Exhibit A

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF WEST VIRGINIA

WHEELING DIVISION

WEST VIRGINIA PARENTS FOR RELIGIOUS FREEDOM, *et al.,* *Plaintiffs,* Against DR. MATTHEW CHRISTIANSEN, *Defendant*.	Civil Action No.: 5:23-cv-00158-JPB

DECLARATION OF AARON SIRI

I, Aaron Siri, Esq., hereby state and declare as follows:

1. I am a partner at Siri & Glimstad LLP and am one of the counsel for Plaintiffs in the above captioned matter. I make the following declaration based on personal knowledge and/or, where noted, based upon public government information and publications, which are accurately and readily determined from sources whose accuracy cannot reasonably be questioned. I have personally examined these government sources, and the links herein are links to those sources. Exhibits attached hereto are original copies with, in some instances, added highlighting.

I. PREVENTING INFECTION & TRANSMISSION

2. Defendant's opposition does not contest that polio, tetanus, diphtheria, pertussis, meningococcal and hepatitis b vaccines, which combined comprise four of the six vaccines required to attend school in West Virginia, do not contribute to preventing infection and transmission of the target pathogen in school.

Polio Vaccine Does Not Prevent Infection & Transmission

3. "Inactivated polio vaccine (IPV) is the only polio vaccine that has been given in the United States since 2000." Attached as **Exhibit 1** is a true and correct copy of a CDC webpage *Polio Vaccination*, available at https://www.cdc.gov/vaccines/vpd/polio/index.html.

4. "IPV does not contain live virus and cannot cause disease. It protects people from polio disease but does not stop transmission of the virus." Attached as **Exhibit 2** is a true and correct copy of a CDC webpage *Polio Disease and Poliovirus Containment*, available at https://www.cdc.gov/orr/polioviruscontainment/diseaseandvirus.htm (first page of Ex. 2) which links to CDC, *et al.*, Polio Global Eradication Initiative webpage https://polioeradication.org/polio-today/polio-prevention/the-vaccines/ipv/ (second page of Ex. 2) which further explains that "IPV induces very low levels of immunity in the intestine. As a result, when a person immunized with IPV is infected with wild poliovirus, the virus can still multiply inside the intestines and be shed in the feces … IPV does not stop transmission of the virus."

Tetanus & Diphtheria Vaccines Do Not Prevent Infection & Transmission

5. "Tetanus … does not spread from person to person." Attached as **Exhibit 3** is a true and correct copy of a CDC webpage *About Tetanus*, available at https://www.cdc.gov/tetanus/about/index.html.

6. "Diphtheria toxoid helps prevent symptomatic disease but does not prevent the carrier state nor stop the spread of infection. … [T]he known importance of carriers in the spread of diphtheria, and the demonstrated failure of toxoid to prevent the carrier state lead us to conclude that the concept of herd immunity is not applicable in the prevention of diphtheria." Attached as **Exhibit 4** is a true and correct copy of a study by CDC's Epidemiology Program *Diphtheria Immunization*, available at https://www.ncbi.nlm.nih.gov/pubmed/5026197.

7. Any immunity provided by tetanus and diphtheria vaccines wanes rapidly requiring a "Td or Tdap booster every 10 years" and in "2019, the proportion of adults aged ≥19 years reporting having received any tetanus toxoid–containing vaccination during the past 10 years was 62.9%, similar to 2018." Attached as **Exhibit 5** is a true and correct copy of Table 1 of CDC's *Recommended Adult Immunization Schedule* available at https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf and **Exhibit 6** is a true and correct copy of *CDC's Vaccination Coverage among Adults*, available at https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/pubs-resources/vaccination-coverage-adults-2019-2020.html.

Pertussis Vaccine Does Not Prevent Infection & Transmission

8. In 1999, CDC provided for "exclusive use of acellular pertussis vaccines for all doses of the pertussis vaccine series." Attached as **Exhibit 7** is a true and correct copy of CDC's *Recommended Childhood Immunization Schedule – United States, 2000*, available at https://www.cdc.gov/mmwr/preview/mmwrhtml/mm4902a4.htm.

