

Energy and Commerce Subcommittee on Oversight and Investigations
Hearing on “Confronting a Growing Public Health Threat: Measles Outbreaks in the U.S.”
February 27, 2019

Questions for the Record

NIAID Director Anthony Fauci

The Honorable Frank Pallone Jr. (D-NJ)

1. The Centers for Disease Control and Prevention (CDC) has determined that receiving the measles, mumps, and rubella vaccine-known as the MMR vaccine- is safer than getting any of the viruses. CDC notes, however, that as with any medication, there is a chance of adverse reaction.
 - a. What range of adverse reactions are associated with the MMR vaccine?

NIAID Response:

The measles, mumps, rubella (MMR) vaccine and the MMRV vaccine, which includes varicella (V - chickenpox), are the two measles-containing vaccines commercially available in the United States. The MMR and MMRV vaccines are 97 % effective against measles and both measles-containing vaccines are very safe. The vast majority of individuals who receive the vaccines experience no adverse reactions coinciding with vaccination and the most common adverse reactions reported with use of the vaccines are mild: low-grade fever, injection site redness or rash, temporary stiffness and pain of the joints, and pain at the injection site. Much less common are temporary adverse reactions reported with use of the vaccines such as: full body rash, low platelet count, and facial swelling. In rare cases, more serious adverse reactions have been reported with use of the vaccines. These include febrile seizures, which can be caused by a variety of conditions that induce fever, including the diseases that the vaccines are designed to prevent. In this regard, up to five percent of young children will have a febrile seizure at some time in their life, usually associated with an infection that they have contracted. Other exceedingly rare adverse reactions reported following use of measles-containing vaccines are anaphylaxis in those with allergies to vaccine components, and, in extremely rare cases, measles inclusion body encephalitis, almost always in individuals with compromised immune systems.

It is important to note that infection with measles virus can result in complications that may include severe, lifelong disability, or even death. About one in ten patients experience ear infections, which can result in deafness, and one in twenty develop pneumonia. One in a thousand are affected by encephalitis, or inflammation of the brain, that can cause seizures and result in deafness or intellectual disability. Two or three infected patients in a thousand will die from measles. In rare cases, a persistent central nervous system infection can also occur, causing a fatal degenerative neurological disease called subacute sclerosing panencephalitis (SSPE). SSPE generally develops seven to ten years after measles infection and is characterized by behavioral changes, mental and motor deterioration, seizures, blindness, and ultimately death within one to three years.

- b. Under what circumstances have more severe reactions been documented?

NIAID Response:

There are certain individuals for whom measles-containing vaccines are medically contraindicated due to risk of severe adverse reactions. It is important that parents or guardians have a conversation with healthcare providers to ensure that a child does not have any preexisting conditions that would indicate they should not receive a measles-containing vaccine. Package inserts^{1,2} for measles-containing vaccines contain a section pertaining to warnings. This section of the labeling includes a description of serious adverse reactions and potential safety risks, limitations in use imposed by them and steps that should be taken if they occur. The labeling also includes information pertaining to contraindications. These include: an immunodeficiency, febrile illness, a hypersensitivity to any of the vaccine components, or an anaphylactic reaction to the vaccine component neomycin. In addition, measles-containing vaccines are contraindicated in pregnant women.

CDC recommends the first dose of measles-containing vaccine be administered to children between 12 to 15 months of age in most circumstances. Infants 6 through 11 months of age should receive one dose of MMR vaccine if they will be traveling internationally. Recent studies have shown that children who receive a delayed initial MMR vaccine dose after 16 months are at an increased risk of febrile seizures.³ This increased risk of seizure lasts for about two weeks after vaccine administration and is most prevalent in the contraindicated group of children with a history, or a family history, of febrile seizures.⁴ The MMRV vaccine also has been shown to be associated with a slightly higher, but still very low, risk of febrile seizures. Notably, children who experience a febrile seizure after vaccination are at no greater risk of epilepsy long-term.

