model development, and expand the numbers of chimpanzees available for HIV studies. The planned testing facilities will be a national resource for the evaluation of candidate AIDS vaccines in these experimental primate systems.

Reagent distribution will be expanded via the HIV Reagent Repository, and efforts are being developed to establish an AIDS Vaccine Information Network, which will provide rapid dissemination of information to all investigators involved in basic, preclinical, and clinical research on AIDS vaccines. This infrastructure of national research resources serves to complement the steps in preclinical AIDS vaccine development. These approaches, coupled with continued efforts by NIH to address the complex issue of AIDS vaccine liability through public-private sector interaction provides greater incentives to commercial firms to commit resources to AIDS vaccine development.

Preclinical development of AIDS vaccines consists of the following steps: identification of the immunogen; choice of the vaccine type; vaccine stock production for preliminary studies; immunogenicity and safety studies in small animals; immunogenicity studies in primates; manufacture and scale-up of vaccine lot; biological products tests; immunogenicity, safety, and efficacy studies in chimpanzees; filing of the IND application with the FDA.

Based on prevention models in other retrovirus systems, the major emphasis in AIDS vaccine development has been directed towards HIV envelope gene products (gp160; gp120; gp41) and fragments of these gene products which contain neutralizing antibody or cell mediated immune epitopes. However, recognizing that other internal core proteins of the virus may be implicated in the host immune response against infection, NIH has allocated resources to both intramural and extramural scientists to explore the role of all HIV gene products and determine their relationship to the host immune response during natural infection. A series of cooperative agreements on vaccine adjuvant development serve to complement these immunogen identification studies by providing resources to evaluate methods of enhancing the immunogenic responses of HIV proteins.

Similarly, research into several types of vaccine approaches is being supported. These include killed virus, natural viral products, recombinant DNA products, synthetic peptides, recombinant viruses, anti-idiotype vaccines, combination vaccine cocktails, and passive immunization. These studies are complemented by a series of resource contracts on animal models for AIDS. Through the AIDS vaccine research and development surveillance mechanisms outlined above, NIH maintains progress updates on all current AIDS vaccine approaches being undertaken by government-industry-academic scientists.

In order to facilitate vaccine stock production for preliminary testing in small animals, the NIH Plan for AIDS Vaccine Development calls for combined efforts of NIH and industry. Research support contracts which will be established to provide reagents for the HIV Reagent Repository may be supplemented to provide vaccine production facilities. In addition, dependent on volume, a small-scale vaccine production facility may be established to assist small biotechnology firms with limited resources in the vaccine development process. In addition, efforts will be expanded to coordinate with industry, in order to insure that this step in the AIDS vaccine development program does not provide a roadblock to vaccine production.

Once a vaccine candidate is produced in sufficient quantities for

preliminary testing, it is subjected to a series of immunogenicity and safety tests in small animal models. Tests for immunogenicity include neutralizing antibody, cell mediated immune responses, cytotoxic antibody, and antibody dependent cellular cytotoxicity. Safety tests include general safety studies and evaluation of any immunologic dysfunction associated with the experimental vaccine. Similar to efforts to facilitate vaccine stock production, NIH is dedicated to insuring that evaluation of candidate vaccines in small animal models does not impede the AIDS vaccine development process. As such, utilizing the research support contract mechanism, NIH proposes to establish a small animal models testing facility for candidate AIDS vaccines. This could serve to complement efforts currently underway in the commercial vaccine industry.

Establishing the immunogenicity of an experimental AIDS vaccine in primate model systems is an important consideration for vaccine manufacturers prior to their decision for large scale production of a vaccine lot. This step does not ordinarily involve chimpanzees, but is limited to other primates such as rhesus macaques. Access to primates for evaluation of candidate vaccines can be a major concern to vaccine manufacturers, particularly those with limited resources, due to the small number of available primates and testing facilities. As the number of experimental vaccines requiring testing increases, the limited numbers of primates and testing facilities takes on added significance. In order to address this potential impediment in AIDS vaccine development, the NIH proposes a major expansion in the both primate breeding and testing facilities. Rhesus macaque breeding facilities would increase in number and size, allowing for both an expanded effort in SIV studies and for immunogenicity studies of experimental HIV vaccines. In addition, a rhesus macaque testing facility would be established to evaluate experimental AIDS vaccines for immunogenicity. This facility would utilize a standard panel of immune response assays (e.g. neutralizing antibody; T-cell activation; T-cell cytotoxicity; cytotoxic antibody; antibody dependent cellular cytotoxicity) and provides a mechanism for expediting primate immunogenicity studies.

The manufacture and scale-up of vaccines requires a major capital investment in technologically sophisticated production facilities. The FDA issues guidelines on good manufacturing practices (GMP) which address topics such as production and process controls, packaging and labeling controls, laboratory controls and others. Manufacturers of vaccines are required to abide by these GMP guidelines. Historically, the production and scale-up of vaccines has been undertaken by commercial vaccine manufacturers. However, the urgency associated with the AIDS pandemic which continues to drive efforts to expedite the vaccine development process, coupled with the diminishing number of major commercial firms participating in vaccine development suggests a need for the establishment of a national AIDS vaccine large-scale production facility. The NIH Plan for AIDS Vaccine Development proposes that a national AIDS vaccine scale-up facility be established, and that this facility be utilized as a national resource to accelerate the vaccine development process.

Following the production of a vaccine lot, the lot is subjected to a series of biological products tests required by the FDA for all biologicals. These tests include the evaluation of safety, identity, purity, sterility, and potency. While manufacturers of vaccines are usually equipped to undertake

these general biological products tests, a research support contractor equipped to run these assays under quality controlled conditions would facilitate this step in the vaccine development process. Finally, the vaccine lot is evaluated in the chimpanzee model system for safety, toxicology and immunogenicity. While efficacy studies in chimpanzees are not currently required for entrance into Phase 1 clinical testing, it is anticipated that efficacy testing may be required either at the Phase 1-Phase 2 interface, or Phase 2-Phase 3 interface. Current estimates indicate that approximately 600 chimpanzees are available for AIDS research. The cost, small numbers, and lack of access to chimpanzees by vaccine manufacturers is viewed as a major impediment to AIDS vaccine development. The NIH proposes to expand the number of chimpanzee breeding facilities, and to establish a chimpanzee testing facility where candidate AIDS vaccines can be tested utilizing standard protocols for dose, route, strain, and form (free versus cell associated) of the challenge virus pool. This national resource would fill a major need in providing for standardized preclinical testing of experimental AIDS vaccines.

The final step in the preclinical AIDS vaccine development process is the filing of the IND application with the FDA for permission to initiate clinical testing of the candidate AIDS vaccine. The IND provides the preclinical safety data and rationale for clinical testing, reviews the manufacturing methods and quality control procedures of the vaccine manufacturer, and contains a plan for the Phase 1 safety and immunogenicity clinical trial. The sponsor of the vaccine trial is required to have the IND approved by the FDA prior to initiation of clinical testing. In addition, federal regulations require that an institution conducting a trial with human subjects must have the protocol approved by the Institutional Review Board before beginning clinical testing.

Several of the preclinical steps described above are currently being undertaken to some degree by commercial vaccine manufacturers. In order to maximize coordination efforts, efficiently utilize resources, and promote technology transfer, reagent distribution, and information exchange, the NIH Plan for AIDS Vaccine Development proposes to establish a blue-ribbon government-industry-academia AIDS Vaccine Development Advisory Panel. Composed of representatives from PHS, academic institutions, pharmaceutical companies, biotechnology companies, WHO, and other institutions, this Panel would provide for a formalized framework to review and advise NIH on prioritizing resource allocations for AIDS vaccine development.

AIDS VACCINE CLINICAL TRIALS

Clinical trials of candidate AIDS vaccines will be done in three phases. Phase 1 trials will examine safety and immunogenicity in small numbers of volunteers, and will provide preliminary dosage information. Phase 2 trials utilize larger numbers of volunteers, comprehensively examine safety and immunogenicity, and provide refined information on dosage and route of administration. Finally, phase 3 trials examine the efficacy of the candidate vaccines in field trials using very large numbers of volunteers.

AIDS vaccine trials portend to be more complex than any vaccine trials ever undertaken, indicating the necessity for comprehensive coordination efforts.

Issues including identification of target populations, limited availability of test populations, vaccine induced seroconversion, liability, and the decision-making process for proceeding to Phase 2 and Phase 3 highlight the need for interagency, public-private sector and international collaboration. The proposed AIDS Vaccine Development Advisory Panel along with the PHS Vaccine Research and Development Subgroup could serve as forums for these collaborations.

NIH proposes a major expansion in international epidemiological studies in collaboration with other PHS agencies and the WHO to define potential populations for vaccine efficacy trials. NIH precedents for international collaboration in vaccine development include pertussis trials in Sweden, meningococcal trials in Finland, and typhoid trials in Egypt. It is anticipated that AIDS vaccine efficacy trials may be carried out in the following population groups at high risk for HIV infection: homosexual men; I.V. drug abusers; prostitutes; partners/spouses of hemophiliacs; prisoners; military/foreign service personnel in countries with high rates of HIV infection; other high risk populations in countries with high rates of HIV infection.

Based on preliminary evidence from the first Phase 1 AIDS vaccine trial currently underway at the NIH, recruiting of volunteers for these trials will require a comprehensive effort. The NIAID already has in place a series of Vaccine Evaluation Units which serve as an international resource to expedite the testing of candidate AIDS vaccines. These Units have several years of experience in testing other viral vaccines, and have developed recruitment strategies to address AIDS vaccine trials. Several of the Units contain isolation facilities for the testing of recombinant virus vaccines. AIDS vaccine testing will utilize the multicenter approach to facilitate the recruitment of volunteers. As the number of candidate vaccines moving into Phase 2 and Phase 3 increases, the NIH stands ready to expand the number of Vaccine Evaluation Units to accelerate vaccine testing.

Vaccine induced seroconversion is a significant issue relating to both recruitment of volunteers, and the welfare of these volunteers during and following their participation in AIDS vaccine trials. Persons immunized with candidate AIDS vaccines who mount an effective immune response will appear positive by HIV antibody ELISA testing. Although Western blot tests can discriminate between vaccine induced seroconversion and HIV infection for the first generation of candidate AIDS vaccines, future combination AIDS vaccine cocktails may be less easily differentiated by Western Blot. Thus, volunteers in the AIDS vaccine trials may be subjected to the social discrimination of appearing to be positive on HIV antibody tests. This social discrimination may include difficulties in donating blood, obtaining life and health insurance, entering foreign countries, joining the military or foreign service, and other elements. In order to address this issue, NIH has engaged in multiple approaches. An extensive information exchange campaign is currently underway to inform representative organizations about the vaccine induced seroconversion issue. In this regard, letters of understanding have now been obtained from more than 100 of the largest health and life insurance companies in the United States indicating that persons presenting with indeterminate Western Blots due to immunization with an AIDS vaccine should not face difficulty in life, medical, or disability insurance applications. Similarly, NIH will offer an identification card

with a toll-free 800 number linked to NIH for all volunteers in the vaccine trials. Should a volunteer become involved in a situation where social discrimination occurs due to vaccine induced seroconversion, he/she can call the NIH to verify his/her participation in an AIDS vaccine trial. A confidential computer registry of participants in the vaccine trials has been established to assure that the verification process can be handled efficiently.

AIDS vaccine liability remains a complex issue which jeopardizes the development of a safe and effective vaccine. The spectrum of participants concerned about the liability issue include the volunteers, investigators and institutions carrying out clinical trials, vaccine manufacturers, interest groups, and the federal government. Product liability is probably the major disincentive to manufacturers for vaccine innovation and production. Recruitment into the vaccine trials is also impeded by liability concerns regarding compensation in the event of severe adverse reactions. Investigators and institutions where vaccine trials will be undertaken share concerns regarding potential legal battles arising from real/alleged AIDS vaccine induced injury. While tort reform measures primarily address liability regarding administration of licensed vaccines, there has been limited movement addressing liability concerns in the pre-licensing phase of clinical development. NIH has actively participated in meetings and workshops addressing these issues, and will continue to explore potential solutions with all interested parties.

Finally, the decision-making process for moving candidate AIDS vaccines from Phase 1 to Phase 2 trials, and from Phase 2 to Phase 3 trials is a centerpiece regarding resource allocation. Because of the extremely large numbers of high risk volunteers that would be required in a statistically significant evaluation of vaccine efficacy, it is anticipated that Phase 3 AIDS vaccine trials will require enormous resources. Thus, it is imperative that the decision-making process for endpoint criteria and movement of candidate vaccines into Phase 2 and Phase 3 trials be expedited in a coordinated fashion. The NIH Plan for AIDS Vaccine Development proposes that these criteria be delineated with input from the FDA Vaccines and Related Biological Products Advisory Committee, the proposed AIDS Vaccine Development Advisory Panel, and the PHS Vaccine Research and Development Subgroup.

PRODUCT LICENSING AND DISTRIBUTION

When a candidate AIDS vaccine has demonstrated efficacy in a Phase 3 clinical trial, the final step before the vaccine is made available to the general public is known as the Product License Application (PLA) which is prepared by the vaccine sponsor for the FDA. The PLA contains preclinical toxicology data, a summary of Phase 1 safety and immunogenicity studies, Phase 2 dose-ranging studies, Phase 3 efficacy studies, an environmental impact assessment, and an on-site inspection of production facilities.

A number of vaccine advisory groups are involved in making recommendations for vaccine use in the United States including the U.S. PHS Immunization Practices Advisory Committee (ACIP), the Committee on Infectious Diseases of the American Academy of Pediatrics, and the Committee on Immunization of the

Council of Medical Societies, American College of Physicians. However, the decision-making process in vaccine distribution is complex, and estimated market size impacts on vaccine innovation and production. NIH proposes that efforts be initiated to educate health care providers and the lay public into the risk/benefits of AIDS vaccine immunization programs. These educational outreach activities surrounding the lay public participation in AIDS vaccine immunization programs would not only enhance the recruitment potential for vaccine trials, but would serve to remove impediments to vaccine utilization following licensing.

Statement of Organization, Functions and Delegations of Authority; Office of the Assistant Secretary for Health

Part H, Public Health Service (PHS), Chapter HA (Office of the Assistant Secretary for Health), of the Statement of Organization, Functions and Delegations of Authority for the Department of Health and Human Services (DHHS) (42 FR 61318, December 2, 1977, as amended most recently at 52 FR 23502, June 22, 1987), is amended to reflect the establishment of a National Vaccine Program Office in the Office of the Assistant Secretary for Health reporting directly to the Assistant Secretary for Health who also serves as the Director of the National Vaccine Program. The Office will provide support to the activities of the National Vaccine Program as described in subtitle 1 of Title III, Pub. L. 99-660.

Office of the Assistant Secretary for Health

Under Part H, Chapter HA, Office of the Assistant Secretary for Health (OASH), Section HA-10, Organization, add to the list of organizations, item 20, National Vaccine Program Office (HA2).

Under Section HA-20, Functions, after the statement for the *National Aids Program Office (HAA),* add the following title and statement:

National Vaccine Program Office (HA2)

The National Vaccine Coordinator serves as the head of the Office and reports directly to the Director of the National Vaccine Program for activities regarding the National Vaccine Program (NVP). The Office: (1) Serves as PHS focus in coordinating a national vaccine program including governmental and nongovernmental vaccine activities; (2) identifies issues, and makes recommendations to the Director, NVP, concerning vaccine activities; (3) develops the NVP Implementation Plan for approval by the Director; (4) develops and maintains a directory of organizations and calendar of events involved in vaccine activities; (5) coordinates PHS public education activities related to vaccines; (6) monitors Federal spending for vaccine activities; (7) provides executive secretary and administrative support to the National Vaccine Advisory Committee; and (8) prepares the National Vaccine Report for the Director, NVP to submit to Congress.

Date: August 13, 1987.

Robert E. Windom,

Assistant Secretary for Health.

[FR Doc. 87-19252 Filed 8-21-87; 8:45 am]

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Assistant Secretary
for Health
Washington DC 20201

SEP 29 [illegible]

Kenneth J. Bart, M.D.
Agency Director for Health
Agency for International Development
Room 709 - SA 18
Washington, D.C. 20523

Dear Dr. Bart:

The National Vaccine Injury Compensation Act of 1986 (PL 99-660) contains a provision (Subtitle I) establishing a National Vaccine Program (NVP) to coordinate vaccine-related activities of the Public Health Service, the Department of Defense, and the Agency for International Development. The Secretary has asked me to serve as Director of the Program. I have recently established a staff office for the NVP and have asked Dr. Alan Hinman (Director, Division of Immunization, Centers for Disease Control) to head that office and report directly to me on NVP activities. The enclosed Federal Register notice formally establishes the NVP office and describes its functions.

To assure optimal coordination of government vaccine efforts, I intend to establish a National Vaccine Program Interagency Group with representatives from the National Institutes of Health, the Food and Drug Administration, the Centers for Disease Control, the Department of Defense, and the Agency for International Development. This Group will be chaired by Dr. Hinman and will replace the existing Interagency Group to Monitor Vaccine Development, Production, and Usage, which has functioned very effectively in the past even though it has not had formal representation from DOD or AID.

The functions of the NVP Interagency Work Group will include (but are not limited to):

- Developing and revising the National Vaccine Program Plan;
- Serving as primary agency liaison with the National Vaccine Advisory Committee;
- Monitoring supply and distribution of currently available vaccines, identifying and attempting to resolve problems affecting vaccine availability;
- Monitoring research and developmental activities with regard to new or improved vaccines and recommending any needed changes in emphasis or levels of support to ensure timely completion of studies and introduction of new products;

- Coordinating public and professional information/education activities with regard to vaccine recommendations, adverse events, and contraindications;

- ensuring continuing availability of vaccines which have limited use; and

- coordinating other vaccine-related issues on an ad hoc basis.

I anticipate the Work Group will need to meet frequently initially but that after the Plan is well underway and the Advisory Committee formed, meetings should be less frequent and many may be able to be accomplished by conference call. Some meetings may only require participation of a single representative from each agency whereas, depending on the issues to be discussed, others may benefit greatly from much wider representation. Although the Work Group will keep abreast of AIDS vaccine development, the lead in this area will come from the AIDS Vaccine Research and Development subgroup of the PHS Executive Task Force on AIDS.

I would appreciate it very much if you could send me, by September 30, the name of your representative for the NVP Interagency Work Group as well as the name of a backup representative. Thank you very much for your continued cooperation.

Sincerely yours,

/s/ Robert E. Windom

Robert E. Windom, M.D.
Director, National Vaccine Program
Assistant Secretary for Health

Enclosure

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

CHARTER

NATIONAL VACCINE ADVISORY COMMITTEE

Purpose

The Secretary of Health and Human Services is mandated under Section 2105 of the Public Health Service Act (42 U.S. Code 300aa-1) to establish a National Vaccine Program to achieve optimal prevention of human infectious diseases through immunization and to achieve optimal prevention against adverse reactions to vaccines. The National Vaccine Advisory Committee shall advise and make recommendations to the Director of the Program on matters related to the Program responsibilities.

Authority

42 U.S. Code 300aa-5, Section 2105 of the Public Health Service Act as amended by Public Law 99-660. The Committee is governed by the provisions of Public Law 92-463 (5 U.S.C. App. 2), which sets forth standards for the formation and use of advisory committees.