9. "Mucosal immunity is essential to prevent colonization and transmission of B. pertussis organisms. Consequently, preventive measures such as aPVs [acellular pertussis vaccine] that do not induce a valid mucosal response can prevent disease but cannot avoid infection and transmission. … aPV pertussis vaccines do not prevent colonization. Consequently, they do not reduce the circulation of *B. pertussis* and do not exert any herd immunity effect. … Lack of mucosal immune responses after aPV administration favor infection, persistent colonization, and transmission of the pathogen." Attached as **Exhibit 8** is a true and correct copy of a CDC final response, dated December 30, 2021, which cites https://pubmed.ncbi.nlm.nih.gov/24277828/ and https://pubmed.ncbi.nlm.nih.gov/31333640/ and the relevant pages of these cited studies.

10. "Many babies who get whooping cough are infected by older siblings, parents, or caregivers who don't know they have it." Attached as **Exhibit 9** is a true and correct copy of CDC's webpage *Pertussis (Whooping Cough): Causes and How It Spread*, available at https://www.cdc.gov/pertussis/about/causes-transmission.html.

11. "Among adolescents who received … DTaP as children, in a matched case-control study, … vaccine effectiveness against pertussis within one year of Tdap vaccination was 73% (95% CI = 60%–82%), but after 2–4 years, postvaccination vaccine effectiveness decreased to 34% (95% CI = -0.03%–58%). Another study that calculated Tdap vaccine effectiveness among adolescents found that, within the first year after vaccination, effectiveness was 68.8% (95% CI = 59.7%–75.9%); by ≥4 years after vaccination, vaccine effectiveness was 8.9% (95% CI = -30.6%–36.4%)." Attached as **Exhibit 10** is a true and correct copy of the relevant pages of *Prevention of Pertussis, Tetanus, and Diphtheria with Vaccines in the United States*, available at https://www.cdc.gov/mmwr/volumes/67/rr/rr6702a1.htm.

Meningococcal Vaccine Does Not Contribute to Herd Immunity

12. "Rates of meningococcal disease have declined in the United States since the 1990s and remain low today. Much of the decline occurred before the routine use of MenACWY vaccines. … [D]ata suggest MenACWY vaccines have provided protection to those vaccinated, but probably not to the larger, unvaccinated community (population or herd immunity)." Attached as **Exhibit 11** is a true and correct copy of a CDC webpage *Meningococcal Vaccination*, available at https://www.cdc.gov/vaccines/vpd/mening/public/index.html.

13. "Protection from MenACWY vaccination wanes in most adolescents within 5 years." Attached as **Exhibit 12** is a true and correct copy of the MenACWY portion of the CDC

webpage *Meningococcal Vaccination for Adolescents*, available at https://www.cdc.gov/vaccines/vpd/mening/hcp/adolescent-vaccine.html.

Hepatitis B Not Transmitted in School Setting

14. "A search of our [CDC] records failed to reveal any documents" of "transmission of Hepatitis B in an elementary, middle or high school setting." Attached as **Exhibit 13** is a true and correct copy of a CDC final response regarding Hep B vaccine.

15. "Transmission of the HBV [hepatitis B virus] can occur through sexual contact, sharing needles, syringes, or other drug use equipment, or perinatally from mother to baby at birth." Attached as **Exhibit 14** is a true and correct copy of the relevant pages of *Viral Hepatitis in West Virginia*, available at https://oeps.wv.gov/hepatitis/documents/data/Summary_2020_Acute_HBV-HCV.pdf.

II. MEASLES AND MEASLES VACCINE

16. Defendant presents evidence regarding measles and measles vaccine in Defendant's Exhibits E, K, and T and in inadmissible Exhibits C and D.

Safety of the Measles Vaccine

17. CDC "Vaccine Information Statement" stating "After MMR vaccination, a person might experience:" "seizure," "deafness," "long-term seizures, coma, or lowered consciousness," and "brain damage." Attached as **Exhibit 15** is a true and correct copy of CDC's Vaccine Information Statement for MMR vaccine.