Exceedingly rare anaphylactic reactions to the MMR vaccine are due to allergies to vaccine components. The MMR vaccine is contraindicated in individuals with a history of an allergic reaction to the vaccine component neomycin due to the presence of trace amounts of this antibiotic in the vaccine. The MMR vaccine also uses gelatin as a stabilizing agent to maintain the potency of the vaccine when exposed to cold or hot conditions. The MMR vaccine is contraindicated in individuals with an allergy to gelatin.⁵

Individuals with a weakened immune system due to disease (such as primary immunodeficiency, cancer, or HIV/AIDS) or medical treatments (such as chemotherapy, radiation, steroids, or immunotherapy) may be at a greater risk of experiencing rare adverse reactions with use of live attenuated vaccines, including measles-containing vaccines. Apart from the issue of response to vaccines, individuals with weakened immune systems are unable to mount an effective immune response against infectious diseases such as measles and are at a greater risk of viral encephalitis from these infections. MMR vaccines contain a weakened vaccine strain of measles that a healthy individual can easily clear while developing long-

¹ MMR-II Package Insert: <https://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm094050.htm>

² ProQuad (MMRV) Package Insert:

<https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM123793.pdf>

³ Rowhani-Rahbar et al. Effect of Age on the Risk of Fever and Seizures Following Immunization with Measles-containing Vaccines in Children. *JAMA Pediatrics* 2013. <https://www.ncbi.nlm.nih.gov/pubmed/24126936>

⁴ Vestergaard et al. MMR Vaccination and Febrile Seizures: Evaluation of Susceptible Subgroups and Long-term Prognosis. *JAMA* 2004. <https://www.ncbi.nlm.nih.gov/pubmed/15265850>

⁵ Kelso et al. Anaphylaxis to Measles, Mumps, and Rubella Vaccine Mediated by IgE to Gelatin. *J Allergy Clin Immunol* 1993. <https://www.ncbi.nlm.nih.gov/pubmed/8473675>

lasting immunity to wild-type measles. Measles-containing vaccines are contraindicated in those with weakened immune systems because they are unable to develop an effective immune response to this vaccine strain, which increases the risk of severe adverse reactions, including encephalitis. Most children with significant primary immunodeficiencies will be identified prior to the age of initial MMR vaccination and the MMR vaccine is contraindicated for such individuals. It is important to note that these individuals with weakened immune systems who do not receive the vaccine rely on the herd immunity that arises from the vaccination of healthy people.

- c. Does the National Institutes of Health concur with CDC's determination that the risks associated with acquiring measles, mumps, or rubella are greater than the possible reactions from the MMR vaccine?

NIAID Response:

The NIH concurs with CDC's determination that the risks associated with acquiring these diseases are significantly greater than the low risk of serious adverse reactions reported with use of the MMR vaccine.

The Honorable Jan Schakowsky (D-IL)

1. When outbreaks occur, our most pressing concern is often an immediate response. However, I believe that we also must reflect on our nation ' s progress in prevention of vaccine preventable diseases. The Department of Health and Human Services (HHS) Healthy People objectives for immunization and infectious disease are a cornerstone for federal, state, and local efforts to protect against vaccine preventable conditions across the lifespan.

I was surprised to learn that the draft Healthy People 2030 objectives include very few immunization objectives in total. At a time when we are seeing increased outbreaks of diseases that were already virtually eliminated in this country, could you explain the rationale behind the reduction in immunization objectives in the draft Healthy People 2030 framework? Do you plan to restore these objectives moving forward?

NIAID Response:

NIAID defers to the Office of the Assistant Secretary for Health for questions regarding the Healthy People 2030 initiative.

The Honorable Brett Guthrie (R-KY)

1. In May 2015, the journal *Science* published a report in which researchers found that the measles infection can leave a population at an increased risk for mortality from other diseases for two to three years. Besides this report, is there evidence that measles increases susceptibility to other infections?

NIAID Response:

There is an extensive body of evidence documenting that measles virus infection causes transient suppression of the host immune system, which increases an individual's susceptibility to other infections and can result in the development of secondary bacterial infections in the lungs during the course of measles infection. In the referenced May 2015 *Science* publication, researchers used population-level data to suggest measles vaccination also can protect against other infectious diseases by preventing the "immune amnesia" that has been associated with immune suppression caused by measles infection.⁶

2. What are antigens? How much are used in MMR vaccine? How does that small amount compare to the antigens that are encountered in the environment?