Function

The National Vaccine Advisory Committee shall:

(1) study and recommend ways to encourage the availability of an adequate supply of safe and effective vaccination products in the States,

(2) recommend research priorities and other measures the Director of the Program should take to enhance the safety and efficacy of vaccines,

(3) advise the Director of the Program in the implementation of sections 2102, 2103, and 2104, and

(4) identify annually for the Director of the Program the most important areas of government and non-government cooperation that should be considered in implementing sections 2102, 2103, and 2104.

Structure

The Committee shall consist of 13 members including the chair. Members and chair shall be appointed by the Director of the Program, in consultation with the National Academy of Sciences, from among individuals who are engaged in vaccine research or the

manufacture of vaccines or who are physicians, members of parent organizations concerned with immunizations, or representatives of State or local health agencies, or public health organizations; and five nonvoting ex-officio members as follows: Director, National Institutes of Health; Commissioner, Food and Drug Administration; Director, Centers for Disease Control; Agency Director for Health, Agency for International Development; and Deputy Assistant Secretary for Professional Affairs and Quality Assurance, Office of the Assistant Secretary for Health, Department of Defense (or designees of such offices).

Members shall be invited to serve for overlapping four year terms, except that any member appointed to fill a vacancy for an unexpired term shall be appointed for the remainder of such term. A member may serve after the expiration of the member's term until a successor has taken office. Terms of more than two years are contingent upon the renewal of the Committee's charter by appropriate action prior to its expiration.

Subcommittees composed of members of the parent committee may be established. The Department Committee Management Officer will be notified upon establishment of each subcommittee, and will be provided information on its name, membership, function, and estimated frequency of meetings.

Management and support services shall be provided by the Office of the National Vaccine Program, Office of the Assistant Secretary for Health.

Meetings

Meetings shall be held approximately four times a year at the call of the chair with the advance approval of a Government official who shall also approve the agenda. A Government official shall be present at all meetings.

Meetings shall be open to the public except as determined otherwise by the Secretary; notice of all meetings shall be given to the public.

Meetings shall be conducted, and records of the proceedings kept, as required by applicable laws and Departmental regulations.

Compensation

Members who are not full-time Federal employees shall be paid at the rate of $150 per day, plus per diem and travel expenses in accordance with Standard Government Travel Regulations.

Annual Cost Estimate

Estimated annual cost for operating the Committee, including compensation and travel expenses for members but excluding staff support, is approximately $40,640. Estimate of annual person-years of staff support required is .76, at an estimated annual cost of $23,050.

Reports

An annual report shall be submitted to the Secretary and the Director, National Vaccine Program no later than September 30 of each year, which shall contain as a minimum a list of members and their business addresses, the Committee's functions, dates and places of meetings, and a summary of Committee activities and recommendations made during the fiscal year. A copy of the report shall be provided to the Department Committee Management Officer.

Duration

Continuing.

The charter for this Committee shall terminate two years from the date of approval.

APPROVED:

JUL 30 1987
Date

Otis R. Bowen M.D.
Otis R. Bowen, M.D.
Secretary

SELECTED CURRENT VACCINE RESEARCH ACTIVITIES

Targeted Vaccines - U.S.

Pertussis (improved): See Section VII of this Report.

Hepatitis B virus (rDNA). In July, 1986, the FDA licensed a yeast cell-derived recombinant DNA HBV vaccine manufactured by Merck, Sharp & Dohme. While licensing of the first rDNA vaccine heralded a new era for vaccines, public health officials were disappointed since Merck indicated that the cost will be the same as for their plasma-derived vaccine. To enhance the potential for cost reduction, the NIAID is assisting other manufacturers by performing phase I (safety and immunogenicity) clinical trials at its Vaccine Evaluation Units. Two such trials have been completed at the Baylor College of Medicine. Both of the rDNA candidate vaccines will be evaluated further through the U.S.-China Joint Health Protocol administered by CDC. AID has sponsored development of a plasma-derived vaccine in Korea which may cost only 1/100th as much as U.S. manufactured vaccine. Trials are currently underway on alternative routes of administration (intradermal injection) which could potentially reduce the cost even further.

Haemophilus influenzae, type b. A polyribosyl phosphate (PRP) polysaccharide vaccine was licensed by Praxis Biologics in April, 1985, and by Connaught and Lederle in January 1986. This is the first new vaccine recommended for universal pediatric use since the introduction of rubella vaccine in 1969. Children 2-5 years of age have been recommended to receive the vaccine as part of their general health care. Unfortunately, polysaccharide is not effective in preventing illness in infants and children less than 2 years old who are at highest risk. The U.S. efforts directed at developing polysaccharide-protein conjugate vaccines were led by investigators at FDA and subsequently at NIH. These vaccines constitute a new class of vaccine and give promise of being effective in those less than two. An efficacy trial was begun in December 1984 to test a new conjugate vaccine developed by Connaught Laboratories in a high-risk population of native Alaskan infants. The vaccine or a placebo control is being administered in a primary series at 2, 4, and 6 months of age simultaneously with DTP. The study is designed to assess the protective efficacy of the vaccine in reducing the incidence of invasive disease caused by Haemophilus influenzae, type b and other less invasive disease. The current activities in Alaska include education and counseling, recruitment, immunization, and the follow-up of study participants. The total number of subjects needed to fulfill the recruitment requirement is 2,000 and this goal

has been achieved. No significant differences have been observed in the reported rates of local and systemic reactions between the vaccine and placebo groups. In addition, none of the reported illnesses, major reactions, or deaths in the study population are attributable to vaccine administration. Efficacy and serology data will not be available until the code is broken, estimated to be August 1988.

Another efficacy trial of the Connaught conjugate vaccine was undertaken in Finland in January 1986. The study was designed so that 50% of all newborns (randomly selected) in 1986 received three injections at 3, 5, and 7 months of age. The other 50% received nothing and served as controls. Data reported recently indicated that the vaccine was highly effective in preventing disease due to Haemophilus influenzae, type b, in this population. The duration of this protection continues to be monitored. Another similar type of conjugate vaccine made by NIH scientists is being evaluated clinically, with some studies taking place in Sweden.

Two new conjugate vaccines were recently introduced into clinical evaluation by Praxis Biologics and Merck, Sharpe & Dohme. Both vaccines were shown to be safe and highly immunogenic for toddler-aged children and infants. Both of these vaccines appear to be highly immunogenic in infants even after one dose, with levels of antibody comparable to those observed after two or three doses for other conjugate products.

Respiratory Syncytial Virus. Investigators have identified the presence of more than one type of respiratory syncytial virus (RSV), necessitating evaluation of type-specific antibodies. Cloning and expression of genes coding for the F and G surface glycoproteins of RSV in vaccinia virus vectors has been independently accomplished in government and academic laboratories. The cloning and expression of other RSV-specific genes is in progress. The identification of protective immune responses in RSV infections is under investigation. Preliminary results, using either the mouse or cotton rat models of RSV infection, suggest that antibodies induced to the F glycoprotein may confer protection against heterologous challenge. Vaccinia virus vectors containing the G glycoprotein were also demonstrated to confer protective immunity, although not to the same extent as those expressing the F glycoprotein. No significant protection against subsequent virus challenge was observed when a vaccinia virus vector containing an RSV nucleocapsid protein was expressed. Other high efficiency vector systems, such as the baculovirus vector, are currently being tested for their ability to express large quantities of antigenic RSV specific surface proteins.

Influenza. Phase 3 clinical trials are in progress to compare the efficacy of the cold-adapted (ca) live, attenuated influenza A virus vaccines and the contemporaneous inactivated trivalent vaccine for their respective abilities to prevent natural influenza infections. The trial is a five-year, placebo controlled study with a projected enrollment of 3,000 volunteers. To date, greater than 90% of the projected number of participants have been vaccinated. Additional, large field trials are under way to compare the duration of immunity and cross-protective abilities of the ca and inactivated vaccines. Similarly, the ca vaccine is being studied in family settings to determine if the vaccine is effective in limiting the spread of influenza virus. The safety, immunogenicity, and reaction rate of the ca vaccine is also being evaluated in high-risk populations, particularly the elderly and those with congestive heart failure.

Phase 1 trials of a ca influenza B vaccine have shown it to be safe and not associated with reactions. The safety and immunogenicity of a ca trivalent vaccine is being assessed in the ferret animal model system. Although the major emphasis on influenza virus vaccines has been the assessment of ca vaccines, studies continue on the influenza avian-human (ah) reassortants, developed by NIAID intramural scientists. For example, clinical evaluation of the comparative effectiveness of the ca and ah vaccines are in progress. Long-term studies on the effectiveness of annual immunization with trivalent inactivated influenza virus vaccines are continuing at the Influenza Research Unit at Baylor Medical School.

Varicella Virus. The etiologic agent of chickenpox, Herpesvirus varicellae, may cause serious illness and death in immunosuppressed children such as those with acute leukemia on chemotherapy . The NIAID evaluated an attenuated varicella virus vaccine--developed by Japanese scientists and manufactured by Merck, Sharp & Dohme--in leukemic children, and demonstrated safety, immunogenicity and efficacy. However, difficulties were encountered when further trials were undertaken with "consistency lots" of vaccine which are prepared using scaled-up production procedures. In an attempt to determine whether the increased reaction rate was due to variations in the vaccines themselves, or differences reflected in the population under study, the trial returned to the use only of research lot material. Seventy-five children with leukemia in remission received the research material and had identical reaction rates to those observed previously when this material was administered; therefore, the "consistency lot" material was different. The manufacturer has carefully analyzed steps in making the vaccine and has prepared new consistency lots that are practically identical to the original research lots. These consistency lots are now being tested in leukemic children in remission for evaluation. The manufacturer has demonstrated that all of the vaccine lots prepared thus far are safe and effective in normal children but is interested in producing a product equivalent in safety and immunogenicity to the research lots for leukemic or immunosuppressed children.

Gonococcus. Investigation to develop a candidate vaccine for Neissaria gonorrheae infections is continuing. Previous approaches through the use of proteins derived from the pili of the bacteria were unsuccessful in protecting sexually active males from infections by different antigenic types of N. gonorrheae. These studies were supported in part by DOD. Other preparations consist of synthetic peptides that have been obtained from the conserved domain of the pilus protein and from outer membrane protein complexes. The synthetic peptides have elicited antibody responses in animals but these responses waned quickly with time. It is unknown whether these responses were protective because there is no adequate animal model for gonorrhea. The lipooligosaccharide (LOS) family of complex macromolecules that are the principal toxins of N. gonorrheae also have been investigated for vaccine potential but their toxicities have mitigated their use. Studies with the P1 protein, a porin of the outer membrane complex, demonstrated that it can translocate from the gonococcal membranes and insert into the membranes of host cells, changing the transmembrane potential and initiating the endocytotic process. When investigated as a potential vaccine, investigators found the P1 protein unevenly distributed on all gonococci within a population. The P1 protein when administered as a vaccine to male volunteers did not protect against intra-urethral challenge even though it elicited a good antibody response.

The H8 protein is a 22kd protein which appears to be highly conserved among a wide variety of strains of N. gonorrheae. Studies are now underway to determine the antigenic variation of H8 and its role as a target for human lytic antibody. Two other membrane proteins, P2 and P3, appear to be highly conserved among strains of gonococci and are subjects of study for vaccine potential. Two different iron repressing proteins may be crucial to the viability and pathogenicity of gonococci since they are apparently expressed during natural infections and react specifically with convalescent antisera. Interest is now focusing on the potential of such proteins as candidate vaccines.

Targeted Vaccines - International

Streptococcus pneumoniae. Since the licensure of the 14-valent pneumococcal vaccine in 1977 and the completion of trials for the prevention of otitis media, the NIAID pneumococcal vaccine program has gradually decreased in size. The present program consists primarily of collaborative studies of vaccine in various patient populations at high risk of pneumococcal infections which are made possible by support of a reference laboratory for performance of pneumococcal antibody assays located at the State University of New York, Downstate Medical Center. Results indicated that immunosuppression, whether the result of treatment or the underlying disease, is important in determining response to the vaccine.

The licensure of the 23-valent pneumococcal vaccine has provided an opportunity to reassess vaccine efficacy and current recommendations for immunization. This vaccine covers over 90% of the strains causing invasive disease both in the U. S. and elsewhere in the world, but, unfortunately, it has not been found to be effective in young children in industrialized countries because they respond poorly to polysaccharide antigens. By contrast, a study in Papua New Guinea did demonstrate efficacy in young children. Most pneumococcal infections in children occur before two years of age. It is estimated that approximately 71% of children born in the U.S. experience at least one attack of otitis media during the first three years of life. Since coupling of H. influenzae polysaccharide to protein carriers renders it more immunogenic, prototypes of pneumococcal conjugate vaccines were developed by NIH scientists and others. This type of vaccine has been tested in rhesus monkeys and human adults for safety and antigenicity with the objective of developing multivalent conjugate vaccines containing the six or eight most important pediatric serotypes. Such vaccines might also be more effective in those with impaired immune responses.

The World Health Organization has estimated that more than three million children die each year from pneumonia, and that one-fourth to one-third of the mortality of children less than five years of age is due to acute respiratory infections. NIAID, in collaboration with the CDC and AID, proposes to develop pneumococcal conjugate vaccines and to select one or more sites where their efficacy can be tested in young children in the developing world. AID is sponsoring trials of the currently licensed unconjugated vaccine in three developing countries for immunogenicity in children less than 2 years old and is also sponsoring an efficacy field trial in The Gambia.

The role of pneumococcal surface proteins in pathogenicity is now being studied to examine whether these proteins can be used to elicit immunity. Monoclonal antibodies to several pneumococcal surface proteins can protect mice from fatal pneumococcal infection, and have been used as a probe for cloning the genes that code for these proteins. Studies are in progress to express these genes using recombinant DNA techniques for the production of such surface proteins as potential vaccine components.

Rotaviruses. Several approaches to the production of rotavirus vaccines are being pursued. One strategy, developed by NIAID investigators, was to attenuate an otherwise virulent strain of human rotavirus by passing it repeatedly in gnotobiotic piglets and cell culture. This attenuated strain, called WA, represented the first oral rotavirus vaccine candidate. It was fed to volunteers, but when questions about its passage history arose, further trials were suspended. The Japanese have under development temperature-sensitive mutants of human serotypes 1 and 2.

Another strategy involves the use of an animal rotavirus strain that can infect man and evoke cross-protective immunity without inducing illness. An animal strain, designated Smith Kline RIT 4237, derived from the Nebraska calf diarrhea strain of bovine rotavirus, provided 80-90% protection against serious rotarvirus diarrhea in Finnish infants over six months of age for at least two years. It also significantly reduced the severity of rotavirus diarrhea, but not its overall incidence, in Sweden and Peru. Unfortunately, the vaccine failed for unknown reasons in trials conducted in The Gambia and Rwanda, and work on RIT 4237 was stopped by the manufacturer.

Another oral vaccine strain derived from animals and developed by NIAID investigators was isolated from a baby rhesus monkey with diarrhea. This strain (MMU 18006) was considerably more immunogenic than RIT 4237 and thus could be used in lower doses. It causes mild fever and occasional mild diarrhea in children older than 5 months, but not in younger infants. In seven ongoing or recently concluded field trials in the U.S. and overseas sponsored by NIAID and AID, the rhesus vaccine gave highly variable results depending upon the trial; in some it failed to protect altogether, in others it offered protection against severe rotavirus diarrhea only, while in others it seemed to reduce the incidence of rotavirus diarrhea as well as of diarrhea of unknown etiology which may have been due to rotavirus. Additional information is needed on the duration of protection, the extent, if any, of heterologous cross-protection against the four human rotavirus serotypes, optimum dose and schedule, the effect of vaccine formulation and breast feeding on vaccine take, and the extent of reciprocal interference between oral poliovirus and the rhesus vaccines.

A third vaccine strain (WC3), derived by investigators at the Children's Hospital of Philadelphia, from a Pennsylvania calf isolate, was suitably safe and effective in reducing the severity of rotavirus diarrhea in children 3 to 12 months of age in Pennsylvania. The WC3 vaccine, itself serotype 3, seemed to cross-protect against a serotype 1 outbreak even though it induced little serotype 1 humoral antibody in the children. More trials are being planned.

In yet another stratagem, fastidious human rotaviruses have been co-cultivated with less fastidious animal rotavirus strains in tissue culture. In this system, designed to produce reassortant rotaviruses, the segmented genes of the non-cultivatable human rotavirus that restrict growth in vitro are replaced by the animal genes permitting such replication, while the genes coding for the antigenic coat of the human strain are preserved. The resulting progeny viruses not only grow efficiently in cell culture, but also have the neutralizing specificity of the human rotavirus parents. Reassortants have been developed at the NIAID combining wild type bovine or rhesus rotavirus and each of the four human rotavirus serotypes. Human safety and antigenicity trials are under way with the rhesus reassortants, serotypes 1 and 2. Also available are seemingly naturally attenuated strains isolated from asymptomatic infants representing each of the four human serotypes. These so-called "nursery" strains could be tested alone as vaccine candidates or after they have been reassorted with virulent human strains. The strategy of using a mixture of reassortants may provide a broader serotype immunity.

The recent availability of both cloned rotavirus genes and the protein sequences of important rotavirus antigens should permit yet additional approaches to vaccine development. For example, cloned rotavirus genes have been incorporated into a prokaryotic expression vector (E. coli K-12) and into vaccinia virus to produce a vaccinia-rotavirus recombinant strain. If the synthesis of rotavirus antigens can be achieved in such systems, a large amount of antigen could be produced for a subunit synthetic vaccine comprised of two or more major neutralization proteins of the rotavirus. The degree of cross-protection between serotypes and the duration of that protection are particularly critical questions, because it is not yet known whether all four serotypes must be included in a vaccine. Whatever vaccine or vaccines emerge, they must be compatible with breast feeding, oral poliovirus vaccine, and the stability requirements of the cold chain.

Malaria. Malaria kills an estimated five million people each year. In Africa alone, it is estimated that one million child deaths each year are associated with malaria.

Research has focused on anti-sporozoite and anti-red cell stages of the parasite; for the most part, investigators have abandoned antigametocyte work. AID and DOD funded research has developed several prototype synthetic and recombinant (produced in E. coli antigens as vaccine candidates against the circumsporozoite protein of P. falciparum. These prototypes have undergone safety, immunogenicity, and limited efficacy trials in human volunteers in the U.S. The immunogenicity of both vaccines was found to be less than anticipated when compared to the results in animal studies. The challenge studies in humans with the synthetic polypeptide demonstrate limited protection suggesting the potential of these candidate antigens. Testing of these antigens as conjugates is currently underway in hopes of both enhancing immunogenicity and eliciting cell-mediated immunity (CMI).

Prototype recombinant antigen candidates against the circumsporozoite protein of P. vivax grown in yeast and E. coli, respectively, are currently completing primate trials for safety, immunogenicity, and efficacy.

AID is sponsoring clinical testing facilities for Phase I and Phase IIb testing in Thailand and a field trial site in Papua New Guinea has been identified for Phase III trials of candidate antigens.