18. Clinical trials relied upon by FDA to license Merck's MMR vaccine in 1978 had a total of 834 children, no control, and 42 days of safety review during which, *inter alia*, around a third developed gastrointestinal issues and a third respiratory issues. Attached as **Exhibit 16** is a

true and correct copy of the relevant pages of the MMR clinical trial reports, full copy available at https://sirillp.com/MMR-clinical-trial.

19. By the mid-1980's there were three routine childhood vaccines – MMR, DTP, and OPV – and the financial liabilities from these products drove the passage of the National Childhood Vaccine Injury Act of 1986 which gave pharmaceutical companies immunity to liability for most injuries and deaths caused by these and future childhood vaccine products. *See, e.g., Bruesewitz v. Wyeth*, 562 U.S. 223 ("[B]y the mid-1980's … the remaining manufacturer … estimated that its potential tort liability exceeded its annual sales by a factor of 200" and "the Vaccine Injury Act pre-empts all design-defect claims against vaccine manufacturers … for injury or death caused by a vaccine side effects."); 42 U.S.C. § 300aa-11 ("No person may bring a civil action … against a vaccine administrator or manufacturer … for damages arising from a vaccine-related injury or death"). Attached as **Exhibit 17** is a true and correct copy of CDC's childhood vaccine schedule from 1983, available at https://www.cdc.gov/vaccines/schedules/images/schedule1983s.jpg.

20. After licensure, federal law requires that the package insert for MMR, prepared by Merck and approved by the FDA, list "*only* those adverse events for which there is some basis to believe there is a *causal relationship* between the drug and the occurrence of the adverse event." 21 C.F.R. 201.57(c)(7) (emphasis added). Adverse events listed in MMR's package insert include:

> vasculitis, pancreatitis; parotitis; thrombocytopenia; purpura; regional lymphadenopathy; leukocytosis; angioedema (including peripheral or facial edema); bronchial spasm; arthritis; arthralgia; myalgia; encephalitis; encephalopathy; measles inclusion body encephalitis (MIBE) subacute sclerosing panencephalitis (SSPE); Guillain-Barré Syndrome (GBS); acute disseminated encephalomyelitis (ADEM); transverse myelitis; febrile convulsions; afebrile convulsions or seizures; ataxia; polyneuritis; polyneuropathy; ocular palsies; paresthesia; pneumonia; pneumonitis; Stevens-Johnson syndrome; acute hemorrhagic edema of infancy; Henoch-Schönlein purpura; erythema multiforme; nerve deafness; retinitis; optic neuritis; papillitis; epididymitis; orchitis

Attached as **Exhibit 18** is a true and correct copy of the package insert for the MMR vaccine, available at https://www.fda.gov/media/75191/download.

21. In 2022, GSK obtained licensure of an MMR vaccine ("Priorix" or "MMR-RIT") based on a clinical trial comparing it to Merck's MMR vaccine ("M-M-R-II") in which both vaccine groups, within six months of administration, had serious adverse events, emergency room visits, and new onset of chronic diseases (*e.g.,* autoimmune disorders, asthma, type I diabetes, vasculitis, celiac disease, thrombocytopenia, and allergies) as summarized by GSK below:

Supplementary Table 6. Incidence of unsolicited adverse events (Day 0–42), serious adverse events, AEs prompting emergency room visits and NOCDs (Day 0–180) (total vaccinated cohort).

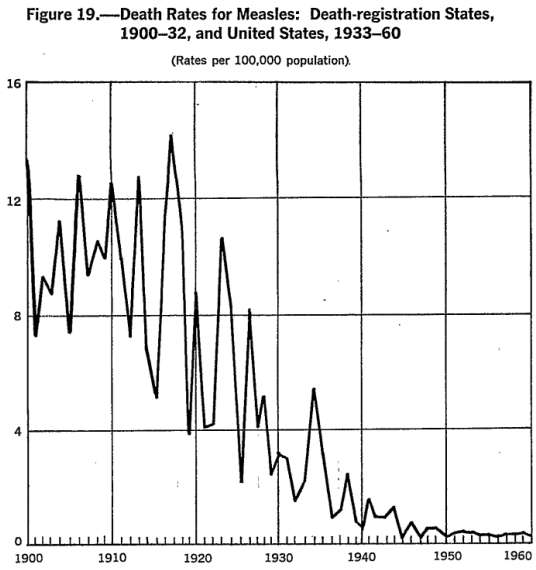
n (%)	MMR-RIT (N=3714)	MMR II (N=1289)
Unsolicited AEs (≥1 symptom)	1857 (50.0)	618 (47.9)
Grade 3	225 (6.1)	85 (6.6)
SAEs (any, ≥1 SAE)	77 (2.1)	25 (1.9)
AEs prompting ER visit	375 (10.1)	134 (10.4)
NOCDs (any, ≥1 NOCD)	128 (3.4)	48 (3.7)

