

STATEMENT OF
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Mr. Chairman and Members of the Subcommittee, thank you for the opportunity to discuss with you the role of the National Institutes of Health (NIH) in the research and development of safer and more effective vaccines against infectious diseases. In addition, I am pleased to discuss the research that the NIH is supporting on thimerosal and its safety as a preservative in vaccines. The National Institute of Allergy and Infectious Diseases (NIAID), a component of NIH, is the lead Federal agency for conducting, supporting, and coordinating research on infectious diseases. As such, NIAID plays a key role in our national effort in the development of safer and more effective vaccines to combat infectious diseases.

Benefits of Vaccines and Role of the NIH

Infectious diseases have afflicted humanity since its inception, and they will continue to confront us as long as man and microbes co-exist. Unfortunately, the viruses, bacteria, and parasites that cause infectious diseases do not remain static, but continually and dramatically change over time as new pathogens emerge and as familiar ones re-emerge with new properties or in unfamiliar settings. Influenza is a classic example of a re-emerging disease; it is not a new disease, but it continually changes. According to new estimates, influenza infections are estimated to result in an average of 36,000 deaths and over 200,000 hospitalizations each year in the United States, and the WHO estimates that the annual average number of deaths worldwide is approximately 500,000. An influenza pandemic could be even more deadly. The influenza pandemic that

occurred in 1918-1919 killed 20-40 million people worldwide, including more than half a million in the United States. The pandemics that occurred in 1957 and 1968 killed approximately 2 million and 700,000 people worldwide, respectively. Such emerging and re-emerging infections have shaped the course of human history while causing incalculable misery and death.

The impact and importance of vaccines to infectious diseases such as influenza cannot be overstated— vaccines provide safe, cost-effective and efficient means of preventing illness, disability and death from infectious diseases. Indeed, vaccination has been recognized as one of the greatest public health achievements of the 20th century. For example, in the United States, the poliovirus, the causative agent of poliomyelitis, once crippled 13,000 to 20,000 people every year. The vaccination of the public against the poliovirus, however, decreased the incidence of polio from more than 18,000 cases in 1954, the year before the vaccine was introduced, to about 2,500 cases in 1957. Today, polio has been eliminated from the Western Hemisphere and is on the verge of being eliminated from most regions in the world.

Acknowledging the extraordinary benefits of vaccines, U.S. government agencies charged with protecting and improving the public health have traditionally made vaccine research and development a top priority. Within the Federal government, more than 20 different agencies have a role in vaccine research and immunization programs. Among these, the NIH, the Centers for Disease Control

and Prevention (CDC), the Department of Defense (DoD), the Food and Drug Administration (FDA), and the United States Agency for International Development (USAID) are the Federal agencies with the largest investment in vaccine research, development, and distribution.

Most currently available vaccines, as well as those in development, have resulted from collaborations between partners in the public and private sectors, including Federal and State governments, global organizations, small and large companies, academic research institutions and non-governmental organizations. Historically, an important focus of these efforts has been to explore concepts that are of great public health importance but may not be of immediate commercial appeal, including those for which the principal market might be less developed countries. For example, NIAID, together with the World Health Organization (WHO), USAID, the Children's Vaccine Program at the Program for Appropriate Technology in Health (PATH), and the London-based Medical Research Council, are currently supporting a randomized, controlled Phase III efficacy trial in The Gambia, West Africa, to evaluate the safety and efficacy of a nine-valent pneumococcal conjugate vaccine manufactured by Wyeth Vaccines (Wyeth is also a partner in this effort) in the prevention of pneumococcal pneumonia.. The trial is designed to determine the impact of the pneumococcal conjugate vaccine on childhood pneumonia, which is a major cause of mortality in children younger than 5 years of age in this region. This effort is reflective of the government's

commitment to ensuring that safe and effective vaccines are available to the world's children.

The NIH has three broad goals in vaccine research:

- To identify new vaccine candidates to prevent diseases for which no vaccines currently exist;
- To improve the safety and efficacy of existing vaccines; and
- To design novel generic vaccine approaches, such as new vectors and adjuvants.

To carry out these goals, NIH supports basic and applied research in fields such as immunology and microbiology that leads to vaccine development. The first step in developing new medical advances often occurs in laboratories such as those at NIH and universities around the world where NIH-supported scientists perform experiments to answer fundamental questions about infectious microbes and the human immune system. Scientific knowledge gained through this basic research provides the foundation to develop new or improved vaccines, treatments, or diagnostics.