Salmonella typhi (typhoid). The development in Switzerland and the successful field trial in Egypt of a live, oral S. typhi vaccine is considered a major advance. This vaccine consists of a mutagenized, enzyme deficient strain of S typhi (Ty2la) that is incapable of utilizing galactose after this sugar enters the bacterium. Ty2la successfully proliferates in sufficient numbers to immunize the bowel before galactose accumulates and kills the bacterial cell. In Chile, ongoing field trials of Ty2la, using a more practical vaccine formulation and dosage schedule than used in Egyptian studies, has shown an efficacy rate of 75% in the first trial year, but only 56% and 65% after the second and third trial years. This is less than the three-year, 95% efficacy rate reported in Egypt. The reason why the Ty2la vaccine has shown lower efficacy in Chile than in Egypt is not clear, although the different attack rates of typhoid fever may affect efficacy. Differences in the vaccine formulation used may also be a factor. The vaccine caused few reactions in both trials. Efforts are now being made to test a more practical liquid formulation in Chile and Indonesia to see if it will confer greater and more sustained protection.

Investigators at Stanford University have attenuated two strains of S. typhi by inducing auxotrophic mutations in them (Aro^-, Pur^-). That is, each has a deletion mutation (therefore incapable of reversion) in a gene such that, in order to replicate, the mutation causes a requirement for one or more metabolites which are not available in mammalian tissues. In consequence, the strains cannot maintain growth and persist in mammalian tissues. One strain (541Ty) contains Vi antigen while the second strain (543Ty) does not. In calves, a similar auxotrophic oral vaccine against S. typhimurium was shown to be safe, genetically stable, and capable of penetrating the intestinal mucosa to attain intracellular sites within the reticuloendothelial system but not capable of persisting long-term therein. The vaccine confers protection against virulent S. typhimurium, and offers hope that an analogous auxotrophic mutant may serve as an improved typhoid vaccine in man. Trials in volunteers show the two Stocker auxotrophic S. typhi vaccines to be safe, infective and immunogenic in terms of stimulating cell-mediated immunity, but less so in stimulating S. typhi antibody. Volunteer trials will proceed with strain 541Ty to evaluate immune response following variations in dosage, immunization schedules and formulations. An alternative auxotrophic mutant strain (Aro^-) is available for volunteers in the event that the Aro^- Pur^- 541Ty strain proves to be overattenuated.

The Vi polysaccharide is a linear homopolymer of galacturonic acid that forms a capsule on the surface of S. typhi; it represents a virulence antigen. A purified Vi polysaccharide antigen preparation developed by an NIH scientist has been tested in volunteers as an alternative killed vaccine that might provide protection after one dose. A purified Vi polysaccharide vaccine prepared in collaboration with the Merieux Institute caused few reactions and produced Vi antibody in $\geq$ 85% of volunteers. A field trial to test the efficacy of this vaccine was performed in Nepal under AID auspices. It has also been given to 6,000 school children by investigators at the South African Institute for Medical Research. The preliminary results of both trials have been reported and are quite encouraging.

Shigella (dysentery). Parenteral, killed, whole-cell Shigella vaccines have failed to provide significant protection. Live, oral Shigella vaccines proved to be safe, but too many doses were required for efficacy, and occasional genetic revertants arose. Currently, genetic engineering techniques are being used to develop several types of Shigella vaccines, the most promising of which are noted below.

Genes coding for the protective O-antigen on Shigella sonnei, and contained within a 140 Mdal plasmid of that species, have been inserted into the genome of the Ty21a vaccine strain of Salmonella typhi by U.S. Army scientists. The resultant transconjugant strain (5076-IC) manifests both S. sonnei and S. typhi antigens; it appeared safe, stable, and protected volunteers effectively against challenge with S. sonnei. However, the variability in the efficacy of different vaccine lots has delayed the initiation of field trials; further studies to determine the reasons for the variability are in progress.

More recently, the 140 Mdal plasmid of S. flexneri 2a that encodes proteins necessary for epithelial cell invasion has been transferred into E. coli K-12, together with the chromosomal genes encoding the group and type-specific O-antigens of S. flexneri 2a. The resultant hybrid E. coli expresses smooth S. flexneri 2a O-antigen and invades epithelial cells, but does not cause fluid secretion in ligated segments of rabbit intestine. This vaccine is both safe and protective in monkeys. In volunteers, the vaccine causes reactions in doses of 10^9 CFU, but not in lower doses of 5×10^6-10^7. Efficacy studies of the lower dose given twice are under way. If successful, analogous E. coli K-12 strains expressing O antigens of S. flexneri 1a and 3a, S. sonnei, and S. dysenteriae 1 have been prepared for studies in volunteers. Such vaccines, when combined into one multivalent preparation, protect monkeys as well as does a monovalent preparation.

As noted above, it is likely that only one, or at most a few Shigella antigens, such as the O-antigen, specific outer membrane proteins, and perhaps a Shiga toxoid, may be required to evoke protection. It may be feasible to construct a series of hybrid plasmids encoding these antigens which could be inserted into selective antigen delivery systems, such as E. coli K-12, attenuated Vibrio cholerae, or auxotrophic mutants of Salmonella typhi. Further research will be required, however, to define the requirements for efficient expression of these antigens in an optimally immunogenic form.

Romanian investigators have developed an attenuated oral vaccine, named strain T32-Istrati, by serially passing Shigella flexneri 2a 32 times on 2% nutrient agar. This vaccine was genetically stable, avirulent in animals and man, and was 87% effective in protecting over 36,000 Romanian children and adults housed in institutional settings against bacteriologically confirmed dysentery. Its efficacy in the field has also been proven in China. The immunoprophylactic effect was equally good against homologous and heterologous species, such as S. sonnei and others. The vaccine was given 5 times over 2 weeks for full effect, but even one dose afforded 37% protection lasting 6 months. Biannual revaccinations were necessary to maintain full immunity. Attempts are underway to obtain this vaccine and confirm these excellent results in the West.

Vibrio cholerae. The search for a better cholera vaccine has been stimulated by studies in volunteers demonstrating that natural infection is followed by solid long-lasting immunity. The goal is to design safe oral vaccines, either killed or attenuated, that can provide 90-100% protection for several years after one dose, or after a closely spaced series of doses. Oral immunization, rather than parenteral immunization, is more likely to stimulate the protective intestinal immune response of secretory IgA antibodies, and live organisms are likely to stimulate a more effective mucosal memory response.

The oral vaccines currently under development are of two classes: 1) inactivated V. cholerae strains combined with altered toxin or purified toxin subunits which do not cause reactions, and 2) attenuated V. cholerae strains, genetically engineered to be deletion mutants or auxotrophic mutants, and hybrid vaccine strains such as E. coli K-12, S. typhi Ty21a, or auxotrophic Salmonella, genetically engineered to carry and express selected virulence genes of V. cholerae. Studies of inactivated vaccines have focused on products combining whole vibrios with either glutaraldehyde-treated toxin, heat-aggregated toxin (procholeragenoid) or the purified B-subunit pentamer of the toxin that binds to the intestine. In a small number of volunteers the protective efficacy of these vaccines was disappointing, ranging from 27% to 67%. Nevertheless, AID sponsored a field trial in Bangladesh of a combined oral B subunit plus killed whole cell vaccine. Preliminary results indicated that the combined vaccine gave 85% protection against cholera for at least 4-6 months, while the whole cell vaccine gave 58% protection. The trial is designed to determine the duration of protection. Other formulations that may be more practical are also under study.

The first live vaccine strain of V. cholerae to be tested in volunteers was prepared by nitrosoguanidine mutagenesis. This strain, Texas Star-SR, produced ample amounts of the nontoxic, antigenic B subunit portion of the toxin molecule, but only very small quantities of the toxic A subunit portion that was activated. Although Texas Star-SR colonized the small bowel and induced antitoxin or vibriocidal antibody responses in 85% of volunteers, it provided only 61% efficacy against diarrhea caused by V. cholerae challenge

and caused mild diarrhea in 24% of vaccinees. Encouraged by these results, investigators attenuated pathogenic V. cholerae by specifically removing genes encoding all other antigens, such as lipopolysaccharide, outer membrane proteins and colonization factors likely to be involved in immunity. This method is free of the disadvantages of nitrosoguanidine mutagenesis, which involves the induction of uncontrolled and unwanted mutations and the theoretical risk of reversion to toxigenicity.

Several strains of V. cholerae with precise genetic lesions have been constructed by DNA recombinant techniques and tested in volunteers. The JBK 70 strain has no cholera toxin genes (A minus, B minus). In the CVD 101 strain, the toxic A subunit gene was deleted while the immunogenic, but nontoxic, B subunit gene was retained and expressed (A minus, B plus). Of a small number of volunteers fed strain JBK 70, 90% were protected against severe illness. Some volunteers, however, developed low-grade diarrhea after vaccination, an occurrence which led to the discovery that strains JBK 70 and CVD 101 each produce one or more toxins different from cholera toxin. The existence of these other toxins in V. cholerae was not previously known. One is a Shiga-like toxin. Attempts are underway to characterize, clone and then remove the gene or genes for these new toxin(s) from these attenuated vaccines in hopes of rendering them less virulent but still protective.

A promising vaccine candidate, CVD 103, an A minus, B plus derivative of a V. cholerae classical Inaba strain, does not produce the Shiga-like toxin found in other cholera vaccine strains. CVD 103 induced mild diarrhea in only 12% of volunteers, significantly less than that produced by other attenuated vaccine strains. A single oral dose of CVD 103 induced vibriocidal and antitoxin antibodies in 95% of volunteers, and afforded 87% protective efficacy against the virulent parent strain and 67-78% efficacy against virulent El Tor and Ogawa strains. It protected against severe, purging diarrhea for as long as 11 months after vaccination. This live, oral vaccine candidate is being developed for field trials overseas.

New auxotrophic mutants of V. cholerae are also being developed. CVD 102, a thymine-dependent derivative of CVD 101, was fed to volunteers; but it colonized poorly and failed to stimulate potent vibriocidal antibody responses. Observations to date in volunteers challenged with attenuated V. cholerae vaccine strains suggest that retaining the ability to colonize the small intestine leaves the strain inherently capable of inducing reactions, while impeding the strain's ability to colonize reduces its immunogenicity. In response to this dilemma, hybrid strains of harmless, non-vibrio enteric bacterial vectors are being engineered to carry genes encoding for the antigens responsible for V. cholerae colonization and other outer membrane virulence antigens in an attempt to attain immunogenicity without unacceptable reaction rates.

Leprosy. A number of Mycobacterium leprae-specific antigens have been identified and purified by NIAID-supported investigators. These natural and semi-synthetic antigens have been shown to be useful for the serodiagnosis of both symptomatic and asymptomatic leprosy.

NIAID-supported investigators have purified a complicated lipoarabinomannan (LAM-B), a major cell wall immunogen from M. leprae. These investigators have also stripped the leprosy bacillus of mycolic acids, lipids, carbohydrates, etc., leaving the cell wall skeleton (CWS). Preliminary information indicates that LAM-B and CWS are powerful immunogens and may be an ultimate source of protective immunity against M. leprae infection.

The World Health Organization (WHO), along with AID, is presently funding the testing of two M. leprae vaccines. A vaccine composed of heat-killed M. leprae and live BCG cells has been tested for activity and safety in Venezuela. The second vaccine is composed of heat-killed M. leprae cells only. It has been tested in the U.S. for adverse reactions, dosage level and activity (skin test reaction). These preliminary tests are now completed, and a trial of the vaccines will be carried out in India. It will be a number of years before their effectiveness can be determined.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Assistant Secretary
for Health
Washington DC 20201

JUL 21 1989

The Honorable Dan Quayle
President of the Senate
Washington, D.C. 20510

Dear Mr. President:

The enclosed report is submitted to you in accordance with Subtitle 1 of Title XXI of the Public Health Service Act, as enacted by Title III of P.L. 99-660, the National Childhood Vaccine Injury Act of 1986, as amended by both P.L. 100-203 and P.L. 100-360.

This report provides information on the implementation of the National Vaccine Program, and discusses the activities planned for Fiscal Year 1989 that are related to the long-term goals of the National Vaccine Plan.

This second report was prepared in consultation with the National Vaccine Advisory Committee, which held its first three meetings in 1988.

Sincerely,

James O. Mason

James O. Mason, M.D., Dr.P.H.
Assistant Secretary for Health,
and Director, National Vaccine Program

Enclosure

OFFICIAL COMMUNICATION
RECEIVED IN THE OFFICE OF
THE PRESIDENT OF THE SENATE
DATE RECEIVED JUL 24 1989
TIME RECEIVED
DATE DELIVERED

NATIONAL VACCINE PLAN

SECOND REPORT TO THE CONGRESS

MAY 1989

Prepared by the National Vaccine Program
U.S. Public Health Service
Department of Health and Human Services

EXECUTIVE SUMMARY

This Second Annual Report on the implementation of the National Vaccine Program (NVP) and the development of an associated long-range National Vaccine Plan, as required under Subtitle 1 of Title XXI of the Public Health Service Act, provides a summary of the efforts of the NVP's first full year of operation in developing a comprehensive Plan and describes the progress of ongoing program activities. This document was prepared by the NVP in consultation with the National Vaccine Advisory Committee. This report covers the eight major areas addressed in the first report and describes the major activities planned for Fiscal Year 1989 within each of these areas.

Responsibilities of the NVP under Subtitle 2 (National Vaccine Injury Compensation Program) of Title XXI call for a variety of specific activities relating to patient/parent notification, reporting of adverse events associated with immunization, and special studies to be carried out. These activities are also described in this report. Many of these activities are currently underway and are being carried out with existing resources.

The report does not attempt to assess the appropriate mix of private and public sector involvement required to achieve National vaccine goals.

This report does not deal specifically with development of a vaccine for AIDS. A summary of AIDS vaccine development is being prepared at the NIH by the National Institute of Allergy and Infectious Diseases (NIAID). Its completion is scheduled for later this year.

1989 NATIONAL VACCINE REPORT TO CONGRESS
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I. BACKGROUND/INTRODUCTION

Subtitle 1 of Title XXI of the Public Health Service Act, enacted by P.L. 99-660, (Appendix 1) as amended by both P.L. 100-203 and P.L. 100-360 establishes a National Vaccine Program (NVP) and calls for the development of a National Vaccine Plan, which is to be submitted to Congress. Subsequent annual reports to Congress serve to update the plan. The Assistant Secretary for Health (ASH) was appointed Director of the NVP. To implement the NVP, the National Vaccine Program Office (NVPO) was created in September 1987 in the Office of the Assistant Secretary for Health, staff were selected, and an NVP Interagency Group (IAG) was created. In addition, the National Vaccine Advisory Committee (NVAC) called for by the legislation was chartered and members were appointed on April 1, 1988.

This document, which is an update of the first vaccine report submitted to the Congress in April 1988, describes 1988 activities of the NVP as well as progress toward the development of a long-term comprehensive National Vaccine Plan. It is clear from the legislation as well as statements by congressional staff that wide input was intended in development of the Plan, particularly from the National Vaccine Advisory Committee. Since being formed, the Committee has held three meetings and has made the development of the Plan its highest priority. Submission of the complete long-term comprehensive National Vaccine Plan to the Congress is projected for early 1990. Consequently, this Report should be read as indicating the major items to be addressed during Fiscal Year 1989 by the National Vaccine Program, one of which is to develop a definitive National Vaccine Plan.

Subtitle 2 of Title XXI, establishing a National Vaccine Injury Compensation Program (NVICP), and related provisions of law mandate a variety of specific activities relating to patient/parent notification, reporting of adverse events associated with vaccination, and special studies to be carried out. Implementation of Subtitle 2 will alter the sections in the 1989 Report dealing with these three issues. The magnitude of the changes is indicated later in the Report. In October 1988, Dr. Otis R. Bowen, Secretary of Health and Human Services, assigned responsibility for Subtitle 2 compensation activities to the Health Resources and Services Administration (HRSA), a Public Health Service (PHS) agency. As a result the National Vaccine Injury Compensation Program Office (NVICPO) was established in HRSA's Bureau of Health Professions.

II. UPDATE OF THE NATIONAL VACCINE PROGRAM 1988 REPORT TO CONGRESS

During Fiscal Year 1988, many NVP activities were directed toward achieving the eight long-term goals enunciated in the 1988 Report: improving coordination of vaccine research, development, use and evaluation; assuring an adequate supply of vaccines; assessing benefits and risks of vaccines and assuring public and practitioner awareness of the benefits and risks; assuring adequate regulatory capacity to evaluate vaccines; improving surveillance of adverse events; establishing research priorities; promoting rapid development and introduction of improved pertussis vaccines; and assuring optimal immunization levels in all target and high risk groups.

This report will give a brief description of the activities to date in these eight areas.

A. IMPROVING COORDINATION OF VACCINE RESEARCH, DEVELOPMENT, USE, AND EVALUATION

AIDS vaccine development is being coordinated by the AIDS Vaccine Research and Development subgroup of the PHS Executive Task Force on AIDS. The NVP collaborates with this subgroup but primarily directs its efforts at non-AIDS vaccines.

The Third Report to Congress in Child Survival by the Agency for International Development (AID), presented to Congress March 1988, summarized the activities and achievements globally against vaccine preventable diseases.

1. Formation and Functioning of the National Vaccine Advisory Committee

Section 2105 of the law requires the establishment of the NVAC and appointment by the NVP Director of members in consultation with the National Academy of Sciences. See Section III. A. of this Report for a description of NVAC activities.

2. Develop a Comprehensive Long-Term National Vaccine Plan

Section 2103 of the law requires the NVP Director to develop a plan to implement NVP responsibilities that cover (a) vaccine research on means to induce human immunity against naturally occurring infectious diseases and to prevent adverse reactions to vaccines; (b) vaccine development, including the techniques needed to produce safe and effective vaccines; (c) safety and efficacy testing of vaccines; (d) licensing of vaccine manufacturers and vaccines by providing for the allocation of resources to support the licensing program; (e) production and procurement of vaccines to ensure that the governmental and nongovernmental production and procurement of safe and effective

vaccines meet the needs of the United States population and fulfill commitments of the United States to prevent human infectious diseases in other countries; (f) distribution and use of vaccines, by providing direction to the Centers for Disease Control and assistance to States, localities, and health practitioners in the distribution and use of vaccines, including efforts to encourage public acceptance of immunizations and to make health practitioners and the public aware of potential adverse reactions and contraindications to vaccines; (g) evaluating the need for and the effectiveness and adverse effects of vaccines and immunization activities; (h) coordination of governmental and nongovernmental activities; and, (i) allocation of supplemental resources to Federal agencies involved in the implementation of the plan for activities not otherwise funded.

See Section III. A. below for information about the development of a long-range National Vaccine Plan.

3. Continue Functioning of the NVP Interagency Group

The IAG, the principal mechanism for coordinating the government-wide implementation of the NVP legislation, held 14 meetings in 1988: January 6, January 27, February 2, February 24, March 8, March 22, April 13, May 17, July 6, August 3, September 7, October 4, November 10 and December 6.

Topics addressed in these meetings included: improving pertussis vaccines, implementation of Subtitle 2 requirements, preparation for NVAC meetings, and preparation of the National Vaccine Plan, among others.

4. Continue Liaison With Other Advisory Groups

Liaison continues with CDC's Immunization Practices Advisory Committee (ACIP), the PHS AIDS Vaccine Research and Development Subgroup and the WHO Executive Board Programme Committee and World Health Assembly.