AE, adverse event; ER, emergency room; N, number of children with the documented dose; n (%), number (percentage) of children reporting the AE at least once; NOCDs, new onset chronic diseases (see definition in Patients and methods); SAE, serious AE.
Grade 3 unsolicited AEs were those preventing normal, everyday activities.

Attached as **Exhibit 19** is a true and correct copy of the relevant pages of the Supplementary Materials for Priorix, available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7192400/, summarizing the content of **Exhibit 20** which is a true and correct copy of the relevant pages of the FDA Clinical Review for Priorix, full version at https://www.fda.gov/media/159591/download; **Exhibit 21** is a true and correct copy of the FDA webpage *What is a Serious Adverse Event?*, available at https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event.

Efficacy of the Measles Vaccine

22. Measles mortality in the United States declined by over 98% between 1900 and 1963, the year the first measles vaccine was introduced. Attached as **Exhibit 22** is a true and correct copy of the relevant pages of the U.S. Public Health Service's *Vital Statistics Rates in the United States 1940-1960* (full version at https://www.cdc.gov/nchs/data/vsus/vsrates1940_60.pdf) providing measles mortality in 1900 was 13.3 deaths per 100,000 individuals and in 1960 was 0.2 deaths per 100,000 individuals, a decline of over 98%, and includes the following chart:



Attached as **Exhibit 23** are true and correct copies of the relevant pages of the *Vital Statistics Rates in the United States 1962* providing measles mortality in 1961 and 1962 was 0.2 deaths per 100,000 individuals, full version available at https://www.cdc.gov/nchs/data/vsus/VSUS_1962_2A.pdf.

23. The over 98% decline in measles mortality in that period had nothing to do with a measles vaccine since none existed during that period.[1] In countries or areas with limited nutrition,

[1] England and Whales had a similar decline of over 99% in its measles death rate between 1900 and 1968 when the first measles vaccine was introduced there, five years after first being introduced in the U.S. *See* https://webarchive.nationalarchives.gov.uk/ukgwa/20160111174808/http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-215593.

sanitation, acute care, and clean water, deaths from measles can still occur at a higher rate and those conditions still existed in pockets of the United States in the early 1960s.

24. There were approximately 400 deaths per year in the United States in the years before the first measles vaccine in 1963. **Exhibit 23 at 3**. This amounts to approximately one measles death for every 500,000 Americans at a time when nearly every American had measles. *See* https://www.census.gov/library/publications/1962/compendia/statab/83ed.html providing the total U.S. population in 1962 was approximately 186 million people.

25. Every year, approximately 28 Americans are killed from lightening and 700,000 from cardiovascular disease. *See* CDC's webpage *U.S. Lightning Strike Deaths*, available at https://www.cdc.gov/disasters/lightning/victimdata/infographic.html, and CDC webpage *Heart Disease* Facts, available at https://www.cdc.gov/heartdisease/facts.htm.

26. Japan tracked over 100,000 of its citizens for over 22 years and found, *inter alia*, a statistically significant reduction in mortality from cardiovascular disease and stroke among those who had measles and mumps as reflected in the following truncated table and chart from the study:

Table 2
Age-adjusted and multivariable hazard ratios (HR) and 95% Confidential Intervals (CI) for Cause-specific mortality according to history of measles or mumps.