Once a candidate vaccine has been developed in a pre-clinical setting, the process by which the vaccine is tested in humans requires three distinct phases of evaluation. Phase I trials are the first human tests of a candidate vaccine, generally conducted on small numbers (10-30) of healthy adult volunteers. The

main goal of a Phase I trial is to evaluate safety and, to a lesser extent, to evaluate the immune responses evoked by the vaccine. In addition, different vaccine doses and immunization schedules are compared. Phase II testing involves a larger number of volunteers (50-500) and is designed to generate additional safety data as well as information to refine the dosage and immunization schedule. Phase III trials are the definitive test of whether a vaccine is safe and effective in preventing disease; these trials involve thousands of volunteers. Successful demonstration of efficacy in a Phase III trial can lead to an application for licensure of the vaccine. These three phases take several years to complete.

At the NIAID, we support a strong clinical research infrastructure to conduct vaccine-related clinical studies in humans. For example, NIAID supports an extramural network of seven Vaccine and Treatment Evaluation Units, which primarily conduct Phase I and II clinical trials. This network has served as a national resource for the independent evaluation of vaccines since 1962. NIAID also supports the Dale and Betty Bumpers Vaccine Research Center (VRC), which provides a unique on-campus resource dedicated to vaccine science. The VRC has three major goals: 1) scientific design and rational development of effective vaccine candidates; 2) evaluation and optimization of immune responses generated by candidate vaccines; and 3) advancement of promising vaccine candidates into human trials. Together, these efforts have created the

strong foundation from which NIAID carries out vaccine research and development activities.

Vaccine Safety

Despite the prominent role that vaccines play in our health care armamentarium, they are not without potential risk. Fortunately, the benefits of vaccines far outweigh the possible risks, and vaccines remain the most effective tool we have to prevent serious and life-threatening infections. Nonetheless, a critical element of all vaccine development efforts is the ongoing evaluation of a vaccine's safety. As I described above, Federal regulations require that vaccines undergo extensive testing before they can be licensed and distributed. Once in use, vaccines continue to be monitored for safety and efficacy. Moreover, the Federal government has numerous checks and balances in place to monitor the safety and efficacy of vaccines and to ensure that recommendations about immunization practices and procedures reflect the best available science.

At the NIH, the evaluation of vaccine safety is an essential part of every vaccine clinical trial that we sponsor. All trials include an assessment of vaccine safety as a primary study objective. Study participants are closely monitored for any adverse effects of the vaccinations they receive. In addition to research on new vaccines, the NIH devotes substantial resources to developing improved vaccines that are more effective and have fewer side effects than currently

licensed vaccines. The NIH also pursues research to address specific vaccine safety research hypotheses as they arise, as in the case with thimerosal.

Thimerosal is a preservative added to some vaccines and other pharmaceutical products because it is effective in killing bacteria and in preventing bacterial contamination of the product. When thimerosal is degraded or metabolized, one product is ethyl mercury. In July 1999, U.S. Department of Health and Human Services (DHHS) agencies, the American Academy of Pediatrics, and vaccine manufacturers agreed that thimerosal should be reduced or eliminated in infant and childhood vaccines as a precautionary measure and to reduce human exposure to mercury from all sources. This decision was based on U.S. and international guidelines for methyl mercury exposure (usually associated with ingestion of certain foods, particularly fish) and the assumption that the health risks from methyl and ethyl mercury were the same.

Additional research is needed to determine whether the guidelines for methyl mercury are also appropriate guidelines for thimerosal. To that end, NIH has initiated several research activities aimed to better understand what happens to thimerosal once it is introduced into the body and how this compares to current knowledge of methyl mercury metabolic pathways.

There are important differences between methyl mercury exposure and thimerosal exposure. Thimerosal contains ethyl mercury, which is structurally

different from methyl mercury. The timing and route of exposure are different for these two chemicals. Generally, in the United States, people are exposed to methyl mercury by eating fish that become contaminated through environmental exposure to mercury. Some of this methyl mercury may be passed from the mother to the fetus before birth and to infants through breast milk. Prior to the removal of thimerosal from childhood-recommended vaccines, infants were exposed to thimerosal and hence ethyl mercury by intramuscular injection during vaccination, not by ingestion. Furthermore, infants received thimerosal from vaccines that were administered days or months apart over a relatively short period of time. In contrast, methyl mercury exposure, primarily from foods, tends to occur over a longer, sustained period of time.

NIH Research on Thimerosal

At the NIH, the NIAID and the National Institute for Environmental Health Sciences (NIEHS) are the two institutes tasked with increasing our understanding of what effects, if any, thimerosal has on humans. As I mentioned above, NIAID funds research that focuses on better understanding what happens to thimerosal once it is introduced into the body and how this compares to current knowledge of methyl mercury pathways. I will briefly describe these studies.

NIAID supported early studies at the University of Rochester Vaccine and Treatment Evaluation Unit to assess mercury levels in blood, hair, and stool samples from infants who received routine vaccines containing thimerosal (this

study was initiated before thimerosal was removed from childhood vaccines). In the study, mercury levels were compared with similar samples from infants who received vaccines without thimerosal.