Various PHS and AID staff continue to participate in meetings of the Committee on Infectious Diseases of the American Academy of Pediatrics, the Task Force on Adult Immunization of the American College of Physicians, the National Advisory Committee on Immunization of Canada, the World Health Organization's (WHO) Expanded Program on Immunization Global and Technical Advisory Group meetings, the Who Scientific Advisory Group of experts on Vaccine Development (SAGE), Technical Advisory Group of the WHO Control for Diarrheal Disease Programme, the Joint Coordinating Board of the World Bank, United Nations Development Programme, WHO-Sponsored Tropical Disease Research Programme (TDR), the Advisory bodies

of the International Center for Diarrheal Disease
- Research in Bangladesh, WHO Technical Advisory Groups, WHO Expert Committees, and International Tripartite meetings including the FDA equivalents of the U.S., Canada and the United Kingdom.

5. Continue Promotion of Dialogue on Vaccine Policies

At the request of the ACIP, and under the sponsorship of the NVP, the Institute of Medicine (IOM) of the National Academy of Sciences in January 1988 convened an expert committee to evaluate polio vaccine policies in the United States. IOM recommendations include: (1) No change in present policy at this time (primary reliance on OPV with enhanced potency IPV as an acceptable alternative and absolute preference for enhanced potency IPV in immunocompromised individuals and families with members who are immunocompromised); and (2) When enhanced potency IPV combined with DTP is licensed, consideration of a regimen of two or more doses of the combined DTP/IPV followed by DTP and OPV at 18 months and at the time of elementary school entry. An ACIP subcommittee reviewed the IOM material and reported to the ACIP at its fall meeting. The ACIP accepted the IOM Report and agreed with its basic recommendations. The IOM Report is included as Appendix 2.

A workshop on the Status of Acellular Pertussis Vaccine and Swedish Trial Update was held in February 1988. See Section II. G. 1. below.

A workshop was held in September 1988 to assess the progress with alternative measles vaccine strains for use in immunization of infants at less than nine months of age. AID has established a Consultative Group on Vaccine Development with liaison members from WHO and HHS to review its vaccine portfolio policies and directions.

6. Meet With Individual Manufacturers, Researchers, Public Health Agencies, etc.

The 22nd National Immunization Conference was held in San Antonio, Texas in June 1988. Meetings and lecturers involved the participation of more than 400 public health professionals from national, State and local health facilities involved or interested in childhood and adult immunization.

The 1988 Meeting of the WHO Expanded Program for Immunization (EPI) Global Advisory Group (GAG) met in October 1988 in Abidjan, Ivory Coast. The PAHO Polio Eradication Technical Advisory Group met in Buenos Aires in November 1988. The WHO Technical Advisory Group in Diarrheal Disease Research met in March 1988. The WHO EPI Research Advisory Group met in October 1988. PHS staff were present at each of these meetings.

FDA has consulted with its Vaccine and Related Biologic Products Advisory Committee (VRBPAC) and ad hoc consultants frequently to discuss relevant issues related to the safety and efficacy of new vaccines.

7. Complete a Survey to Inventory Current Vaccine Research

In April 1988 the NVP asked academic, industrial and governmental organizations, known to be interested in biomedical research to develop new and improve existing vaccines, for information about current and projected levels of vaccine research activity. The NVP received more than 80 responses. This baseline profile of research activity will assist the NVP to monitor current vaccine research and development efforts and, in consultation with the National Vaccine Advisory Committee, develop priorities to achieve national goals and describe an optimal use of resources to conduct priority activities. A tabulation of the responses is included as Appendix 3.

8. International Efforts

a. Support for Polio Eradication - PAHO set the goal of elimination of polio from the Americas in 1986. Confirmed cases of polio have fallen to 395 at the end of 1988. In 1988, the World Health Assembly passed a resolution to eradicate polio globally by the year 2000. A global plan was reviewed at the EPI GAG in October 1988. CDC and AID are supporting this effort with technical assistance and resources.

b. Declaration of Measles Elimination from the English-speaking Caribbean - In 1988, the PAHO member States from the English speaking Caribbean established the goal of measles elimination by 1995.

c. Global Immunization Progress - Immunization services were virtually nonexistent in developing countries in 1974. Today, sixty percent of the world's children have received Bacillus Calmette-Guerin (BCG) by their first birthday; sixty percent have received DTP III; sixty-one percent, Polio III; and fifty-five percent measles.

During 1988, HHS and AID signed an agreement with the government of India to undertake a Vaccine Action Program as part of the US-INDIA Science and Technology Initiative. The program supports collaborative vaccine research in both countries directed at the problems of developing countries. AID continued its support for the International Centre for Diarrheal Disease Research in Bangladesh, including oral cholera vaccine trials.

B. ASSURING AN ADEQUATE SUPPLY OF VACCINES

1. Purchase Additional Vaccines for Stockpile

The table below summarizes the status of the stockpile by antigen and by number of weeks' supply at the end of Fiscal Year 1988 and projected for Fiscal Year 1989.

VACCINE	SUPPLY	
	1988	1989
DTP	15.2 weeks	17.0 weeks
MMR	20.8 weeks	20.8 weeks
OPV	20.5 weeks	20.5 weeks
IPV	16.6 weeks	16.6 weeks
DT	20.8 weeks	20.8 weeks
Td	20.8 weeks	20.8 weeks

2. Determine Whether Other Vaccines Should be Included in the Stockpile

Other vaccines which might be considered included for inclusion are Haemophilus influenzae type b vaccines, pneumococcal polysaccharide vaccine and hepatitis B vaccine. Although CDC contracts have permitted States to purchase pneumococcal vaccine for the past two years fewer than 25,000 doses have been purchased for the target population. Hepatitis B vaccines are not available via CDC contracts; however, the vaccine is readily available from the single licensed manufacturer. Influenza vaccine, although widely used, is not amenable to the stockpile approach since its composition changes each year. These issues will be brought to the NVAC for consideration.

3. Develop Approaches to Ensure Supply of Vaccines of Limited Use

The NVAC has begun discussions on this subject.

4. Consider Longer-Term Approaches to Assuring Adequate Supplies

The implementation of the National Childhood Vaccine Injury Compensation Act of 1986, as amended, may encourage additional manufacturers to enter the market. The NVAC has begun discussions on this subject.

C. ASSESSING BENEFITS AND RISKS OF VACCINES AND ASSURING PUBLIC AND PRACTITIONER AWARENESS OF THE BENEFITS AND RISKS

1. Continue Assessing the Benefits and Risks of Immunization

a. Continue the review of preclinical and clinical data submitted as part of investigational new drug (IND) or license applications.

FDA review of preclinical and clinical data (including pre and post marketing data) continues and relevant actions are taken.

b. Maintain and improve national and international surveillance systems for major vaccine-preventable diseases.

Surveillance activities this year included three field investigations of measles outbreaks, involving students at a public four-year college in Durango, Colorado; Amish communities in Lawrence, Indiana; Lebanon County, Pennsylvania; and unvaccinated preschool children and infants in Los Angeles.

A cluster of several cases of flaccid paralysis with onset during August 1987 was investigated. Results indicate that the causative agent was enterovirus 71. This is considered an important investigation since cases had clinical symptoms possibly compatible with paralytic poliomyelitis.

An outbreak of pertussis in Arizona, primarily located in Maricopa County, was investigated. Emphasis was placed on a case-control study looking at risk factors for pertussis and associated knowledge, practices and attitudes related to vaccine usage and disease.

Standardized case definitions for vaccine-preventable diseases were accepted by the Council of State and Territorial Epidemiologists. Standardized definitions, when implemented by the States, will improve the quality of reporting.

Consultation was provided in October 1988 to the Government of Israel during an outbreak of poliomyelitis. The investigations offered the opportunity to evaluate the impact of polio vaccine in preventing disease and impeding spread of wild virus to susceptible individuals.

FDA participated with CDC in monitoring the performance of licensed childhood vaccines in field use conditions. In these collaborative investigations, FDA performed specialized laboratory tests contributing to the elucidation of vaccine efficacy in instances of disease outbreaks in vaccinated high school and college student populations.

CDC is working with developing countries through the Field Epidemiology Training Program to increase epidemiological skills in those countries.

AID is working with 12 African countries to develop surveillance and health information and response capacity through the "Combating Childhood Communicable Diseases/Acute Respiratory Infection" project.

c. Develop and use tools which may facilitate diagnosis of illnesses such as pertussis, pneumococcal pneumonia, etc.

FDA continues to evaluate the ELISA methodology for use in diagnosis of pertussis. Studies have been initiated in cloning an antigen which may be useful in the serodiagnosis of pneumococcal disease, i.e., pneumolysin.

In the viral diagnostic area, FDA is also extensively involved in studies evaluating the significance and correlation of standard antibody methodologies (e.g., hemagglutination inhibition and virus neutralization) to newer assay methods such as the ELISA techniques. If validated, the newer techniques, which are more efficient and faster, can replace the older, more cumbersome assays, and be used in epidemiology or vaccine performance studies. These ongoing studies include measles, mumps, rubella and polio viruses.

The NIH continues to support research to develop new and improved diagnostic capabilities for all infectious disease agents. Academic, corporate, and intramural research scientists are involved. Small Business Innovative Research (SBIR) funding is a new resource for work of this nature. Monoclonal antibodies, ELISAs, rDNA probes, and polymerase chain reactions are new techniques being applied. This year a new specific effort was funded to develop diagnostic reagents for enteric viral pathogens.

AID is working to develop rapid diagnostic tests for both epidemiological and clinical use. Studies include emphasis on polio, acute respiratory infection, malaria, diarrheal disease and typhoid. AID has also supported investigation of the epidemiology and etiology of acute respiratory infection in 12 countries through the National Academy of Sciences.

d. Maintain, improve, and establish surveillance systems for adverse events following immunization.

FDA's spontaneous reporting system continues to receive and review adverse reaction reports for vaccines submitted by the private sector, manufacturers and other sources. CDC's Monitoring System for Adverse Events Following Immunization (MSAEFI) receives and reviews reports from the public sector.

FDA and CDC continue to evaluate adverse reaction reports received via the spontaneous reporting system following administration of the Haemophilus b polysaccharide and conjugate vaccines. Reports of disease temporally following immunization resulted in extensive evaluation and additional studies of the Haemophilus b polysaccharide vaccines. Studies have been initiated to monitor events following licensure of the Haemophilus b conjugate vaccines. Post licensure studies to evaluate safety of the polysaccharide vaccines are being conducted by the manufacturers.

CDC's Adverse Events Following Immunization Surveillance Report No. 3 is scheduled for distribution in the second quarter of FY 1989. A survey of opinions of State adverse event personnel concerning MSAEFI and cost was conducted by questionnaire. Analysis is underway.

Contact has been made with other organizations having large linked data bases to determine the practicality of evaluating various events temporally and possibly causally related to vaccination. See also Section III. D. 3. c.

e. Maintain, improve and establish surveillance systems for specific events following the administration of certain vaccines.

Case records of all suspected cases of paralytic poliomyelitis reported with onset during 1987 were evaluated by expert consultants. As a result, five cases of paralytic poliomyelitis, all related to the vaccine, are being officially reported for 1987.

An alternative classification system for cases of paralytic poliomyelitis has been developed. It is based on laboratory and epidemiologic criteria and provides more detailed breakdown of cases and is made possible by improvements in laboratory methods particularly in molecular virology. A manuscript describing the new classification has been accepted by the American Journal of Public Health.

FDA maintains a contract to monitor the possible association between measles immunization and subacute sclerosing panencephalitis (SSPE).

f. Identify other data bases which may be useful in estimating the incidence and severity of vaccine-preventable diseases in the U.S. and abroad. Alternative surveillance for tetanus was undertaken, using National Center for Health Statistics (NCHS) mortality data and State mortality records and case reports. Initial results indicate underreporting of deaths both to the NCHS and the standard CDC morbidity reporting system. This suggests underreporting of tetanus cases to States and to CDC. Further analysis is underway and a paper is being prepared for publication.

AID is continuing its program of demographic and health surveys in developing countries including assessment of immunization status of children and women.

g. Conduct basic, applied, and operational research in the U.S. and elsewhere.

CDC staff participated in the evaluation of the immunization programs and other components of primary health care in Pakistan and Lesotho. CDC also participated in epidemiologic and operational studies and evaluations in several countries in Africa. In addition, AID sponsored CDC and Johns Hopkins University participation in studies in Mexico and Haiti evaluating Edmonston-Zagreb measles vaccine in 6-month-old children.

FDA was another participant in the collaborative study in Mexico providing overall laboratory support utilizing a highly sensitive antibody measurement test (plaque reduction neutralization test, PRNT). In addition, FDA served as the reference laboratory for measuring the potency of measles vaccine used in six independent studies on measles immunization in developing countries, sponsored under the aegis of the WHO.

NIAID staff has assessed emergency room patient utilization of and interest in vaccination. A significant proportion of resistance to use of influenza and pneumococcal vaccines in targeted populations comes from the practicing physician rather than the patient. Furthermore, a substantial proportion of appropriate patients who are offered pneumococcal vaccine in an emergency room setting are ready to accept it.

As an extension of a previous study in Baltimore, FDA participated in a challenge study to determine intestinal immunity following the use of oral poliovirus vaccine or the enhanced potency inactivated poliovirus vaccine. FDA performed serologic assays and conducted an analysis of data from the study.

Basic and applied research on vaccine preventable diseases and vaccines under development is a major effort in FDA biologics laboratories. Special emphasis is given to research involving analysis of the molecular basis of attenuation of the Sabin poliovirus strains with the intent to develop strains of poliovirus devoid of neurotropic potential.

Various laboratories in FDA serve in many capacities as reference laboratories for WHO and PAHO programs. For example, FDA is a reference laboratory for PAHO for the control of yellow fever vaccines produced in the Americas, as well as rabies, diphtheria and tetanus toxoid. FDA also serves as the WHO Collaborating Center for Research on Pertussis Vaccines.

Ongoing research activities are required to ensure the availability of influenza virus vaccines appropriate to the epidemiology of disease. FDA laboratories analyze the antigenicity of new influenza viral isolates collected world wide, and prepare appropriate reagents against these isolates for distribution to manufacturers and other reference and national control laboratories. This research is conducted to provide the most relevant viral antigens for inclusion into vaccines prepared for the upcoming influenza season.

AID is sponsoring research to investigate the optimal formulation of oral polio vaccine. A vaccine efficacy trial of the currently licenced pneumococcal vaccine is being supported in the Gambia to assess its impact on infant mortality secondary to pneumococcal pneumonia. Rotavirus vaccine research is underway in Bangladesh and Venezuela, and low dose hepatitis vaccine research is underway in Baltimore, Maryland. The AID-sponsored new typhoid Vi vaccine has been conjugated and is to be investigated. The oral whole cell with B sub-unit cholera vaccine is to complete its fourth year of efficacy trial in Bangladesh. AID is also sponsoring the development of non-reusable, disposable syringes for use in international immunization programs to reduce the potential risk of the transmission of AIDS during immunization. Indication devices to monitor the cold chain and adequate sterilization are being field tested.

2. Improve Practitioner Awareness

a. Publish information and surveillance summaries in Morbidity and Mortality Weekly Reports and the FDA Drug Bulletin and elsewhere.

Requirements for recording and reporting as described under the Act were published in the MMWR and FDA Drug Bulletin and subsequently in several medical publications. A copy of the requirements was sent to all State Immunization Project Directors, Immunization Public Health Advisors, MSAEFI Coordinators, State and Territorial Epidemiologists and State and Territorial Health Officers.

Nine articles were published in the Morbidity and Mortality Weekly Report including: "ACIP Recommendations for Haemophilus Influenzae Type b Disease;" "Measles in the United States First 26 Weeks 1987;" "ACIP Recommendations for Immunization of Children Infected with HIV;" "Requirements for Permanent Vaccination Records and for Reporting of Selected Events After Vaccination;" "Paralytic Poliomyelitis--Senegal, 1986-1987; Update on the N-IPV Efficacy Study;" "Measles--United States, 1987;" "Mumps in the Workplace--Chicago;" "Progress Toward Achieving the National 1990 Objectives for Immunization;" and "Poliomyelitis--Israel."

Health Information for International Travel, 1988 is now available and being distributed.

AID is working with practitioners through its health communication project in developing countries to increase their awareness of vaccine preventable diseases and to facilitate the incorporation of immunization in their routine practices.

AID is also supporting the American Medical Association for pilot projects with local medical associations in Indonesia and Thailand to involve private practitioners in the delivery of immunization and other child survival services.

b. Update manufacturer's package inserts when indicated. See Section III. C. 3.

Manufacturers' vaccine products package inserts are reviewed for consistency with ACIP recommendations or with Important Information Sheets if one has been prepared for the vaccine addressed by the package insert.

For those vaccine products covered by the National Vaccine Injury Compensation Program (D,T,P,M,M,R, OPV, or IPV, either singly or in combination), package inserts are being reviewed and will be revised consistent with the procedures required by the Act. In addition to publication in the Federal Register, procedures will include discussion with the Advisory Commission on Childhood Vaccines as well as the National Vaccine Advisory Committee.

c. Present surveillance and other data at scientific meetings.

CDC staff presented a review of pertussis cases and epidemiology for 1982-1986 at the Pertussis Symposium, East Berlin, April 1988; at the fourth International Symposium on Pertussis, Copenhagen, September 1988; and at the Interscience Conference on Antimicrobial Agents and Chemotherapy in Los Angeles, October 1988.

Immunization recommendations for international travellers were presented at the International Symposium on Travellers Health, Zurich in May 1988 by CDC staff. Symposium proceedings are to be published.

Preliminary results from the Edmonston-Zagreb measles vaccine trial were presented at the September 1988 Alternative Measles Vaccines Workshop in Washington, D.C.

AID presented progress with global immunization programs at the American Public Health Association Meeting in October 1988 and at the Annual Meeting of the National Council for International Health in May 1988.

d. Continue to work with various advisory groups.

See Section II. A. 4. above.

e. Prepare, update, and distribute "Important Information Statements."

Work proceeds on development of the new Information Statements required by the National Childhood Vaccine Injury Act of 1986, as amended. See Section III. D. 3. a. for more details. These Statements will, among all other things, explain the risks and benefits of those vaccines covered by the National Vaccine Injury Compensation Program. The Vaccine Information Statements are to be given to every person to whom any health care provider intends to administer a covered vaccine. Three draft Statements have been prepared for OPV/IPV, DTP, and MMR. When the review process is completed, draft copies of the proposed vaccine information statements will be

published in the Federal Register. This will begin a 90-day period during which written comments about the vaccine materials are invited from health care providers, parents organizations, and other interested parties. Also a public hearing will be held at CDC approximately 30 days after the publication in the Federal Register.

During 1988, Important Information Statements for DTP, MMR, and Rubella were revised, printed, and distributed to the immunization projects in camera-ready format. For the first time a separate Statement was developed which deals specifically with Td vaccine. A new statement for the Haemophilus influenza b Conjugate vaccine was developed and distributed. The annual influenza statement was revised to reflect changes appropriate for the 1988-1989 flu season and was supplied to immunization projects and to participating HCFA influenza demonstration projects. Camera-ready copy of Chinese, French, Spanish, and Vietnamese translations of the DTP, MMR, and Haemophilus influenzae conjugate statements will be made available to the States.

f. Coordinate various vaccine-preventable disease-related educational programs with private and public organizations.