History of measles or mumps	Men				Women			
	None	Measles only	Mumps only	Measles and mumps	None	Measles only	Mumps only	Measles and mumps
No. at risk	21,245	14,671	730	7043	24,950	21,202	1256	12,739
Person-years	326,940	236,327	11,802	116,443	411,090	358,358	19,963	209,207
Total stroke, n	946	613	11	159	803	640	31	193
Age-adjusted HR (95% CI)	1.00	0.97 (0.87–1.07)	0.52 (0.29–0.94)	0.83 (0.70–0.98)	1.00	1.07 (0.96–1.18)	1.24 (0.86–1.77)	0.85 (0.73–0.99)
Multivariable HR (95% CI)[a]	1.00	0.95 (0.85–1.06)	0.52 (0.29–0.94)	0.83 (0.70–0.99)	1.00	1.06 (0.95–1.19)	1.27 (0.88–1.82)	0.85 (0.72–0.99)
+ history of CVD[b]	1.00	0.95 (0.85–1.06)	0.52 (0.28–0.94)	0.83 (0.69–0.98)	1.00	1.06 (0.94–1.19)	1.22 (0.87–1.75)	0.84 (0.71–0.99)
Total cardiovascular disease, n	2243	1383	38	365	1913	1378	57	439
Age-adjusted HR (95% CI)	1.00	0.92 (0.86–0.99)	0.76 (0.55–1.04)	0.80 (0.71–0.89)	1.00	0.97 (0.91–1.05)	0.98 (0.75–1.27)	0.83 (0.75–0.92)
Multivariable HR (95% CI)[a]	1.00	0.92 (0.86–0.99)	0.75 (0.55–1.04)	0.81 (0.72–0.91)	1.00	0.98 (0.91–1.06)	1.01 (0.78–1.32)	0.83 (0.75–0.93)
+ history of CVD[b]	1.00	0.92 (0.85–0.99)	0.75 (0.54–1.04)	0.80 (0.71–0.90)	1.00	0.97 (0.90–1.05)	0.97 (0.75–1.27)	0.83 (0.74–0.92)

[a] Adjusted for age, body mass index, history of hypertension, history of diabetes, family history of CVD, alcohol intake, energy intake, smoking status, walking, sports, perceived mental stress and education.
[b] Further adjustment for history of CVD. CVD indicates cardiovascular disease.

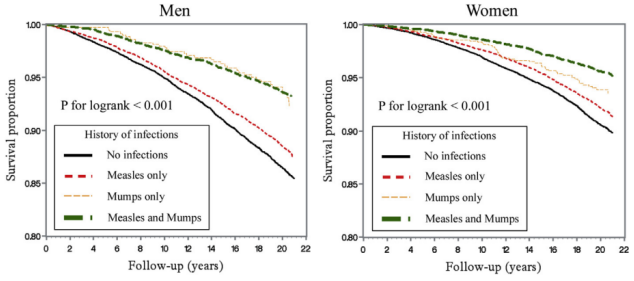


Fig. 1. Kaplan-Meire survival curves of mortality from total cardivascular disease according to the history of infections among men and women.

Attached as **Exhibit 24** is a true and correct copy of *Association of measles and mumps with cardiovascular disease: The Japan Collaborative Cohort (JACC) study*, available at https://pubmed.ncbi.nlm.nih.gov/26122188/.[2]

27. The MMR and chicken pox vaccines involve harvesting live parts of aborted babies and include, in each vaccine dose, DNA and cellular material derived therefrom. (ECF 49-3 ¶¶ 2-6).

III. SMALLPOX, OTHER PATHOGENS, & GENERAL SAFETY

28. Smallpox vaccine is not required to attend school in West Virginia. Attached as **Exhibit 25** is the West Virginia Immunization Requirements, available at https://oeps.wv.gov/immunizations/Documents/school/New_School_Entry.pdf and https://oeps.wv.gov/immunizations/Documents/school/7-12_School_Entry.pdf.