NIAID Response:

An antigen is a substance that can trigger an immune response, resulting in the host immune system's production of an antibody or cellular response as part of the body's defense against infectious agents and other foreign substances. Many antigens are foreign proteins (those not found naturally in the body). For example, the hemagglutinin and fusion proteins of measles virus are antigens that stimulate our immune cells to attack the virus. Every microbe carries its own unique set of antigens, which are central to creating vaccines. Upon birth, the infant leaves the protected environment of the womb and is exposed to the outside world, which contains an almost infinite array of microbes and antigens. Within hours, the newborn's skin and upper respiratory and intestinal tracts are colonized by a variety of microorganisms with their own set of antigens.

Each dose of the measles, mumps, and rubella vaccine contains 24 viral antigens.⁷ In contrast, recent systems biology studies have found that a single bacterial infection may potentially expose an individual to hundreds to thousands of antigens.^{8,9} In addition, although the current immunization schedule contains several more vaccines than in past decades, the total number of antigens contained in the vaccines has actually decreased predominantly as a result of the removal of the whole-cell pertussis vaccine.

Many well-executed studies have been conducted and have not found increased risks of

⁶ Mina et al. Long-term Measles-induced Immunomodulation Increases Overall Childhood Infectious Disease Mortality. *Science* 2015. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4823017/>

⁷ Plotkin et al. *Plotkin's Vaccines* (Seventh Edition). Elsevier. 2018.

⁸ Liang et al. Systems Biology Approach Predicts Antibody Signature Associated with *Brucella melitensis* Infection in Humans. *J Proteome Res* 2011. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3189706/>

⁹ Darton et al. Identification of Novel Serodiagnostic Signatures of Typhoid Fever Using a *Salmonella* Proteome Array. *Front Microbiol* 2017. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5609549/>

adverse health outcomes related to the number of vaccines or vaccine antigens received early in life. Taken together, these findings strongly suggest that the number of antigens in vaccines recommended in the official CDC immunization schedules do not pose a health risk.

3. What is your professional judgment of the likely public-health impact of state vaccination exemptions based on personal or professional beliefs?

NIAID Response:

In my lifetime, I have seen first-hand the devastating effects that measles can have on the health of unvaccinated individuals. Prior to the availability of a vaccine, three to four million measles cases occurred each year in the United States, resulting in approximately 48,000 hospitalizations and 400 to 500 deaths. Globally, there were approximately 110,000 measles deaths in 2017, mostly among children under the age of five. Without a vaccine, it is estimated that 21.1 million people in the world would have died of measles from 2000 to 2017. Now that we have a very safe and highly effective measles vaccine, we must ensure that vaccination rates remain high enough to maintain herd immunity to protect those for whom the vaccine is contraindicated. We know from experience that if for any reason the vaccination rate decreases below the level required to maintain herd immunity – generally from 93 to 95 percent in crowded populations – the result will be more outbreaks of measles and measles-associated complications. We are seeing examples of this currently in Rockland County, New York, and other locations in the United States where the level of measles vaccination has fallen below the critical level.

As a public health official, I strongly recommend that anyone eligible receive the measles vaccine. We must ensure that parents and guardians have accurate and evidence-based information on the safety, efficacy, and benefit of vaccines. We need to better understand what information is available to concerned parents seeking knowledge about vaccines to combat misinformation. We also seek to understand what is motivating individuals to seek personal or professional belief exemptions from vaccination to better inform public health messaging and increase vaccine acceptance. Widespread exemptions due to personal or professional beliefs pose a risk of measles outbreaks (as we are currently seeing) with their associated health consequences at the individual and community levels. Our focus is on helping parents and guardians understand how vaccines protect their children as well as their community from serious and potentially deadly diseases such as measles.

4. What has your institute learned from research about why measles spreads so efficiently? How will this improved understanding help develop novel therapeutic strategies?

NIAID Response:

Measles virus is one of the most infectious viruses on Earth. There are three aspects of the measles virus that make it spread so efficiently: first, individuals are infectious for a few days before it is obvious that they have measles virus infection; second, small amounts of virus are sufficient to cause infection and large amounts of virus are expelled from an infected patient; and third, the virus can stay viable in the air and on surfaces for extended periods. In this

regard, it is estimated that if an unvaccinated individual is in an enclosed space with an infectious person, there is a 90 percent chance that they will become infected with measles. In addition, measles virus can linger in the air as infectious droplets for up to two hours after an infected person leaves an area. Transmission of measles virus also may occur through contact with surfaces.¹⁰

The initial infection with measles virus occurs in the respiratory tract and then spreads via infected immune cells to organs throughout the body, as well as to the cells in the upper airway.¹¹ It is the sloughing of this infectious tissue in the upper airway that induces coughing and sneezing of aerosolized respiratory droplets, facilitating transmission from person to person. The knowledge of where in the body measles virus infects and what cells in those organs are infected can help inform which host pathways can be targeted to inhibit viral replication and transmission. In addition, NIAID is funding basic research to explore the measles virus replication cycle, which may lead to the identification of components of the virus that can be targeted with novel therapeutic strategies.