Five 3-day courses and one 5-day course on Epidemiology, Prevention, and Control of Vaccine Preventable Diseases were conducted in selected locations in the United States.

g. Conduct knowledge, attitudes, and practices survey of health care providers and of the public.

See Section H. 7. below.

The Communication for Child Survival Project conducted "Knowledge-Attitude-Practice" surveys in developing countries with AID support as part of its efforts to promote maternal and child immunization.

h. Prepare prototype educational materials of primary-care physicians and other providers.

Adult immunization materials developed under contract with Abt Associates have been edited, formatted, and duplicated. These materials include a slide presentation which is accompanied by an audiocassette for use with lay and professional audiences. An additional audiocassette provides current information about hepatitis B disease and vaccine use. The packet of material contains a variety of pamphlets in camera ready form and other material including two video tapes discussing adult immunization themes. The "Arm with the Facts" kit was distributed during the fourth quarter of 1988 to immunization programs and other interested parties to provide information and updated material to physicians and the lay public.

An adult immunization slide set of 134 slides has been compiled. It illustrates disease impact, missed opportunities, vaccine usage, and profiles of high risk individuals. The slide set was distributed during the fourth quarter of 1988 to State immunization programs and selected groups for use in making presentations to lay and professional audiences.

i. Prepare prototype manuals for vaccination programs in hospitals, HMOs, and other outpatient settings.

"Immunization Recommendations for Health Care Professionals" has been distributed to immunization projects and other organizations.

3. Improve Public Awareness

a. Prepare and distribute lay publications.

To replenish CDC's exhausted supply of the "Parents Guide to Childhood Immunization," the 1985 Guide was revised and an additional 40,000 copies printed. Each immunization project received 250 printed copies of the Parents Guide and camera-ready copy for their printing needs.

"Questions and Answers Regarding Pertussis and Pertussis Vaccine" continues to be CDC's most frequent mail out when responding to requests for information about the risks and benefits of pertussis immunization.

"A Call to Action" is the adult immunization booklet CDC most frequently supplied in both printed and camera-ready form.

Follow up information on children who were studied in the FDA-sponsored UCLA study of adverse reactions to DTP vaccine was summarized in FDA Consumer Reports, September, 1988.

b. Promote the use of patient education materials and attempt simplification of the "Important Information Statements."

CDC has worked with the American Academy of Pediatrics, Lederle Laboratories, Connaught Laboratories, and Mead Johnson in having these health related organizations include the Important Information Statement material in the AAP Redbook and other physician education publications. The CDC Immunization Division also mails camera-ready copy of the Statements to physicians on request.

c. AID has increased lay awareness of the benefits of immunization internationally by supporting intensive educational and promotional efforts through the Communication for Child Survival project, bilateral projects and support of private voluntary organizations.

D. ASSURING ADEQUATE REGULATORY CAPACITY TO EVALUATE VACCINES

1. Continue to Review Existing INDs and License Applications, Perform Control Tests, Inspect, Perform Research, Prepare Regulations, and Monitor Adverse Reactions

FDA continues to receive increasing numbers of applications for investigational studies of vaccines (INDs) as well as new product licenses or amendments to licenses for vaccines. New complex technological processes are being used in many of these applications requiring specialized skills in the review. Control activities such as testing, inspections, and monitoring reports of adverse reactions continue.

AID is sponsoring development of an FDA equivalent with the Government of India to enhance the capacity to evaluate new drugs and biologicals, perform controlled testing and ensure quality controls.

2. Assure Prompt Evaluation of New Vaccines

Resources necessary to enable the prompt evaluation of vaccine applications, including monies, staff, and facilities are being identified. Efforts are being made to maintain adequate staffing consistent with the increasing regulatory responsibilities. The Center for Biologics Evaluation and Review (CBER) has expanded its laboratory facilities related to the evaluation of new pertussis vaccines. See Section G. below.

3. Assure Continuation of the Necessary Research Base

The existence of a strong scientific capability to enhance regulatory responsibilities is essential to expedite the review process. Reviewers involved in the vaccine application approval process must have a close familiarity with many scientific disciplines. This is best accomplished by having an active and broad laboratory based research program. FDA's Center for Biologics Evaluation and Review (CBER) has intensified recruitment of scientists to maintain adequate staffing to keep pace with scientific developments and an expanding workload. Research conducted by CBER scientists is made available by publication or presentation at scientific meetings, and is used in FDA regulatory programs.

FDA has been involved in a number of research studies evaluating ways to replace tests in animals by in vitro assays in areas of vaccine control, safety and potency assessment. This research is directed at developing more economical and quantitative assay methods, while at the same time alleviating public concerns about the extensive use of animals in vaccine research and control.

Such studies have been completed for yellow fever vaccine and are in use by the FDA, other national control authorities and by the manufacturers.

Studies to replace the rabies vaccine potency assay (in mice) and the inactivated poliovirus potency assay (in primates) with in vitro methods are under development.

4. Complete the Reorganization of the Center for Biologics Evaluation and Research

The new structure for CBER was published in the Federal Register in March 1988. Selection of staff and training for various scientific programs continues. The reorganization of the Division of Virology has allowed staff to focus on viral vaccines and related manufacturing and safety issues. Other types of immunological agents are now the responsibility of a new Division of Cytokine Biology.

5. Continue Discussion Through Appropriate Channels for New Laboratory Facilities as Requested in the President's Fiscal Year 1989 Budget Request

FDA's FY 1989 request for funding of a new laboratory facility on the NIH campus has been approved by Congress and signed by the President. Monies for construction have been appropriated. Activities related to the planning and construction of the new building are now underway.

E. IMPROVING SURVEILLANCE OF ADVERSE EVENTS

1. Improve Reporting of Adverse Events

a. Information concerning recording and reporting of information as required by the National Childhood Vaccine Injury Act was published in the MMWR and distributed to the entire MMWR mailing list. A section on NVP reporting requirements has been included in each Vaccine Preventable Diseases course.

Reporting has also been stimulated by publication of the mandatory reporting requirements in the FDA Drug Bulletin, and by articles reprinted in the Journal of the American Medical Association.

b. A memorandum from the Director of CDC's Center for Prevention Services and a preprint of the MMWR article were provided to Immunization Project Directors, Immunization Public Health Advisers, MSAEFI Coordinators, State and Territorial Epidemiologists, State and Territorial Health Officers, and Regional Offices. Ongoing consultation is provided to these health officials on interpretation of recording and reporting requirements.

c. Reporting requirements were discussed with all Immunization Project Directors and staff attending the National Immunization Conference in San Antonio in June 1988.

d. CDC's Adverse Events Following Immunization Surveillance Report No. 3 (1985-1986) is scheduled for distribution in the second quarter of FY 1989.

2. Improve Adverse Events Surveillance System

a. CDC surveyed State MSAEFI Coordinators to elicit opinions on the current reporting system, suggestions for improvements, methods to increase reporting, and costs of MSAEFI. Analysis of this information is underway.

b. FDA/CDC cooperation continues. Discussions have taken place between FDA and CDC concerning a single adverse event reporting system to be developed and operated under contract. See Section III. C. 3. c. for further details.

c. The enhanced potency IPV is available to providers. Post-marketing surveillance by FDA and CDC for serious adverse events is continuing.

3. Implement the National Childhood Vaccine Injury Act

This has been completed. See Section III. C for more details.

4. Investigate Additional Approaches for Adverse Event Surveillance

See 5. below.

5. Examine Specific Research Questions

IOM is scheduled to review National Childhood Encephalopathy Study (NCES) data concerning residual neurologic illness following pertussis vaccine in early 1989.

CDC/Vanderbilt Cooperative Studies

A CDC contract to review a Medicaid data base to examine the relationship between neurologic illnesses and vaccination with DTP and measles vaccines is being successfully completed. This effort is also supported in part through an FDA cooperative agreement. Events of interest in the Medicaid population have been identified from 1978 through 1984 and are being linked with immunization histories. Data collection on inpatient events of interest has been completed and work on outpatient events is continuing. A separate study on SIDS and vaccination in this population has been completed and published. Additional funds have been made available to extend the work on vaccine-related adverse events.

Study of Neurologic Illness in Childhood (SONIC)

This study to assess the feasibility of repeating and improving upon the National Childhood Encephalopathy Study (NCES) has progressed satisfactorily. The CDC contract to the University of Washington was awarded in late 1986 and the study began officially in August 1987 after several months of preparation. Surveillance for acute neurologic events and interviews of cases and controls was completed July 31, 1988. Additional funds have been obtained to complete feasibility evaluations, including an assessment of the completeness of reporting from different sources and a survey of immunization coverage in the population. Because the number of cases detected is larger than originally anticipated, the study could provide a sample size large enough to provide additional evidence on the relationship between some acute neurologic events (including febrile seizures lasting 15 minutes or longer and non-febrile seizures) and DTP vaccination.

FDA/Boston Collaborative Study

As part of the FDA cooperative agreement with the Boston Collaborative Drug Surveillance Project, an analysis of data concerning neurological events following DTP vaccine was performed and has been reported (Walker et al, Pediatrics, 1988, 81:345-349).

F. ESTABLISHING RESEARCH PRIORITIES

1. Current Situation

Since the first report to Congress was submitted, research on new vaccines has continued along the lines reported previously. With the efforts to develop an improved vaccine for pertussis and one for AIDS (noted in the first report), the research program continues to conform to the needs and opportunities outlined in the 1985 IOM report, Vaccine Supply and Innovation.

2. Activities During FY 1988 (Excluding AIDS)

a. Reevaluate or Reassess the Institute of Medicine Priorities for Vaccine Research

A reevaluation of the IOM study of vaccine research priorities by NIAID staff suggested the list was reasonably current in identifying priorities based on estimates of the burden of diseases. However, if recent scientific advances in several areas were incorporated in the model, priorities could be slightly rearranged.

An abbreviated version of the IOM study is under consideration in which the disease burden estimates generated previously would be matched to new scientific knowledge.

As directed by the National Vaccine Act, NIAID is negotiating an agreement with the IOM to conduct a literature search on certain adverse reactions associated with whole cell pertussis vaccine and other specified vaccines.

AID continued its support for the International Centre for Diarrheal Disease Research in Bangladesh, including oral cholera vaccine trials.

b. Continue Emphasis on the Development of Improved, Acellular Pertussis Vaccines

The results of the Swedish trial of two acellular pertussis vaccines showed that the acellular vaccines protect against pertussis but at levels currently thought to be less than desired. Also, results of tests of sera collected in the trial have failed to establish serological correlates,

although all analytical avenues have not yet been exhausted. Interagency cooperation through the NVP Interagency Pertussis Subcommittee continues to drive plans for additional field trials of newer candidate acellular vaccines. The new trials will provide a direct comparison of acellular and whole cell vaccines.

c. Continue Emphasis on the Development of Improved Vaccines to Prevent Disease Caused by Haemophilus Influenzae Type B

The clinical trial in Alaska of one conjugated Hemophilus influenzae type b (Hib) vaccine produced results which were significantly less encouraging than trials of similar vaccines elsewhere. Investigators are comparing the immunogenicity of all available Hib conjugates to determine if the problem is with the vaccine used in the trial or the immune response of the Alaskan native population to the vaccine. Invasive disease caused by Hib continues to be the most serious infectious disease in that population in terms of mortality and serious morbidity, and development of an effective vaccine continues to be a high priority for the Indian Health Service as well as other PHS agencies.

d. Stimulate Basic and Clinical Research on Targeted Vaccines

The vaccine research portfolio of NIAID continues to respond to the priorities identified in the IOM report and to needs and opportunities identified since that report was issued.

AID has established a Consultative Group on Vaccine Development to review its vaccine portfolio, policies and directions in light of the IOM recommendations on priorities for vaccine research for developing countries.

The vaccine research portfolio of AID is based on the IOM report, part II, addressing the needs of developing countries. These priorities have been reviewed by the Agency's Research Advisory Committee and are to be presented to the newly established Consultative Group on Vaccine Development established to oversee the Agency's vaccine portfolio.

e. Stimulate Basic and Clinical Research on Other Important Vaccines

See d) above.

f. Establish Liaison With Members of the Pharmaceutical Industry

FDA continues its close interactions with individual pharmaceutical companies, domestic and international, in their research and development, licensing and post-licensure marketing programs. In addition, FDA has maintained its close interaction with the industry associations.

NIAID staff maintains close contacts with individual vaccine manufacturers. Government and industry scientists work closely in the clinical evaluation of candidate vaccines. This includes performing trials in NIAID contract funded Vaccine Evaluation Units, whose capabilities include testing inactivated and live, attenuated vaccine candidates in all age groups.

g. Complete a Survey to Inventory Current Vaccine Research

An update of the NIAID report on Accelerated Vaccine Development and the AID report on vaccine development are underway. Also, see Section II. C. 7. above.

G. PROMOTING RAPID DEVELOPMENT AND INTRODUCTION OF IMPROVED PERTUSSIS VACCINES

1. Analyze and Present the Clinical Results from the Swedish Trial

The main analysis from the AID sponsored Swedish trial is completed and the results were published in The Lancet on April 30, 1988. The results have been presented to vaccine advisory bodies such as the ACIP and the Committee on Infectious Diseases of the American Academy of Pediatrics (Redbook Committee), and two major meetings have been held (in Stockholm in December 1987 and in Bethesda in 1988) to disseminate the results to the scientific and lay communities in the U.S. and abroad. The transcript of the Bethesda meeting has recently been published. The data generated by the study were of the highest quality.

The major issue remaining is the interpretation of these data. The trial did not include a direct comparison of the acellular pertussis vaccines with the whole cell pertussis vaccine.

2. Test Blood Specimens from Sweden and Correlate Results With Clinical Findings

Serologic results from the Swedish trial have been obtained and presented in the report of the trial in The Lancet. Plans to repeat some of the original serologic work are progressing. An FDA laboratory scientist is scheduled to visit Stockholm to make final testing arrangements.

3. Continue IND Reviews and License Application Evaluations on New Candidate Vaccines

See II. D.

As pertussis vaccine applications arrive at the FDA, they are processed as expeditiously as possible. Samples of products provided by the manufacturer to be considered for clinical use are evaluated in FDA laboratories.

4. Carry Out Clinical Studies of Candidate Vaccines in NIAID Vaccine Evaluation Centers

At present, acellular pertussis vaccines are undergoing clinical evaluation at Vanderbilt and Marshall Universities. At least four other acellular pertussis vaccines have been proposed for evaluation within NIH Vaccine Evaluation Units (VEU). Two of these vaccines contain only the lymphocytosis promoting factor (LPF), similar to the content of one of the vaccines tested in Sweden. The other vaccines contain combinations of LPF, agglutinogens and/or fimbrial hemagglutinin. The clinical studies in the VEU's are being performed in both infants and children for safety and immunogenicity. Another candidate vaccine is currently being tested for safety and immunogenicity in infants on a large scale basis outside of NIH.

5. Assess Feasibility of a Large Scale Safety and Efficacy Trial in the U.S.

Such studies would be expensive and of long duration because of the large number of subjects needed and the low incidence of disease and are therefore not felt to be feasible at this time.

6. Standardize Serologic Tests for Pertussis

The Pertussis Laboratory at the FDA has initiated efforts to carry out this work. The lab has prepared standard pertussis sera which can be made available to other labs for the purpose of comparing lab results. Reagents and methods have been exchanged with Swedish investigators as well as with other investigators and manufacturers. FDA and Swedish serologists have collaborated extensively, including visits to each other's laboratories for closer analysis of methodology.

7. Complete Evaluation of New Diagnostic Tests for Pertussis

New diagnostic tests for pertussis have been developed under CDC contract, including DNA probes and assays to measure secretory IgA and adenylate cyclase in nasal secretions. The sensitivity and specificity of these new tests are being evaluated and the expectation is that these new tests will provide greater sensitivity than is currently possible using culture alone. Further field testing is currently underway. FDA and CDC have collaborated in studies to evaluate serological (ELISA) methods for the diagnosis of disease.

8. Complete Pilot Study of Neurologic Illness in Children

See Section E. 5. above.

9. Continue Intramural Research on Pertussis at FDA, NIH and CDC

Ongoing intramural research activities at FDA focus on the identification and characterization of pertussis antigens which might be included in new vaccines. This research includes the development of procedures for purification of antigens, development of laboratory models to study pathogenesis and disease prevention, and procedures to evaluate the immune response. The tools of molecular biology and hybridoma technologies are being used in these studies. NIH sponsors research designed to make use of recombinant DNA techniques to develop and produce antigens suitable for new vaccines. NIH scientists have initiated Phase I studies with a Pertussis toxoid. CDC and FDA laboratories have been involved in the development and evaluation of improved serologic techniques for pertussis.

H. ASSURING OPTIMAL IMMUNIZATION LEVELS IN ALL HIGH RISK AND TARGET GROUPS

1. Assess Appropriate Mix of Private and Public Sector Involvement to Achieve Optimal Immunization Levels in High Risk and Target Groups

The efforts of the public and private sector to cooperate in the area of childhood immunization range from the use of volunteers in clinic settings to the long standing ties with national organizations. Informal cooperative ventures include the use of hospital auxiliary members and volunteers, together with State and local health staff, who are experienced in the distribution of educational materials in the form of pamphlets and videotape presentations to mothers of newborns and to the parents of elementary and day care students who volunteer to review the immunization status of their children.

More formal involvement with national organizations includes educational efforts and follow up of high risk infants by such groups as the Junior Chamber of Commerce, the American Red Cross, the American Lung Association, and the March of Dimes for specific efforts related to adult immunization. See 3 below.

Internationally, AID is continuing its efforts to expand the capacity of non-governmental organizations and the private sector in the provision of immunization services.

2. Revise Adult Immunization Action Plan

The Division of Immunization, CDC, inaugurated a review of the current adult action plan in conjunction with CDC's Training and Laboratory Program Office in January of 1988. The review process involves the identification of a series of program performance problems which currently face the nation in the area of adult immunization. These problems are then discussed and categorized based on the perceptions of the management group.

After the problems and their perceived causes are enumerated, an action plan is developed to address each of the problems outlined. A summary of the action steps is now being collected. The revised plan will be reviewed by CDC immunization grantees in FY 1989. A separate plan is under development to eliminate Hepatitis B by the year 2015.

3. Form an Ad Hoc Committee to Promote Information and Education on the Need for Adult Immunization

In January 1988, the Centers for Disease Control, the American Public Health Association, and the National Foundation for Infectious Disease hosted a workshop to outline a combined public and private sector initiative to further the goals of adult immunization in the United States. Further meetings took place during the spring of 1988 which involved representatives of the original three organizations as well as representatives from the American College of Physicians and the American Association of Retired Persons. The meetings resulted in the formation of the National Coalition for Adult Immunization, an informal group of more than 50 organizations and individuals with the common aim of improving the immunization status of adults through the conduct of informational and educational campaigns.

4. Implement Cooperative Agreement for Studying Health Maintenance Organizations

Five HMOs are currently conducting retrospective reviews of their adult ($\geq$ 15 years) members to: determine vaccine coverage with the seven adult antigens; and measure the impact of morbidity and mortality on utilization of services and costs in vaccinated and unvaccinated populations. The results of these studies were presented at the Medical Issues and Data Conference of the American Medical Care and Review Association in January 1989.

The major problems encountered in the study are (1) difficulty in determining vaccination status in outpatient populations, especially in the IPA (Individual Practice Association) model HMO; and (2) cross-referencing vaccination status with disease diagnoses for either inpatients or outpatients.