29. There are over 1,000 known pathogens for which no vaccine exists. *Compare* https://wwwnc.cdc.gov/eid/article/11/12/05-0997_article ("literature survey identified 1,407

[2] Similar to the finding regarding heart disease, but in studies less robust, studies reflect having measles appears to confer other health benefits. For example, the International Agency for Research on Cancer found that those who never had measles had a 66% increased rate of Non-Hodgkin Lymphoma and a 233% increased rate of Hodgkin Lymphoma. *See* https://pubmed.ncbi.nlm.nih.gov/16406019/ (See Table 2 and in the Non-Hodgkin's Lymphoma (NHL) column divide the odds ratio 1 (never had measles) with .6 (had measles) which results in a 66% increased risk, and in the Hodgkin's Lymphoma (HL) column divide the odds ratio 1 (never had measles) with .3 (had measles) which results in a 233% increased risk.); https://seer.cancer.gov/statfacts/ (an estimated 21,170 Americans died of these cancers in 2022); https://pubmed.ncbi.nlm.nih.gov/4574047/ (reporting remission of Hodgkin's disease after having measles). Researchers at the Department of Health Care and Epidemiology at the University of British Columbia and the Department of Biology at the University of Victoria found that those who never had measles had a 50% increased rate of ovarian cancer. *See* https://pubmed.ncbi.nlm.nih.gov/16490323/; https://seer.cancer.gov/statfacts/html/ovary.html. (an estimated 12,810 died of this cancer in 2022). Other studies have reached similar conclusions that measles as well as mumps, rubella, pertussis and chickenpox, reduce the rate of various forms of other cancers, including a study from researchers at the University of Berne, Switzerland that specifically reviewed these fever inducing (*i.e.,* febrile) infections and found that the "study consistently revealed a lower cancer risk for patients with a history of FICD [febrile infectious childhood diseases]." https://pubmed.ncbi.nlm.nih.gov/9824838/. Studies have also found that children who have had measles have far less allergies and atopic diseases, such as asthma, and adults who had measles have a reduced risk of Parkinson's Disease. *See* https://pubmed.ncbi.nlm.nih.gov/19255001/; https://pubmed.ncbi.nlm.nih.gov/16854347/ and https://pubmed.ncbi.nlm.nih.gov/4061437/.

recognized species of human pathogen") *with* https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states ("Vaccines Licensed for Use").

30. Merck, GSK, and Sanofi make all the vaccines products required to attend school in West Virginia, and these companies disclose in Section 6.2 of the package insert for each numerous serious adverse events they have a basis to believe are casually related to these products. A true and correct copy of the FDA's *Vaccines Licensed for Use in the United States* webpage is available at https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states (links to copies of each package that disclose "*only* those adverse events for which there is some basis to believe there is a *causal relationship* between the drug and the occurrence of the adverse event" 21 C.F.R. 201.57(c)(7) (emphasis added), and reflect in Section 6.1 that none were licensed based on a long-term placebo controlled trial).

Pursuant to 28 U.S.C. §1746, I declare under penalties of perjury under the laws of the United States of America that the foregoing Declaration is true and correct to the best of my knowledge and belief and that such facts are made based on my personal knowledge.

Executed on July 21, 2023

/s/ Aaron Siri
Aaron Siri

Exhibit 1

Polio Vaccination

Pronounced [PO-lee-oh]

Polio, or poliomyelitis, is a disabling and potentially deadly disease. It is caused by the poliovirus. The virus spreads from person to person and can infect a person's spinal cord, causing paralysis (can't move parts of the body).

There is no cure for polio, but it can be prevented with safe and effective vaccination. Inactivated polio vaccine (IPV) is the only polio vaccine that has been given in the United States since 2000. It is given by shot in the arm or leg, depending on the person's age. Oral polio vaccine (OPV) is used in other countries.

CDC recommends that children get four doses of polio vaccine. They should get one dose at each of the following ages:

- 2 months
- 4 months
- 6 through 18 months
- 4 through 6 years

Polio Vaccination: What Everyone Should Know

Polio Vaccination: Information for Healthcare Professionals

Page last reviewed: August 11, 2022

Exhibit 2

CDC Centers for Disease Control and Prevention

U.S. National Authority for Containment of Poliovirus

Polio Disease and Poliovirus Containment

Poliovirus Containment

Poliovirus containment is focused on eradicated polioviruses. Wild poliovirus type 2 (WPV2) and wild poliovirus type 3 (WPV3) were declared eradicated in 2015 and 2019, respectively. Containment measures are in place for laboratories and other facilities that handle or store eradicated polioviruses.