NIAID will continue to support research to better understand measles virus transmission, pathogenesis, and mechanisms of immune evasion as well as host innate immune responses. For example, NIAID is supporting research to understand measles virus replication and spread in primary cultures of human airway epithelial cells and in a rhesus monkey model. NIAID-supported basic research on measles virus provides the foundational knowledge required for the identification and development of novel measles therapeutics. NIAID also is planning a scientific workshop on the development of antivirals to treat measles.

5. What does the research so far show about using a third dose of MMR vaccine to further boost the immune response?

NIAID Response:

Two doses of the MMR vaccine are approximately 97 percent effective in preventing measles if a person is exposed to the virus. CDC considers people who received two doses of measles vaccine as protected for life. However, in rare cases, people who have had two doses of the MMR vaccine can still get measles if exposed to the virus. It is unclear why these individuals are not immune to the virus. In a recent study of registered, laboratory-confirmed measles cases in California between 2000 and 2015, 46 out of 232 measles cases (20 percent) with a documented vaccine history had received at least one dose of measles-containing vaccine, indicating the potential lack of an adequate immune response to the measles component of the vaccine, or the occurrence of waning immunity to measles in these individuals. NIAID is supporting research at the Mayo Clinic in Minnesota to understand whether a third measles vaccination will boost the immune response of individuals who do not exhibit a sufficient immune response after two doses. The findings of this research could inform whether investigation is warranted for a third dose of MMR vaccine for protection against measles.

¹⁰ Bischoff et al. Detection of Measles Virus RNA in Air and Surface Specimens in a Hospital Setting. *JID* 2015. <https://www.ncbi.nlm.nih.gov/pubmed/26386428>

¹¹ Griffin et al. The Immune Response in Measles: Virus Control, Clearance and Protective Immunity. *Viruses* 2016. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5086614/>

In contrast to generally successful protection against measles from the MMR vaccine, a 2018 study estimated that immune protection against mumps wanes to the point of making an individual susceptible to infection again 27 years after last mumps vaccination on average, suggesting the potential need for a third vaccine dose.¹² CDC, based on advice from the Advisory Committee on Immunization Practices, now recommends a third dose of a mumps virus-containing vaccine such as MMR for individuals previously vaccinated with two doses who are identified as being at increased risk for acquiring mumps because of proximity to a mumps outbreak. This recommendation is designed to improve protection against mumps virus infection and related complications in these individuals. It is important to note that there are no data available to demonstrate how long a third dose of MMR vaccine provides additional protection from mumps.

6. Is there reason to believe that there are differences in immune responses between sexes?

NIAID Response:

For some vaccines, biological sex can be a strong determinant of vaccine response, with females demonstrating higher antibody responses. However, previous studies of measles vaccine-induced immune responses have not resulted in definitive conclusions regarding the role of biological sex. Studies on sex-based differences in antibody production resulting from administration of the measles vaccine have shown conflicting results, some suggesting that either males or females were more likely to develop a strong antibody response and some indicating that there were no sex-based differences in antibody response. In 2016, a NIAID-supported analysis for sex differences in antibody responses to measles vaccination in three cohorts (2,872 children total) found no evidence for sex differences.¹³ NIAID will continue to support research to improve understanding of the host immune response to vaccination, including potential sex differences.

7. What is the concern with "waning immunity," and how can it be addressed?

NIAID Response:

The overwhelming majority of measles cases in the United States occur in unvaccinated persons with no immunity against measles virus. However, as noted in the response to question 5, there have been reports of laboratory-confirmed measles cases in individuals previously vaccinated against measles, indicating the possibility of inadequate initial immunity or waning immunity, which is a decreased immunity against the virus over time. Additional studies would be required to more precisely estimate the level of waning immunity to measles in high vaccine coverage settings. NIAID is supporting research to understand the difference between immunity following measles vaccination and immunity gained by natural infection.