CDC hopes to develop methods to measure these indicators and views the immunization study as a prototype for evaluation of other HMO cost containment and quality assurance programs.

AID has provided technical assistance in Indonesia to develop and strengthen an HMO to improve health care delivery services. Feasibility studies have also been carried out in several countries including the Philippines.

5. Distribute and Promote Use of Adult Immunization Materials

See Section C. 2. h. above.

National Adult Immunization Awareness Week was held during the last week of October. A press conference was held on October 24, 1988, in conjunction with the Interscience Conference on Antimicrobial Agents and Chemotherapy to promote the activity.

6. Monitor Activities Outlined in Program Grant Guidelines

The May 1987 revision in program guidelines allows immunization project grantees to expand their role to include promotion of adult and additional childhood immunizations through education as a part of grant supported activities. Many areas have developed approaches that could be used by other immunization programs around the nation to assist in the promotion of adult and childhood immunization.

These new programs and activities are summarized on a quarterly basis and shared with other State and local projects through the "Vaccine Preventable Disease Highlights" and by exchange of ideas during program site visits. The elimination of indigenous rubella in the United States was also added as an overall program goal and efforts to achieve this and monitor progress will be continued.

7. Conduct Surveys to Establish Baseline Data

The Hawaii State Department of Health and the CDC have completed plans to conduct a survey of physicians in Hawaii to obtain information concerning physicians' knowledge, attitudes, and vaccine usage in the adult population focusing on influenza and pneumococcal vaccines.

Appropriate methods to establish baseline data in certain areas including size of target population, immunization coverage, and vaccine usage in public and private sectors will be necessary. Studies will be designed that will measure knowledge, attitudes, and practices in nursing homes, hospitals and selected physicians' practices.

Many immunization projects are conducting surveys of hospitals and nursing homes to gather this information. Statewide surveys of nursing homes are evaluating the use of a manual "Managing an Influenza Vaccination Program in the Nursing Home."

Responses have been received from 24 out of 63 projects. In summary, 60 percent of the licensed nursing homes responded. The estimated median vaccine coverage rate for patients in 1987-88 was 83.1 percent. The policy for 74 percent of the nursing homes was to offer influenza vaccine to all residents. Ninety-five percent of the respondents indicated the manual "Managing an Influenza Vaccination Program in the Nursing Home" had not changed their existing influenza immunization policies.

Influenza and pneumococcal vaccine uptake baseline data for adults will be collected using the NCHS Health Interview Survey (HIS) methodology during FY 1989. Discussions concerning the feasibility of including childhood immunization questions on future HIS questionnaires are continuing.

Many projects are now using school and day care immunization records to conduct retrospective immunization level surveys.

AID has conducted numerous baseline and "Knowledge-Attitude-Practice" surveys under the HEALTHCOM Project to improve our understanding of existing immunization and other child survival practices and to develop more effective communications messages to target audiences.

8. Develop and Implement Appropriate Strategies to Improve Immunization Levels in High Risk Groups

Currently underway is the development of profiles on 15 counties that have reported at least five measles cases every year for the past three years or reported more than 50 preschool measles cases over the three year period with more than 30 percent of total cases occurring in the preschool-age group. CDC hopes to identify common factors that contribute to the continuation of measles in these counties and develop better prevention strategies.

Under authority of the Public Health Service Act allowing use of up to 10 percent of grant funding for research purposes, up to $1 million will be made available in Fiscal Year 1989 for cooperative agreements for Immunization Demonstration projects in the areas of immunization assessment and intervention, with special emphasis on inner-city high risk areas.

Ten demonstration grant awards have been made by CDC, in collaboration with the Health Care Financing Administration (HCFA), to test the cost effectiveness of furnishing influenza vaccine under the Medicare program. The first report to Congress is due October 1, 1990. If after two years the coverage under Medicare is cost effective, the demonstration stops and coverage under Medicare becomes effective November 1, 1990. If the coverage under Medicare is not cost-effective or the results are inconclusive, demonstrations continue for another 24 months, or until October 1, 1992. If, at that time, the coverage under Medicare is cost-effective, coverage becomes effective the first day of the first month after the final report is submitted. If found to be cost-effective, 29 million Part B Medicare beneficiaries will be covered. Internationally, AID, through its focus on immunization within its Child Survival Action Program, has sought to identify the reasons for low immunization coverage. Specific attention in A.I.D-supported immunization programs is being given to "missed opportunities", i.e., times when mothers and their infants visit health facilities but are not being immunized. Studies in Peru and Bangladesh are identifying high risk infants and children to target for immunization and other child survival services.

9. Distribute Automated Patient Recall Systems

An automated data system has been developed under contract to assist clinics in patient recall and program management. If costs of the Immunization Control and Evaluation (ICE) system can be reduced, it will be considered for installation in three additional project sites over the next year. Subsequent installations will depend on the successful installation, operation, and maintenance of the program in the four test sites. If successful, ICE should allow programs to assess levels of coverage in preschool populations and assist providers in tracking and follow-up of those shown to be delinquent in immunizations.

10. Review Effectiveness of Preschool Efforts

Preliminary data evaluating the effectiveness of current efforts to vaccinate preschool children including immunization education programs directed at mothers of newborns and active recall systems in public clinics were presented at the National Immunization Conference in June 1988 in San Antonio, Texas.

A new reporting format for vaccine administered in the public sector was approved by the Office of Management and Budget (OMB) and implemented in January 1988. This new format allows better determination of vaccine coverage, age-appropriate administration of vaccine, and estimates of coverage levels in specific age groups. These evaluations will be shared with State and local projects.

11. Convene a National Immunization Conference

The 22nd National Immunization Conference was held June 20-24, 1988. The theme of the Conference stressed the issues, problems, and proposals for improving vaccine coverage in both preschool and adult populations. Almost 400 persons from all 50 states and the District of Columbia participated.

III. UPDATE OF NATIONAL VACCINE PROGRAM (NVP) ACTIVITIES IN 1988

A. FORMATION AND FUNCTIONING OF THE NATIONAL VACCINE ADVISORY COMMITTEE (NVAC)

Since submission of the first National Vaccine Report to the Congress, the National Vaccine Advisory Committee (NVAC) has been established. After consultation with the Institute of Medicine (as called for by the legislation), members were appointed to the NVAC for staggered terms beginning April 1, 1988. The Committee has held three meetings--June 9-10, 1988, September 18-19, 1988, and December 13-14, 1988. Membership on the Committee as well as minutes of the meetings are included as Appendix 4.

The first NVAC meeting, held June 9-10, 1988, focused on presentation by NVAC liaison members of vaccine activities conducted by the agencies coordinated by the NVP: Agency for International Development (AID), Centers for Disease Control (CDC), Department of Defense (DOD), Food and Drug Administration (FDA) and

National Institutes of Health (NIH). The NVAC also discussed the history of public and congressional interest in vaccine research, supply, production and liability; the allocation of resources for the NVP to conduct vaccine activities; defining the NVAC's role and structure; developing strategies to identify vaccine issues; program definition and identification of issues for future NVAC discussions; and stimulation of public and private entities to support immunization as a model for disease prevention.

The second NVAC meeting was held September 19-20, 1988. The National Vaccine Program Interagency Group liaison members presented their recommendations of essential NVP tasks/activities to be included in a long-range, comprehensive National Vaccine Plan, and an analysis of problem areas perceived to be impeding agency work in completing the Plan tasks. Several documents addressing national vaccine policy issues were provided to Committee members.

The Committee decided on seven areas representing the major elements of the National Vaccine Plan. These were: 1) Resources and Funding; 2) Improving Existing Vaccines; 3) Adverse Events; 4) Vaccine Utilization; 5) Vaccine Supply; 6) Vaccine Licensing; and 7) Development of New Vaccines. The NVAC believes that improving existing vaccines and adverse events are overlapping issues. The members felt that the first three issues should receive immediate attention. In addition, it was felt important to draft a Mission Statement for the NVAC and an overall National Vaccine Policy Statement which would serve as the basis for developing the Plan. Committee members formed subgroups to address the development of a vaccine policy statement; the development of a NVAC mission statement; resources and funding; and improving existing vaccines and adverse events.

Under the resources and funding category, the following major subheadings were identified: vaccine supplies; third party payment for immunizations; the excise tax; the role of competition; and domestic and international differences in vaccine prices. Under the category of improving existing vaccines, the following subheadings are being addressed: vaccine field trials; efficacy and safety issues; the limitations of the vaccine market; stimulation of resource development; combination and conjugate vaccines; improvements in the public and private sectors on basic research and development of vaccines as well as the application of new research technologies; and improving public support of vaccine development.

The third NVAC meeting was held December 13-14, 1988. The NVAC discussed and adopted the NVAC Mission Statement and the National Vaccine Policy Statement (Appendixes 5 and 6). The Subgroup on Improving Existing Vaccines met and discussed draft outlines. In connection with the concerns of the two subgroups regarding resources needed to implement NVP activities, the NVAC drafted a letter to Dr. Windom to serve as an end of the year report to the NVP Director. A copy of the letter and Dr. Windom's response to it are included as Appendix 7.

B. NVP INTERAGENCY GROUP (IAG) AND PERTUSSIS SUBCOMMITTEE

In early January, 1988, the NVP IAG and Pertussis Subgroup received draft conclusions and recommendations from the pertussis meeting held in Stockholm in December 1987, and the manuscripts on the Pertussis vaccine trials conducted in Sweden. In addition, the NVP sponsored a pertussis workshop at NIH in February of 1988. The proceedings of the NIH meeting are included as Appendix 8.

Due to the lack of conclusive data on efficacy and the absence of serological correlates of immunity in the Swedish Pertussis Vaccine trial, the IAG and the Pertussis Subcommittee recommended additional clinical trials to compare the efficacy of acellular pertussis vaccines with that of a current whole cell pertussis vaccine. Several countries in Europe--Denmark, Germany, Italy, Sweden, the United Kingdom--and Asia--Japan, Taiwan and Thailand--were identified as potential sites to conduct these trials. The NVP provided resources to allow NVP IAG members from CDC, FDA and NIH to visit potential sites in Denmark, Germany, Italy, Japan, Sweden and the United Kingdom. The NVP also supported a visit to Washington by the Director General of the Ministry of Health of Thailand and representatives of the Children's Hospital of Thailand to discuss with the IAG the possibility of conducting a pertussis vaccine trial in Thailand. The NVP will be providing additional resources for travel by NVP IAG representatives to other countries that may be potential candidates for conducting pertussis vaccine trials.

C. DEVELOPMENT OF YEAR 2000 PREVENTION OBJECTIVES

NVP staff and IAG members participated in the development of Prevention Objectives for the Year 2000 in the area of Immunization and Infectious Diseases.

The NVP Coordinator co-chaired the PHS working group which drafted the objectives. These draft objectives are currently being reviewed by a large panel of expert reviewers outside the PHS and will be modified appropriately before being made available for public comment and final revision. The final objectives will be published in 1990.

D. IMPLEMENTATION OF THE NATIONAL VACCINE INJURY COMPENSATION PROGRAM

1. Formation of the National Vaccine Injury Compensation Office

In October 1988, the Bureau of Health Professions in the Health Resources and Services Administration (HRSA), a component agency of the Public Health Service, was assigned functional responsibility for administering those portions of the National Vaccine Injury Compensation Program (NVICP) concerned with the processing and review of petitions for compensation and advising the Secretary regarding proposed awards. Included in HRSA's responsibilities is oversight of operations of the Advisory Commission on Childhood Vaccines (ACCV). Before formation of the NVICP office, NVP staff prepared letter responses and direct answers to the public on questions about vaccine injury compensation matters and disseminated materials developed by the U.S. Claims Court to persons seeking information about procedures for filing petitions for vaccine injury compensation. The NVP assisted HRSA in its assumption of responsibilities for the new program functions. In addition, NVP and CDC staff briefed HRSA and Department of Justice staff about NVP activities and information about the status of vaccine injury research results.

2. Formation of the Advisory Commission on Childhood Vaccines (ACCV)

The National Vaccine Program Office assisted in the formation of the Advisory Commission on Childhood Vaccines in the following ways: ACCV Charter development; development of Federal Register notices establishing the Commission and seeking nominations for membership on the Commission; preparation of more than 50 letters to professional and public interest organizations, parent groups, vaccine manufacturers and government entities seeking nominations for membership on the Commission; and response to public inquiries about the ACCV functions and membership requirements. The NVICP then took over the task of preparing and submitting to the Secretary a slate of nominees for the Advisory Commission on Childhood Vaccines. The NVP and the NVICP will continue to work closely together.

3. Noncompensation Aspects of the Compensation Program

Responsibility for noncompensation activities described in parts B and C of Subtitle 2 of Title XXI remain with the NVP. These include improvements in licensing, manufacturing, processing, testing, labeling, warning, use instructions, distribution, storage, administration, field surveillance, adverse reaction reporting, vaccine recall, and research in order to reduce the risks of adverse reactions to vaccines.

a. Vaccine Information Statements

The Notice of Proposed Rulemaking of the Vaccine Information Statements required by the National Childhood Vaccine Injury Act is now under final development and review. These Statements will explain the risks and benefits of vaccines covered by the National Vaccine Injury Compensation Program. The Vaccine Information Statements are to be given to every person to whom any health care provider intends to administer a covered

vaccine. Three draft statements have been prepared: Oral Poliovirus and Inactivated Poliovirus (OPV/IPV); Diphtheria, Tetanus, Pertussis (DTP); and Measles, Mumps and Rubella (MMR) vaccines. The proposed vaccine information statements will be published in the Federal Register. This begins a 90-day period during which written comments about the vaccine materials are invited from health care providers, parents organizations, and other interested parties. A public hearing will be held at CDC approximately 30 days after publication in the Federal Register.

b. Reporting Requirements

The law requires mandatory reporting to the Secretary of Health and Human Services of all adverse events associated with certain vaccines normally given to children. The public was formally advised in an April 1, 1988 Federal Register notice and the April 8, 1988 MMWR (included as Appendixes 9 and 10) that as of March 21, 1988, health care providers who administer the specified vaccines and toxoids are required to record permanently certain information and to report certain vaccine-related adverse events, specified in Section 2114 of the law. Providers were advised to direct their reports to either CDC or FDA, depending on whether vaccines were purchased with public or private funds. In addition, FDA provided the same information in the FDA drug bulletin (Appendix 11). Health care providers were also advised of this requirement through their professional journals.

c. Monitoring System for Adverse Events

CDC currently monitors adverse events associated with public sector vaccines and FDA monitors those associated with vaccines purchased with private sector funds.

CDC's currently operating Monitoring System for Adverse Events Following Immunization (MSAEFI) is a consumer-based, stimulated passive surveillance system for adverse events following administration of vaccines purchased with public funds. The system depends on a parent (informed through the information statement) making a connection between the immunization and the adverse event and getting that information to the health department. The event is then investigated and reported to CDC. Approximately 2,000 reports are received each year.

MSAEFI has a variety of objectives. One is to provide data on reporting trends and secular trends in adverse events reporting. The system also has the capacity for evaluating long-term followup of persons reported with adverse events. The system can identify areas for further epidemiologic investigation and research. Limitations of MSAEFI include underreporting, inaccuracies due to reporting and recording by non-medical personnel, the inclusion of events not causally related to immunization, simultaneous administration of multiple vaccine antigens, individual bias in recall, incorrect attribution by the recipient or parent of illness close to the date of vaccination and the lack of background rate data to assess causation.

FDA's spontaneous reporting system, SRS, collects adverse drug and biologic reaction reports and provides information for FDA's post-marketing surveillance of approved drugs and biologics. Since 1969, more than 400,000 reports of adverse reactions have been received and computerized. However, it has only been in the last five years that reports of adverse reactions to biologics have been incorporated into a unified adverse reaction system.

In 1987, of the approximately 54,000 reports received, six percent or approximately 3,500 were for biologics. Of these, 30 percent or approximately 1,000 were for NVP-covered products. Approximately 85 percent of biologic reports are received from the manufacturer rather than directly from health care professionals and consumers.

Data elements from each report are entered into the SRS computerized database after the reported reactions have been described using standardized terminology for later retrieval and analysis. Reports are evaluated for completeness of data elements, to determine whether the reactions were appropriately coded and to add any relevant information to the comments section which will help in assessing the report. Assessments are made as to which reports might warrant further followup based on items such as the severity of the reaction, resulting in hospitalization, disability, or death.

Adverse reaction monitoring provides a profile of the types of reactions that may be occurring to one biologic or a group of biologics. It can also provide information on patient risk factors which may be later investigated in more formal epidemiologic studies.

Limitations to adverse reaction monitoring include inadequate information for assessment, effect on data by other drugs or disease, under reporting, reporting biases and reporting unrepresentative of actual rates of occurrence.

CDC and FDA are currently developing a scope of work to contract for the development of a single system for reporting and evaluating adverse events. Issues associated with current efforts to move towards a single reporting system include determination of a timetable; resolution of differences of how data are collected under the current two systems; reporting criteria; forms design; how reporting will be promoted; routing of reporting; data analyses to be performed; data storage; and type and extent of followup.

d. Special Studies

To comply with sections 312 and 313 of the law, the NVP is to conduct reviews of published technical literature which describe the association between the use of childhood vaccines, especially pertussis and MMR, and certain specified illness and conditions and to study the broad risks associated with vaccines for which injuries are compensable under the law. The responsibility of overseeing this activity has been delegated to the NIH.

The law stipulates that the Institute of Medicine (IOM) be offered the opportunity to conduct the studies so that the most scientifically competent investigators are made available for this activity. The NVP is taking steps to begin this study.

e. Mandate for Safer Childhood Vaccines

To comply with Section 314 of the Act, FDA has been delegated the responsibility to review the warnings, use instructions, and precautionary information presently issued by manufacturers for the vaccines covered by the Compensation Program (diphtheria, measles, mumps, pertussis, poliomyelitis, rubella, tetanus, either singly or in combination) and to determine by rule whether such warnings are adequate. These activities are ongoing.

Section 2128 requires manufacturers to record and report certain information pertinent to the manufacture and control testing of the relevant vaccines. FDA has been delegated the responsibility to assure compliance with this Section; implementing procedures have been initiated.

IV. PLANNED NVP ACTIVITIES FOR 1989

During 1989, NVP activities will continue in the same areas as during 1988 with some modifications of emphasis.

A. IMPROVING COORDINATION OF VACCINE RESEARCH DEVELOPMENT, USE AND EVALUATION

Working with the NVAC, NVP staff and IAG members will complete the first National Vaccine Plan and submit it to the Director, NVP, by the end of calendar year 1989. The plan will be a major part of the 1990 Report to Congress.

The IAG (a list of members is included as Appendix 12) will continue to meet regularly and provide the primary vehicle for governmental activities of the NVP. During 1989 more emphasis will be placed on liaison with industry about general issues relating to vaccine development and manufacture. Close liaison currently exists on issues relating to specific vaccines.

B. ASSURING AN ADEQUATE SUPPLY OF VACCINES

Steps will continue to try to exempt vaccines in the vaccine stockpile from payment of the excise tax until they are sold/distributed for use. The number of doses added to the stockpile in 1989 will be dependent on the outcome of this activity.

Longer-term approaches to assuring adequate supplies will be addressed in the National Vaccine Plan.