Polio, or poliomyelitis, is a crippling and potentially deadly infectious disease.
Learn more about the symptoms and how the virus is spread from person-to-person.

Polio vaccine provides the best protection against polio disease.Two types of vaccines are used to prevent polio disease– inactivated polio vaccine (IPV) and oral polio vaccine (OPV).

CDC and its international partners have made significant progress towards polio eradication.
Learn more about CDC's polio eradication efforts and the Global Polio Eradication Initiative.

There are three types of wild poliovirus (WPV): type 1, type 2, and type 3. People must protect themselves against all three types of the virus to prevent polio disease. Polio vaccination is the best protection.

Type 2 wild poliovirus was declared eradicated in September 2015. The last detection was in India, 1999. Type 3 wild poliovirus was declared eradicated in October 2019. It was last detected in November 2012. Only type 1 wild poliovirus remains.

There are two vaccines used to protect against polio disease: oral polio vaccine and inactivated poliovirus vaccine. For more information see OPV Cessation – GPEI (polioeradication.org) .

Oral polio vaccine

The oral poliovirus vaccine (OPV) is used in many countries to protect against polio disease. Oral poliovirus vaccine contains attenuated or weakened version of either one (monovalent OPV), two (bivalent OPV), or all three (trivalent OPV) poliovirus types.

After wild poliovirus type 2 was declared eradicated in 2015, the world switched from trivalent OPV to bivalent OPV. Bivalent OPV contains poliovirus type 1 and 3. This switch means that the bOPV used globally no longer protects against WPV2. Countries that use bOPV for routine immunization have added a single dose of IPV to protect against WPV2.

In rare instances, the vaccine-virus may be able to circulate over time and mutate in communities with insufficient immunity or immunocompromised individuals. These mutated OPV strains can cause polio disease. They are called vaccine-derived polioviruses (VDPVs).

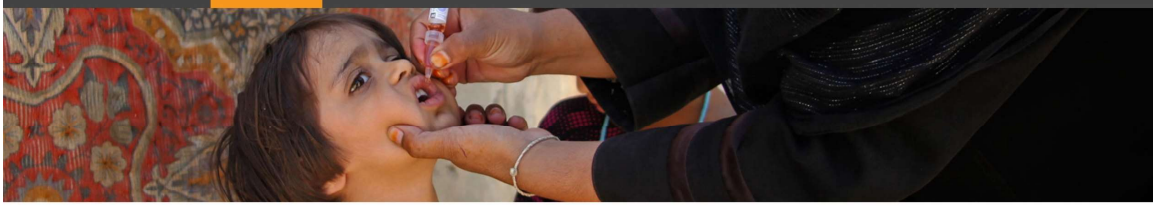
For more information on polio vaccination see Polio Vaccination | CDC.

Inactivated poliovirus vaccine

IPV protects people against all three types of poliovirus. IPV does not contain live virus and cannot cause disease. It protects people from polio disease but does not stop transmission of the virus.

OPV can be used to contain a polio outbreak. Use of all OPV will stop when polio is eradicated globally. This will prevent re-establishment of transmission from VDPVs. For more information on polio vaccination see Polio Vaccination | CDC.

Last Reviewed: December 2, 2022, 10:55 AM



IPV

Inactivated poliovirus vaccine

© GAVI

Inactivated polio vaccine (IPV) was developed in 1955 by Dr Jonas Salk. Also called the Salk vaccine IPV consists of inactivated (killed) poliovirus strains of all three poliovirus types. IPV is given by intramuscular or intradermal injection and needs to be administered by a trained health worker. IVP produces antibodies in the blood to all three types of poliovirus. In the event of infection, these antibodies prevent the spread of the virus to the central nervous system and protect against paralysis.

Advantages

- As IPV is not a 'live' vaccine, it carries no risk of VAPP.
- IPV triggers an excellent protective immune response in most people.

Disadvantages

- IPV induces very low levels of immunity in the intestine. As a result, when a person immunized with IPV is infected with wild poliovirus, the virus can still multiply inside the intestines and be shed in the faeces, risking continued circulation.
- IPV is over five times more expensive than OPV. Administering the vaccine requires trained health workers, as well as sterile injection equipment and procedures.