Several important results have been obtained from this study. Mercury levels in blood were low in all infants studied and uniformly below the Environmental Protection Agency (EPA) safety guidelines for methyl mercury at all of the time points measured. Mercury levels in the stool of infants receiving vaccines containing thimerosal were relatively high compared to mercury levels in the stool of infants who were not exposed to thimerosal. These results indicate that thimerosal appears to be removed rapidly from the blood and body. The levels of thimerosal administered in vaccinations, which are lower than the EPA guidelines for methyl mercury, offer an even greater margin of safety. These results were published in *The Lancet* in 2002.

NIAID is supporting a follow-up study with a larger group of infants (216) in Argentina, where routine childhood vaccines still contain thimerosal; results are anticipated next spring. NIAID is planning an additional study in Argentina that will complement the ongoing assessment of mercury levels in samples of blood and feces from infants receiving thimerosal-containing vaccines as part of their routine care. This new study will enroll premature (32 to 37 weeks gestational age) and low birth weight (2000 to <3000 grams) infants. The goals of these studies are to assess the levels of mercury in the blood and other samples from

infants receiving thimerosal-containing vaccines as part of their routine immunization schedule and to obtain more samples closer to the time of vaccination.

NIAID, in collaboration with NIEHS, has conducted studies in infant monkeys to compare the pharmacokinetics and tissue distribution of thimerosal and methyl mercury. Data analysis for these studies is close to completion. Results from these studies will provide information to address whether or not the guidelines for methyl mercury are also appropriate for thimerosal. Preliminary results indicate that methyl mercury (ingested orally) and thimerosal (injected intramuscularly with vaccines) are both readily absorbed and distributed into blood and brain. However, levels of mercury measured in blood and in brain were lower after thimerosal exposure than after methyl mercury exposure. In addition, mercury was cleared from both blood and brain faster after thimerosal exposure when compared to methyl mercury exposure. Moreover, during weekly doses of methyl mercury, total mercury in blood continued to accumulate, while during weekly doses of thimerosal, there was little accumulation of total mercury in blood. These studies provide evidence that thimerosal is eliminated from the body more quickly than methyl mercury.

Three projects within the NIEHS-supported Center for Children's Environmental Health and Disease Prevention Research at University of California, Davis include work on thimerosal. These projects include a case-controlled

epidemiological study of environmental factors in the etiology of autism. In this study, thimerosal is one of many environmental chemicals being investigated to determine if exposure may act synergistically with unidentified genetic susceptibility factors to produce autism spectrum disorders. A second study is examining the effects of various agents (e.g., thimerosal) on the development and performance of social behaviors. The third project seeks to identify molecular and cellular mechanisms that may underlie responses in autistic children to chemicals to which they are exposed during fetal development and/or periods of early postnatal brain development.

Other Efforts

In addition to the ongoing studies described above, the Institute of Medicine (IOM)—at the request of the CDC and NIH—established the Immunization Safety Review Committee in the fall of 2000 to evaluate the evidence on possible causal associations between immunizations and certain adverse outcomes. The Committee analyzed relevant epidemiologic evidence, case reports, and clinical evidence. The Committee also reviewed information from the authors of key papers and evaluated unpublished research. After each review, the Committee reported its findings and provided recommendations for future research studies or policy review. The Immunization Safety Review Committee met twice to address the issue we are discussing today, which is whether there is any evidence that the vaccine additive thimerosal causes harm.

The Committee first met to address this issue in October 2001. At that time, the Committee examined the hypothesis of whether or not the use of vaccines containing thimerosal causes neurodevelopmental disorders, e.g., autism or attention deficit/hyperactivity disorder. The IOM Committee determined that the evidence did not show an association between the measles-mumps-rubella (MMR) vaccine and autism, but that there was not enough evidence to determine whether thimerosal was associated with neurodevelopmental disorders such as autism.

More recently, in May 2004, the Committee held its eighth and final meeting to revisit this issue. In light of additional evidence gathered since their first meeting, the Committee concluded that neither thimerosal nor the MMR vaccine is associated with autism. Moreover, the Committee concluded that the hypotheses regarding how the MMR vaccine and thimerosal could trigger autism lacked supporting evidence and are theoretical only. These conclusions draw on several well-designed studies that were conducted in the years following the first IOM report mentioned above, as well as subsequent review of the literature that the Committee had previously considered. In summary, its findings indicated that childhood vaccines are not associated with autism.

Conclusion

While the issue of thimerosal is a relatively new concern, vaccine safety in general is not a new issue and remains a very important component of all NIH-

supported vaccine research efforts. Vaccine safety research has been and will remain a top priority for NIH, and we will continue to aggressively address vaccine safety concerns as they arise to ensure that the safest and most effective vaccines are available to the public.

Thank you for the opportunity to testify today. I would be pleased to respond to any questions that you may have.