FDA's control testing will continue to be performed concurrently with the manufacturers to expedite the release of vaccines where needed. FDA will continue to work closely with manufacturers when problems potentially affecting supply are identified.

C. ASSESSING BENEFITS AND RISKS OF VACCINES AND ASSURING PUBLIC AND PRACTITIONER AWARENESS OF THE BENEFITS AND RISKS

Surveillance systems for vaccine-preventable diseases will be maintained and improved where possible. Surveillance summaries will be published in MMWR and other publications.

The single system for monitoring adverse events following immunization will be implemented during calendar 1989. The vaccine information pamphlets required by PHS Act section 2126 will be completed and put into use.

Recommendations of advisory groups such as the Advisory Committee on Immunization Practices and the Committee on Infectious Diseases of the American Academy of Pediatrics will be published in MMWR and elsewhere. The "Arm with the Facts" kit on adult immunization will be put into widespread use.

D. ASSURING ADEQUATE REGULATORY CAPACITY TO EVALUATE VACCINES

Activities are ongoing to identify appropriate resources to enable the prompt evaluation of new and existing products. These activities include identifying monies, staff and facilities.

Plans for the new CBER laboratory facility will be developed during 1989 and construction will begin in 1990.

E. IMPROVING SURVEILLANCE OF ADVERSE EVENTS

See Section III C. 3. The SONIC will be completed in 1989 and decisions will be made about conducting a full-scale study. Collaborative studies will continue with Vanderbilt and other linked systems for post-marketing surveillance.

F. ESTABLISHING RESEARCH PRIORITIES

Current efforts will continue.

G. PROMOTING RAPID DEVELOPMENT AND INTRODUCTION OF IMPROVED PERTUSSIS VACCINES

Re-testing of serological samples from the Swedish pertussis vaccine field trial will be accomplished. One or more sites will be selected for additional field trials of comparative studies of whole cell pertussis and acellular pertussis vaccines. Development of standardized serologic tests and improved diagnostic tests will continue.

H. ASSURING OPTIMAL IMMUNIZATION LEVELS IN ALL HIGH RISK AND TARGET GROUPS

The National Vaccine Plan will address the appropriate mix of private and public sector involvement. The National Coalition for Adult Immunization will continue and expand its efforts. Demonstration efforts will be undertaken to develop improved approaches to assuring immunization of inner-city pre-school youngsters. A National Immunization Conference will be held in San Diego in June 1989.

GLOSSARY

AAFP	- American Academy of Family Physicians
AAP	- American Academy of Pediatrics
ACIP	- Immunization Practices Advisory Committee
ACP	- American College of Physicians
AFEB	- Armed Forces Epidemiological Board
AID	- Agency for International Development
AIDS	- Acquired Immunodeficiency Syndrome
AMCRA	- American Medical Care and Review Association
APHA	- American Public Health Association
ASH	- Assistant Secretary for Health
BCG	- Bacillus Calmette-Guerin
CBER	- Center for Biologics Evaluation and Research
CDC	- Centers for Disease Control
CMI	- Cell-Mediated Immunity
DHHS	- Department of Health and Human Services
DOD	- Department of Defense
DT	- Diphtheria and tetanus toxoids (pediatric formulation)
DTP	- Diphtheria and tetanus toxoids and pertussis vaccine
EPI	- Expanded Programme on Immunization
FDA	- Food and Drug Administration
FHA	- Filamentous hemagglutinin
GAG	- Global Advisory Group
GAO	- Government Accounting Office
HBPV	Haemophilus B polysaccharide vaccine
HRSA	- Health Resources and Services Administration
HMO	- Health Maintenance Organization
IAG	- National Vaccine Program Interagency Group
IIS	- Important Information Statements
IND	- Investigational New Drug
IOM	- Institute of Medicine
IPV	- Inactivated poliovirus vaccine
JE	- Japanese B encephalitis
LPF	- Lymphocytosis promoting factor
MMR	- Measles, mumps, and rubella virus vaccines (combined)
MMWR	- Morbidity and Mortality Weekly Reports
MSAEFI	Monitoring System for Adverse Events Following Immunization
NACI	- Canadian National Advisory Committee on Immunization
NAS	- National Academy of Sciences
NCDB	- National Center for Drugs and Biologics
NCHS	- National Center for Health Statistics
NIAID	- National Institute of Allergy and Infectious Diseases
NICHD	- National Institute of Child Health and Human Development
NIH	- National Institutes of Health
NVAC	- National Vaccine Advisory Committee
NVP	- National Vaccine Program
NVPO	- National Vaccine Program Office
NVICP	- National Vaccine Injury Compensation Program

NVICPO	- National Vaccine Injury Compensation Program Office
OBRR	- Office of Biologics Research and Review
OPV	- Oral poliovirus vaccine
OTA	- Office of Technology Assessment
PHS	- Public Health Service
PRP	- Polyribosylphosphate
PT	- Pertussis toxin
PTA	- Parent Teacher Association
rDNA	- Recombinant DNA (desoxyribonucleic acid)
RSV	- Respiratory Syncitial Virus
SIDS	- Sudden Infant Death Syndrome
SONIC	- Study of Neurologic Illness in Childhood
SRS	- Spontaneous Reporting System
Td	- Tetanus and diphtheria toxoids (adult formulation)
VAC	- National Vaccine Advisory Committee
VPD	- Vaccine-preventable diseases
VRBPAC	- Vaccines and Related Biologic Products Advisory Committee
WHO	- World Health Organization

NACCHO
National Association of County & City Health Officials
The National Connection for Local Public Health

March 5, 2019

The Honorable Lamar Alexander
Chairman
Committee on Health, Education, Labor and Pensions
United States Senate
Washington, DC 20510

The Honorable Patty Murray
Ranking Member
Committee on Health, Education, Labor and Pensions
United States Senate
Washington, DC 20510

Dear Chairman Alexander and Ranking Member Murray

On behalf of the National Association of County and City Health Officials (NACCHO), representing the nearly 3,000 local health departments across the country, I write to thank you for highlighting the importance of immunizations to keeping our communities healthy through the hearing entitled, "Vaccines Save Lives: What Is Driving Preventable Disease Outbreaks?" Local health departments are on the front lines responding to emerging health threats, including vaccine-preventable disease outbreaks.

Vaccines are a cost-effective tool for protecting children and adults against serious and potentially fatal diseases.[1] Vaccines have been proven to be safe and highly effective at reducing disease rates when public health recommendations are followed. Immunization has been one of the most successful public health measures available to populations worldwide, with an unparalleled record of disease reduction and prevention. This is not just an issue about children. Vaccines across the lifespan are important, life-saving measures, particularly in our efforts to protect those who are at-risk or most vulnerable to contracting a vaccine-preventable disease.

Local health departments are key participants in our nation's immunization infrastructure, with 90% of departments reporting that they participate in direct immunization efforts.[2] Beyond service delivery, local health departments also promote the importance of immunizations through education and policy, and they monitor, prevent, and control disease to reduce the health risks and financial burden of infectious disease cases and outbreaks. Local health departments also use community, provider, and school-based immunization coverage rates to assess and ensure protection against vaccine-preventable diseases.

However, there are real and perceived barriers to achieving optimal immunization rates to keep outbreaks at bay and our communities thriving. According to NACCHO's 2017 National Assessment of

[1] Centers for Disease Control and Prevention. (1999). Impact of vaccines universally recommended for children — United States, 1900–1998. MMWR, 48(12), 243–248.
[2] See NACCHO's 2018 Forces of Change Report, available at http://nacchoprofilestudy.org/forces-of-change/

Local Health Department Immunization Programs, over half of local health department respondents report vaccine hesitancy as a barrier to their immunization programs, with lack of vaccine education and confidence also noted as barriers.[3] Local health departments play a significant role in communicating with parents about the importance of vaccination, and often provide training to healthcare providers on how to strongly recommend vaccines, such as the human papillomavirus and influenza vaccines.

While vaccine hesitancy puts many at risk, it is not the only factor contributing to lower vaccination rates. The CDC recently released a study examining vaccination coverage for children age 19 to 35 months, which found that the percentage of children under two years of age who had not received any vaccination quadrupled during the last 17 years, with the lowest coverage among uninsured children and children living in rural areas. The researchers offered two reasons for this change: access and affordability. Some families believe they simply cannot afford to vaccinate their child. For others, there is no hospital, health department, medical center, or pediatrician close to home to facilitate access to them.

Unfortunately, while working to address these barriers, many local health departments are operating at a diminished capacity due to budget pressures on federal, state, and local governments. In the area of immunization, that means that there are fewer epidemiologists to track the spread of diseases and identify pockets of underserved areas within the community with lower vaccination coverage rates. There are also fewer nurses to staff immunization clinics, provide vaccines, and conduct outreach within communities. As several states and counties across the nation are currently experiencing outbreaks of vaccine-preventable disease, it is important that we continue promote vaccine confidence, while continuing to work to improve access and affordability.

Simply put: vaccines are the best defense against the threat of vaccine preventable diseases and play a vital role in protecting the health of communities. Immunization has been one of the most successful and safest public health measures available to populations worldwide, with an unparalleled record of disease reduction and prevention. The success of vaccines highlights the importance of continued vigilance in promoting vaccine confidence and access.

Given this evidence, NACCHO strongly urges all levels of government to collaborate with community stakeholders in addressing misinformation about vaccine safety and lack of accessibility to immunization services. We support strong immunization requirements to maintain high immunization rates and protect communities from vaccine-preventable diseases.[4] We call on the federal government to continue support for local efforts to protect people from disease through high rates of immunization.

Thank you again for raising the issue of vaccine-preventable disease amid the ongoing measles outbreaks and looks forward to working with Congress to address this problem. Please contact Adriane

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[3] See "Local Health Department Immunization Programs: Findings from a 2017 NACCHO Assessment," available at https://essentialelements.naccho.org/archives/10940

[4] See NACCHO's Policy Statement, "School and Child Care Immunization Requirements," available at https://www.naccho.org/uploads/downloadable-resources/16-01-School-and-Child-Care-Immunization-Requirements.pdf

Casalotti, MPH, MSW, NACCHO Chief of Government and Public Affairs at acasalotti@naccho.org or 202-507-4255 if you require additional information or have any questions.

Sincerely,

Lori Tremmel Freeman, MBA
Chief Executive Officer

[STATEMENT OF SENATOR CASEY]

Pennsylvania has worked hard to improve the percentage of toddlers up-to-date on their Measles, Mumps, and Rubella (MMR) vaccine from a recent low of 87 percent in 2012 to 93 percent in 2016. 1A[1] This seemingly small change is crucially important, as measles is the most contagious serious childhood infectious disease and population vaccination rates need to be 93 percent or higher to prevent community outbreaks.[2] Keeping measles vaccine rates high is also essential for populations that are especially vulnerable, such as children in their first year of life (as the first dose can't be given until age 1), people with immune system disorders, and people taking medications that suppress their normal immune functions. And measles is not the only vaccine-preventable disease that regularly causes harm. The United States experienced 13,439 confirmed cases of Pertussis ("whooping cough") in 2018, including, and 10 children died as a result.[3] Our health as a nation is dependent upon a robust system of immunization to keep us all healthy.

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[1] *https://www.health.pa.gov/topics/HealthStatistics/HealthyPeople/Documents/current/state/iid-7-4-measles-mumps-rubella-mmr-vaccination-coverage-level-children-19-to-35-months.aspx*

[2] *https://www.who.int/immunization/sage/meetings/2017/october/2.—target—immunity—levels—FUNK.pdf*

[3] *https://www.americashealthrankings.org/explore/annual/measure/pertussis/state/PA*

Recommendations for live viral and bacterial vaccines in immunodeficient patients and their close contacts

Medical Advisory Committee of the Immune Deficiency Foundation

***Principal authors*: William T. Shearer, MD, PhD,[a] and Thomas A. Fleisher, MD,[b]**
***Participating authors*: Rebecca H. Buckley, MD, Chair,[c] Zuhair Ballas, MD,[d] Mark Ballow, MD,[e] R. Michael Blaese, MD,[f] Francisco A. Bonilla, MD, PhD,[g] Mary Ellen Conley, MD,[h] Charlotte Cunningham-Rundles, MD, PhD,[i] Alexandra H. Filipovich, MD,[j] Ramsay Fuleihan, MD,[k] Erwin W. Gelfand, MD,[l] Vivian Hernandez-Trujillo, MD,[m] Steven M. Holland, MD,[n] Richard Hong, MD,[o] Howard M. Lederman, MD, PhD,[p] Harry L. Malech, MD,[n] Stephen Miles, MD,[q] Luigi D. Notarangelo, MD,[g] Hans D. Ochs, MD,[r] Jordan S. Orange, MD, PhD,[a] Jennifer M. Puck, MD,[s] John M. Routes, MD,[t] E. Richard Stiehm, MD,[u] Kathleen Sullivan, MD, PhD,[v] Troy Torgerson, MD, PhD,[r] and Jerry Winkelstein, MD[p]**

Houston and Shenandoah, Tex, Bethesda, Columbia, and Baltimore, Md, Durham, NC, Iowa City, Iowa, Buffalo and New York, NY, Boston, Mass, Memphis, Tenn, Cincinnati, Ohio, Denver, Colo, Miami, Fla, Shelburne, Vt, Seattle, Wash, San Francisco and Los Angeles, Calif, Milwaukee, Wis, and Philadelphia, Pa

The present uncertainty of which live viral or bacterial vaccines can be given to immunodeficient patients and the growing neglect of societal adherence to routine immunizations has prompted the Medical Advisory Committee of the Immune Deficiency Foundation to issue recommendations based on published literature and the collective experience of the committee members. These recommendations address the concern for immunodeficient patients acquiring infections from healthy subjects who have not been immunized or who are shedding live vaccine–derived viral or bacterial organisms. Such transmission of infectious agents can occur within the hospital, clinic, or home or at any public gathering. Collectively, we define this type of transmission as close-contact spread of infectious disease that is particularly relevant in patients with impaired immunity who might have an infection when exposed to subjects carrying vaccine-preventable infectious diseases or who have recently received a live vaccine. Immunodeficient patients who have received therapeutic hematopoietic stem transplantation are also at risk during the time when immune reconstitution is incomplete or while they are receiving immunosuppressive agents to prevent or treat graft-versus-host disease. This review recommends the general education of what

From [a]Baylor College of Medicine and Texas Children's Hospital, Houston; [b]National Institutes of Health Clinical Center, Bethesda; [c]Duke University School of Medicine, Durham; [d]University of Iowa and Iowa City Veterans Affairs Medical Center, Iowa City; [e]State University of New York, Children's Hospital of Buffalo; [f]Immune Deficiency Foundation, Columbia; [g]Boston Children's Hospital; [h]University of Tennessee Health Science Center and St Jude Children's Research Center, Memphis; [i]Mt Sinai Medical Center, New York; [j]Cincinnati Children's Hospital; [k]Ann & Robert H. Lurie Children's Hospital of Chicago; [l]National Jewish Health, Denver; [m]Miami Children's Hospital; [n]National Institute of Allergy and Infectious Diseases, Bethesda; [o]Private practice, Shelburne; [p]Johns Hopkins University School of Medicine, Baltimore; [q]All Seasons Allergy, Asthma & Immunology, Shenandoah; [r]Seattle Children's Hospital; [s]University of California San Francisco; [t]Children's Hospital of Wisconsin, Milwaukee; [u]UCLA School of Medicine, Los Angeles; and [v]Children's Hospital of Philadelphia.

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Corresponding author: William T. Shearer, MD, PhD, Department of Pediatrics and Immunology, Baylor College of Medicine, Allergy and Immunology Service, Texas Children's Hospital, 1102 Bates St, Suite 330, Houston, TX 77030-2399. E-mail: wtsheare@TexasChildrensHospital.org.

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is known about vaccine-preventable or vaccine-derived diseases being spread to immunodeficient patients at risk for close-contact spread of infection and describes the relative risks for a child with severe immunodeficiency. The review also recommends a balance between the need to protect vulnerable subjects and their social needs to integrate into society, attend school, and benefit from peer education. (J Allergy Clin Immunol 2014;133:961-6.)

Key words: *Live viral and bacterial vaccines, primary immunodeficiency disease, severe combined immunodeficiency disease, cellular immune reconstitution*

Discuss this article on the JACI Journal Club blog: www.jaci-online.blogspot.com.

Immunization with live viral or bacterial vaccines is a known hazard to patients with serious immunodeficiencies of T-cell, B-cell, and phagocytic cell origin. Although the risk of acquiring live vaccine–related disease by means of immunization might be well known to families of severely immunocompromised children, the concept of parents, relatives, or nonfamily members (who have not been immunized or who have been recently immunized with live vaccines) serving as a source of infection to an immunodeficient patient has not had sufficient attention. Succinct information on the risk of inadvertent spread of live or attenuated viral or bacterial infection can be found in the *Red Book: 2012 Report of the Committee on Infectious Diseases* section on immunocompromised children,[1] and the previous recommendations of the Centers for Disease Control and Prevention.[2] Recommendations are made for the 4 principal types of primary immunodeficiency: T-cell, B-cell, complement, and polymorphonuclear leukocyte. The appropriate and inappropriate vaccinations of primary immunodeficient children as provided by the *Red Book* (Table I) are reviewed with comments by the Immune Deficiency Foundation Medical Advisory Committee members based on their collective clinical expertise.[1]

For B-cell primary immunodeficiency, such as X-linked agammaglobulinemia and common variable immunodeficiency (CVID), vaccines to be avoided include oral poliovirus, yellow fever, live attenuated influenza, and live bacterial (eg, typhoid [*Salmonella typhi*, *Ty21a*]) vaccines (Table I). Table I mentions the uncertainty of risk and effectiveness of the measles and varicella vaccines for immunodeficient patients because of the lack of specific evidence for protection. Most antibody-deficient patients treated with intravenous immunoglobulin do not have the capacity to generate protective antibody responses. Patients with X-linked agammaglobulinemia have a predilection for central nervous system enteroviral infections, including oral poliovirus vaccine infection,[3] and rarely, this complication has been encountered by patients with CVID with severe hypogammaglobulinemia.[4] A study of 50 patients with X-linked agammaglobulinemia given BCG vaccine as infants did not reveal systemic infection, suggesting this immunization does not pose a major risk (personal communication, Sergio Rosenzweig, MD, October 4, 2013). Although proscribed by the *Red Book: 2012*, there are no reports that patients with CVID who received attenuated live influenza vaccine became infected or spread live virus to others.[1] It is also true that close contacts immunized with the live influenza vaccine rarely, if ever, have transmitted the virus to patients with CVID.[5] On the basis of current recommendations and the variable level of T-cell defects, it is unclear what level of risk for vaccine-acquired disease exists in patients with CVID. This might be related, at least in part, to the later onset of CVID that results in a different pattern of vaccine exposure compared with X-linked agammaglobulinemia. For IgA deficiency and IgG subclass deficiencies, current information suggests that all vaccines are considered safe. It is uncertain that vaccinations will be effective for patients receiving replacement intravenous immunoglobulin therapy.