¹² Lewnard et al. Vaccine Waning and Mumps Re-emergence in the United States. *Science Translational Medicine* 2018. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5899613/>

¹³ Voigt et al. Genetically Defined Race, but not Sex, is Associated with Higher Humoral and Cellular Immune Responses to Measles Vaccination. *Vaccine* 2016. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5278779/>

8. Why are there no antiviral therapies currently available to treat measles? Is it because it is particularly challenging or a lack of market interest?

NIAID Response:

NIAID recognizes the need for antiviral therapies to treat measles and is planning a scientific workshop to accelerate the development of measles antivirals. NIAID also is supporting efforts to screen antiviral compounds for activity against measles. The lack of antivirals against measles virus is not due to any significant scientific challenge, but more likely the relatively low number of cases in the United States, the late stage of diagnosis (usually after rash), and the highly effective vaccine, which has a dampening effect on the interest of researchers and industry in developing new antiviral therapies. However, NIAID will continue to support research on the identification and development of novel measles antivirals. In addition, existing antiviral therapies, such as interferon and ribavirin, have been tested clinically against measles with varied results.¹⁴

It is important to note that CDC provides recommendations to healthcare providers for situations where an individual has been exposed to measles and has no evidence of immunity via vaccination or prior infection. If these patients present to their healthcare provider within 72 hours of exposure, they can be offered post-exposure prophylaxis (PEP) in the form of the MMR vaccine. Alternatively, immunoglobulin can be administered within six days. PEP has been found to be highly effective at preventing or limiting infection. Vitamin A also has been shown to prevent some of the adverse effects of measles and CDC recommends severe measles cases among children, such as those who are hospitalized, should be treated with vitamin A.¹⁵ This is particularly useful in settings where vitamin A deficiencies are common.

¹⁴ Plemper et al. Measles Control – Can Measles Virus Inhibitors Make a Difference? *Current Opinion in Investigational Drugs* 2009. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2728049/>

¹⁵ <https://www.cdc.gov/measles/hcp/index.html>

The Honorable Michael C. Burgess, M.D. (R-TX)

1. What steps can parents take to best protect their children from infectious diseases like measles?

NIAID Response:

Vaccination is the best step parents can take to protect their children from infectious diseases such as measles. We must ensure that parents and guardians have easy access to accurate and evidence-based information on the safety, efficacy, and benefit of vaccines. The measles, mumps, rubella (MMR) vaccine and the MMRV vaccine, which includes varicella (V - chickenpox), are the two measles vaccines commercially available in the United States. The MMR and MMRV vaccines are 97 % effective against measles and both measles-containing vaccines are very safe. Two doses of the MMR vaccine are approximately 97 percent effective in preventing measles if a person is exposed to the virus.

2. What are some of the sideeffects associated with measles, and how often do these occur?

NIAID Response:

Infection with measles virus can result in complications that may include severe, lifelong disability or even death. One in ten patients experience ear infections, which can result in deafness, and one in twenty develop pneumonia. One in a thousand develop encephalitis, or inflammation of the brain, that can cause seizures and result in deafness or intellectual disability. Two to three infected patients in a thousand will die from the measles. In rare cases, a persistent central nervous system infection occurs, causing a fatal degenerative neurological disease called subacute sclerosing panencephalitis (SSPE). SSPE generally develops seven to ten years after measles infection and is characterized by behavioral changes, mental and motor deterioration, seizures, blindness, and ultimately death within one to three years. Vaccination is the best step parents can take to protect their children from these measles-associated complications.

3. Some people say that measles is not serious and did not cause great harm in the past. Can you talk about the historic impact of measles in the past both in the U.S. and globally?

NIAID Response:

Prior to the availability of a vaccine, three to four million measles cases occurred each year in the United States, resulting in approximately 48,000 hospitalizations and 400 to 500 deaths. Globally, even though a safe and effective vaccine is now available, there were still approximately 110,000 measles deaths in 2017, mostly among children under the age of five. Without a vaccine, it is estimated that 21.1 million people in the world would have died of measles from 2000 to 2017. We must ensure that vaccination rates remain high enough to maintain herd immunity to protect those for whom the vaccine is contraindicated. We know from experience that if the vaccination rate decreases below the level required to maintain herd immunity for any reason, the result will be more outbreaks of measles and measles-associated complications.