Abbreviations used
CVID: Common variable immunodeficiency
HCT: Hematopoietic stem cell transplantation
Hib: *Haemophilus influenzae type b*
SCID: Severe combined immunodeficiency disease

For patients with severe T-cell deficiencies before immune reconstitution (eg, severe combined immunodeficiency disease [SCID] and complete DiGeorge syndrome), no live viral (oral poliovirus, measles, mumps, rubella, varicella, yellow fever, herpes zoster, smallpox, rotavirus, or live attenuated influenza virus) or live bacterial (BCG or *S typhi*, *Ty21a*) vaccines should be administered. Immunodeficient patients who have received hematopoietic stem cell transplantation (HCT) but who continue to have incomplete immune reconstitution or are undergoing immunosuppression should not be given live viral or bacterial vaccines.[1] For the patients with HCT with full immunologic reconstitution, individual assessments of the risk/benefit ratio of live viral vaccines should be made by clinical immunology experts.

In patients with partial T-cell deficiencies (eg, partial DiGeorge syndrome or Wiskott-Aldrich syndrome), the *Red Book* states that all live viral vaccines are to be avoided, although inadvertent immunization with the measles, mumps, and rubella vaccine has not produced clinical infection.[6] Individual assessment of a patient's immune status is recommended before consideration of any live viral vaccines in this group of patients. Live measles, mumps, rubella, and varicella vaccines can be considered with the above caveats. The *Red Book: 2012* recommends that a level of 500 CD4 T cells/mm^3 be required for immunization with these vaccines. Children less than 6 years of age must have higher levels of CD4 T cells to consider these immunizations (ie, 1-6 years, 1000 CD4 T cells/mm^3; <1 year, >1500 CD4 T cells/mm^3), as recommended by the Centers for Disease Control and Prevention.[7] Although recommended for HIV-infected children, these levels of CD4 T cells are consistent with the lower range of age-matched healthy children. On the other hand, inactivated viral vaccines can be used safely, but the degree of effectiveness depends on the level of immunocompetence in the patient at the time of vaccination. Pneumococcal, meningococcal, and *Haemophilus influenzae type b (Hib)* vaccines are recommended for these patients because they are T cell–independent antigens. In addition, seasonal killed influenza vaccines are also recommended because they could provide some degree of protection with little or no risk to these patients.

The determination of immune competence in post-HCT children with SCID would include lymphocyte subsets (eg, CD3, CD4, CD8, CD20, and CD56); proliferation of lymphocytes to normal ranges with PHA, anti-CD3 antibody, and recall antigens, such as *Candida* species; and production of antibodies to recall (eg, tetanus) and new (eg, bacteriophage phi-X174) antigens. Parents need to be made aware of the risks of inadvertent

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TABLE I. Immune Deficiency Foundation Medical Advisory Committee recommendations for immunization of children and adolescents with primary immune deficiencies

Category	Example of specific immunodeficiency	Vaccine contraindications, *Red Book: 2012*	Effectiveness and comments, including risk-specific vaccines*	Observations of PID physicians#
Primary†				
B lymphocyte (humoral)	Severe antibody deficiencies (eg, X-linked agammaglobulinemia and CVID)	OPV,‡ smallpox, LAIV, YF, and most live bacteria vaccines§; consider measles vaccine. There are no data for varicella or rotavirus vaccines.	Effectiveness of any vaccine is uncertain if it depends only on humoral response (eg, PPSV23 or MPSV4). IGIV therapy interferes with measles and possibly varicella immune response. Efficacy of pneumococcal vaccination is not documented in severe antibody deficiency. Consider measles and varicella vaccines.	Agree with statements on XLA but little vaccine-related viral infection is seen in patients with CVID.
	Less severe antibody deficiencies (eg, selective IgA deficiency and IgG subclass deficiencies)	OPV,‡ BCG, YF vaccines; other live vaccines‖ appear to be safe, but caution is urged.	All vaccines are probably effective; immune response might be attenuated. Pneumococcal vaccine and *Hib* are recommended.	Agreement
T lymphocyte (cell-mediated and humoral)	Complete defects (eg, severe combined immunodeficiency, complete DiGeorge syndrome)	All live vaccines§‖¶	All vaccines are probably ineffective. Pneumococcal vaccine and *Hib* are recommended.	Agreement
	SCID given HCT	Live virus and live bacteria vaccines, depending on immune status§‖	Effectiveness of any vaccine depends on degree of immune suppression. Pneumococcal, meningococcal, and *Hib* vaccines are recommended.	Careful assessment of immune competence is required before any live virus vaccination.
	Partial defects (eg, most patients with DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia telangiectasia)	Selected live vaccines§‖	Effectiveness of any vaccine depends on degree of immune suppression. Pneumococcal and *Hib* and meningococcal vaccines are recommended. Consider *Hib* vaccine if not administered during infancy.	Weight of clinical evidence does not support strict avoidance of all live viral vaccines. Documentation of adequate T-cell numbers (>500 $CD4^+$ T cells/mm^3) is required.
Complement	Persistent complement component, properdin, or factor B deficiency	None	All routine vaccines are probably effective. Pneumococcal and meningococcal vaccines are recommended.	Agreement
Phagocytic function	Chronic granulomatous disease, leukocyte adhesion defects, myeloperoxidase deficiency	Live bacterial vaccines§	All inactivated vaccines are safe and probably effective. Live virus vaccines are probably safe and effective.	Agreement
IFN-γ–IL-12 pathway defects	Predilection for BCG vaccine in acquired infections	BCG§	No reported live attenuated viral vaccine–induced infection, but caution is urged.	There are very few data on live vaccine other than that for BCG.

Adapted from Pickering LK, Baker CJ, Kimberlin DW, Long SS, editors. Red Book: 2012 Report of the Committee on Infectious Diseases. 29th ed. Elk Grove Village (IL): American Academy of Pediatrics; 2012.

Age-related levels of immunocompetence proposed by the CDC are as follows: <1 year, 1500 $CD4^+$ T cells/mm^3; 1-5 years, 1000 $CD4^+$ T cells/mm^3; and >6 years, 500 $CD4^+$ T cells/mm^3. These can also be used for patients with HIV.

IGIV, Immune globulin, intravenous; *LAIV*, live attenuated influenza vaccine; *MMR*, measles, mumps, and rubella; *OPV*, oral poliovirus; *PID*, primary immunodeficiency disease; *XLA*, X-linked agammaglobulinemia; *YF*, yellow fever.

*Other vaccines that are recommended universally or routinely should be given if not contraindicated.

†All children and adolescents should receive an annual age-appropriate inactivated influenza vaccine. LAIV is indicated only for healthy subjects 2 through 49 years of age.

‡OPV vaccine is no longer available in the United States.

§Live bacteria vaccines: BCG and Ty21a *S typhi* vaccine.

‖Live virus vaccines: LAIV, MMR, measles-mumps-rubella-varicella (MMRV), herpes zoster (ZOS), OPV, varicella, YF, vaccinia (smallpox), and rotavirus.

¶Regarding T-lymphocyte immunodeficiency as a contraindication to rotavirus vaccine, data only exist for severe combined immunodeficiency syndrome.

#Opinions of consensus of PID experts who authored this policy statement.

vaccine-related infections and provide signed consent for the child to receive live attenuated vaccines.

For complement deficiencies, early components (eg, C1, C2, and C4) and the late components C5 to C9, all viral vaccines, can be administered, and pneumococcal, *Hib*, and meningococcal vaccines for the early- and late-acting complement components, respectively, are strongly recommended because of the predilection of complement-deficient patients to acquire these bacterial infections. Therefore all childhood vaccines can be given to complement-deficient patients, with special emphasis on the pneumococcal and meningococcal vaccines using both the unconjugated and conjugated forms, as appropriate, to retain protection levels of antibodies.[8]

For white blood cell disorders (eg, neutropenias, chronic granulomatous disease, and leukocyte adhesion deficiency), all routine childhood vaccines can be given. Patients with chronic granulomatous disease should not be given the live bacterial vaccines, BCG, and *Salmonella Ty21a*. Similarly, patients with IFN-γ–IL-12 pathway defects should not receive BCG and *Salmonella Ty21a* vaccination because of their predilection for these infections.[9]

CLOSE CONTACTS

Close contacts of patients with compromised immunity should not receive live oral poliovirus vaccine because they might shed the virus and infect a patient with compromised immunity. Close contacts can receive other standard vaccines because viral shedding is unlikely and these pose little risk of infection to a subject with compromised immunity.[1]

Particularly important are annual immunizations with inactivated influenza vaccine; scheduled periodic pertussis vaccine (Tdap); pneumococcal vaccine; measles, mumps, and rubella vaccine; and varicella vaccine for older contacts whose routine immunizations might not be up to date.

The only vaccines pregnant women should routinely receive are the Tdap and inactivated influenza vaccines. However, mothers at high risk for a child with primary immunodeficiency and without an up-to-date immunization history should also receive pneumococcal, *Hib*, and meningococcal vaccines so that maternally transferred IgG antibodies can protect the potentially immunodeficient newborn child during the first few months of life while definitive diagnosis and treatment are undertaken.

If a varicella rash develops in a close contact after immunization with the varicella or zoster vaccines, the risk of transmission to the immunocompromised subject is minimal unless blisters develop at the site of the vaccine administration. In this case isolation of the patient is recommended, and varicella zoster immune globulin could be given prophylactically. Treatment of the close contact or the patient, if infected, would consist of intravenous acyclovir or oral valacyclovir. Killed trivalent influenza vaccine is preferred for close contacts, although live attenuated influenza vaccine can be given to close contacts because of its low rate of transmission to other subjects.[1]

EXAMPLES OF INADVERTENT TRANSMISSION OF LIVE VIRAL VACCINE–RELATED INFECTION

Vaccine-derived poliovirus

In 2010, an infant in South Africa received 3 doses of poliovirus vaccine (oral vaccine at birth and inactivated vaccine at 10 and 14 weeks of life) before identification of his diagnosis of SCID.[10] At 10 months of life, the child had fever, vomiting, tonic-clonic seizures, and acute flaccid paralysis. Poliovirus 3 was identified in a stool sample and cerebrospinal fluid. Viral analysis revealed vaccine-derived poliovirus, and the child was left with lower limb paralysis.

In 2005, an Amish infant in Minnesota who had not been immunized with oral poliovirus before diagnosis of SCID had fever, respiratory tract infections, failure to thrive, bloody diarrhea, and anemia.[11] A stool specimen revealed the presence of live oral polio vaccine–derived poliovirus. Fortunately, the child had no flaccid paralysis, and a successful bone marrow transplantation cleared the vaccine-derived poliovirus from her stool. An extensive investigation of the child's Amish community of several hundred persons revealed the presence of high-titer neutralizing antibodies to poliovirus 1, and many of these subjects had stool specimens that were positive for vaccine-derived poliovirus. Altogether, 35% of this isolated community had serologic or virologic evidence of the vaccine-derived poliovirus, including the patient's 3 siblings, who had never been immunized with either the oral poliovirus vaccine or the inactivated poliovirus vaccine. This outbreak of a vaccine-derived poliovirus infection shows how in an undervaccinated community vaccine-derived virus can spread to others and, in the case of the child with SCID, might lead to vaccine-derived poliovirus infection and clinical disease. Beginning in 2000, only the inactivated poliovirus vaccine was available for routine use in the United States and Canada.[12]

Vaccine-acquired rotavirus

Since 2009, 9 cases have been published describing rotavirus vaccine–derived infections that have threatened the health of children later discovered to have SCID.[13] Because rotavirus infection is a diarrheal disease causing high morbidity in infants, efforts to produce a vaccine that reduces the incidence of acute viral gastroenteritis in infants older than 3 months of life were certainly warranted. The reports of acute illness associated with vaccination in children with undiagnosed SCID led to a modification in the package insert to warn against use in immunosuppressed infants so as to avoid vaccine-related disease in infants with SCID. However, the American Academy of Pediatrics has recommended that all infants be given this vaccine at 6 to 8 weeks of life, a time before infants with SCID typically have serious problems, and thus an affected infant would likely not receive a diagnosis. Fortunately, the implementation of newborn screening for SCID should identify infants with SCID early enough to prevent the accidental administration of rotavirus vaccine to these affected infants.[14] There have been no reports of household contacts spreading rotavirus disease to infants with SCID.

LOSS OF HERD IMMUNITY IN THE GENERAL POPULATION: IMPLICATIONS FOR CHILDREN WITH PRIMARY IMMUNODEFICIENCY

For many decades, the public has grown complacent with the rare occurrence of potential deadly childhood infections, such as pertussis (whooping cough), measles, mumps, and rubella. The advent of effective immunization is most certainly the reason that these former scourges of pediatric infection became rare. The public has a mistaken belief that these diseases are gone and will not return, resulting in more children not receiving standard childhood vaccines. In addition, some parents have a suspicion that childhood immunizations have severe side effects, including

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the development of autism, despite overwhelming scientific evidence to the contrary. Clinical and epidemiologic research has witnessed a disturbing resurgence of these childhood illnesses. Adding to this potentially dangerous situation is the evidence that newer vaccines with extremely rare side effects might provide a shorter interval of protection compared with older vaccines with a higher rate of untoward reactions, even though reactions were confined to a very small proportion of the pediatric population (generally 2 per 100,000 injections).[15] Without herd immunity to the infectious epidemics of the past, unimmunized members of society not only fall prey to morbid and possibly lethal infections that will spread from children to adults but also the reverse. Herd immunity to poliovirus, for example, protects against wild-type poliovirus transmitted by newly arrived immigrants from other countries where poliovirus infection still exists. Herd immunity also protects against the spread of vaccine-derived live poliovirus infections. Parents who elect not to vaccinate their children are actually placing themselves and their children at increased risk of serious infection and even death.[16] A case in point is that pertussis infections are now being seen in tens of thousands of young infants from largely unvaccinated communities. In the 1940s, when the pertussis vaccine was first introduced, the number of US pertussis cases decreased from hundreds of thousands annually to an average of 5000 cases per year.[17] However, starting in the 1990s, the number of pertussis cases began to increase, with a recent peak of 41,000 cases per year in the United States. This has prompted new recommendations regarding reimmunization schedules for children and adults.

The threat of pertussis and other childhood communicable diseases to children with immunodeficiency is particularly alarming. The increased risk of disease in the pediatric population, in part because of increasing rates of vaccine refusal and in some circumstances more rapid loss of immunity, increases potential exposure of immunodeficient children. The immunosuppressed subject is particularly at risk in crowded living conditions because of the spread of these diseases by aerosol droplets or through the oral-fecal route.

INTEGRATION OF THE IMMUNORECONSTITUTED IMMUNODEFICIENT CHILD INTO SOCIETY

The protective instincts of parents for the child who has an immunodeficiency must maintain a balance with the needs of the child to develop socially and educationally. A limited study of 16 infants with SCID treated with HCT reported a significant deficit in mental development and psychomotor validated scale index scores in the first few years after HCT.[18] In a larger number of infants with SCID receiving HCT in the United Kingdom, Titman et al[19] reported an increase in behavioral disorders and neurocognition problems. A related study of cognitive and psychosocial outcomes in 21 children treated with HCT for hemophagocytic lymphohistiocytosis found that affected children had a lower full-scale IQ score of 81 compared with national control scores of 100 or sibling control IQ scores of 99.[20] A high level of support at school was necessary to prevent affected children from falling further behind their classmates. Whether these problems are only a consequence of the chemotherapy given to these children before HCT or infections is not known. Regardless, development of the child as a social being is extremely important, and the child cannot remain housebound for fear of infectious susceptibility. The authors urged long-term systematic follow-up of these patients to make possible early recognition, effective measurement, and proper school interventions to address these conditions.

SUMMARY

The development of immunizations for common bacterial and viral infections has represented a major advance in the battle against microbial organisms that constantly threaten the welfare of humankind and particularly the pediatric population. However, the alarming increase in nonimmunized persons could lead to a return of the epidemics seen in the past. Although the benefits of immunization to the general population have been enormous, special caution and considerations must be made for subjects with primary immunodeficiency disorders. Subjects who lack adaptive and some cases of defective innate immunity are at considerable risk when immunized with live or attenuated viral or bacterial vaccines because their complete or partial lack of immunity might prevent them from halting the growth and spread of the vaccine-derived live infectious agent. Close contacts might carry vaccine-derived virus and cause the horizontal spread of the virus to a child with primary immunodeficiency. Special precautions must be taken with family members to avoid live poliovirus immunizations, but almost all other vaccines can be given with appropriate explanation of the risks and benefits of immunizations and the very low transmission rate to immunodeficient subjects.[1]

Killed vaccines will not cause infection in immunodeficient or any other children. The fear of increased community-acquired vaccine-preventable diseases should lead to adherence to and completion of recommended immunization schedules in the community to reinforce herd immunity, such that all vaccine-preventable diseases become exceedingly rare.

Immunodeficient children who have attained full immune reconstitution after bone marrow, blood, or cord blood stem cell transplantation might have sufficient T-cell responses to protect against exposures to horizontal viral infection, but careful evaluation of the degree of immune reconstitution of an HCT-treated immunodeficient patient must be made before live viral vaccines are administered. This precaution for proper immunologic evaluation has been reinforced recently by the development of central nervous system vasculopathy secondary to vaccine strain varicella in an undiagnosed child with dedicator of cytokinesis 8 (DOCK-8) deficiency.[21] However, immunodeficient children who have successfully reconstituted immune function after HCT should not be isolated from society because of their equally important need to become part of normal society. School attendance is essential for their neuropsychological adjustment.

Children with some of the common immune deficiencies (eg, X-linked agammaglobulinemia, partial DiGeorge, and IgA deficiency) or with a narrow infection phenotype (eg, X-linked thrombocytopenia) can be immunized with live viral vaccine (other than poliovirus), but the advice of a clinical immunologist who cares for immunodeficient children is strongly recommended before immunization regarding the risk versus the benefit. Education of families with immunodeficiencies is a must to avoid complications of live viral vaccines. Further information on the management of immunodeficient children and other patients can be found at the following Web links: the Online Mendelian Inheritance in Man Web site (www.ncbi.nlm.nih.gov/omin/); the European Society for Immune Deficiencies Web site

(www.esid.org/), and the Immune Deficiency Foundation Web site (www.primaryimmune.org).

RECOMMENDATIONS

1. Educate parents and physicians about the critical need for maintenance of herd immunity in the population at large. It is particularly important for family members of patients with defective T and B lymphocyte–mediated immunity to receive all of the available standard immunizations (excluding live poliovirus).
2. Avoid live viral and bacterial vaccines in all patients with significant T- and B-cell deficiencies. Early diagnosis afforded by newborn screening for low numbers of T cells with the T-cell receptor excision circle assay will alert physicians and parents of the need to avoid live viral and bacterial vaccines, including the live rotavirus vaccine, which can produce severe diarrhea in infants with serious T-cell compromise. For any infants born into an extended family with a history of infants with life-threatening immune deficiency, defer all live viral and bacterial vaccines until the infant has been tested to rule out a serious T-cell immunodeficiency. This precaution is particularly important for high-risk families living in states that do not have T-cell receptor excision circle–based newborn screening for serious T-cell deficiencies.
3. Determine the degree of immune reconstitution in patients treated with HCT, enzyme therapy, or gene therapy before live vaccine treatment. Vaccinate only after consultation with a clinical immunologist proficient in the diagnosis and management of primary immune deficiency who can explain the risk/benefit ratio for parents or patients.
4. Balance the need of the immunoreconstituted child to be protected from exposure to infection from live vaccines and close contact–transmitted vaccine-derived infection with the need of the child to integrate into society and develop social and learning skills in group environments.

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[Whereupon, at 11:50 a.m., the hearing was adjourned.]

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