Safety

IPV is one of the safest vaccines in use. No serious systemic adverse reactions have been shown to follow vaccination.

Efficacy

IPV is highly effective in preventing paralytic disease caused by all three types of poliovirus.

Recommended use

An increasing number of industrialized, polio-free countries are using IPV as the vaccine of choice. This is because the risk of paralytic polio associated with continued routine use of OPV is deemed greater than the risk of imported wild virus.

However, as IPV does not stop transmission of the virus, OPV is used wherever a polio outbreak needs to be contained, even in countries which rely exclusively on IPV for their routine immunization programme.
Once polio has been eradicated, use of all OPV will need to be stopped to prevent re-establishment of transmission due to VDPVs.

Related Resources

IPV and routine immunization

Exhibit 3

Centers for Disease Control and Prevention

Tetanus

Tetanus Home

About Tetanus

Tetanus is different from other vaccine-preventable diseases because it **does not spread from person to person**. The bacteria are usually found in soil, dust, and manure and enter the body through breaks in the skin — usually cuts or puncture wounds caused by contaminated objects.

Causes and How It Spreads

Diagnosis and Treatment

Symptoms and Complications

Prevention

Related Resource

Tetanus Communication and Print Resources

Last Reviewed: August 29, 2022

Exhibit 4

Diphtheria Immunization

Effect Upon Carriers and the Control of Outbreaks

Louis W. Miller, MD; J. Justin Older, MD; James Drake; and Sherwood Zimmerman, Austin, Tex

A diphtheria epidemic in a small central Texas community centered in the elementary school. Epidemiological investigation at the school included throat cultures and immunization histories of 306 of the 310 students and staff. Of these, 104 (34%) had culture-proven diphtheria infections; 15 were symptomatic cases and 89 were carriers. There was no statistical difference in the risk of diphtheria infection among those with full, lapsed, inadequate, or no previous diphtheria immunizations. However, the risk of symptomatic diphtheria was 30 times as great for those with none, and 11.5 times as great for those with inadequate immunizations as for those fully immunized. Diphtheria toxoid helps prevent symptomatic disease but does not prevent the carrier state nor stop the spread of infection. Identifying, isolating, and treating carriers are very important aspects in the control of diphtheria outbreaks.

With the increase in the number of cases of diphtheria in the United States during the past few years, the effect of immunization on the control of outbreaks has become an important question. In the Austin, Tex, diphtheria epidemic of 1967-1969[1] cases continued to occur despite the administration of 155,200 doses of diphtheria toxoid and the concomitant rise in immunization levels of school age children from 68% to 89%. Data from the Austin outbreak suggested that a large reservoir of carriers was important in the continued transmission of *Corynebacterium diphtheriae*. Other diphtheria outbreaks have shown that epidemics occur in populations with high immunization levels.[2-4] A diphtheria outbreak in an elementary school in Elgin, Tex, in the spring of 1970 provided an opportunity to study the effects of immunization on carriers and on the control of an epidemic situation.

Table 1.—Definitions of Immunization Status*

Status	Definition
Full	Primary series (three or more injections), or a primary series plus a booster, completed within ten years.
Lapsed	Primary series, or a primary series plus booster, completed more than ten years ago.
Inadequate	Uncompleted primary series (less than three injections) at any time.
None	No diphtheria toxoid ever received.

* Adapted from the Center for Disease Control.[6]

Materials and Methods

When it became obvious in the Elgin diphtheria epidemic (Older JJ et al, unpublished data) that cases were clustered in the elementary school, a special throat culture and immunization survey was begun there. Throat cultures were obtained from and immunization status was determined for 306 of 310 students and staff. Throat swabs were taken on three separate occasions from each person: April 7, April 17, and May 4. These were streaked on Loeffler blood serum or Pai medium and incubated overnight. Cystine tellurite blood agar and Tinsdale medium were used for isolation, Elek-King agar diffusion plates were used for toxigenicity determination.

Immunization status information was

Received for publication Oct 11, 1971; accepted Dec 6.

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obtained by personal interview and review of available school and medical records. The status of each person classified as "adequate," "lapsed," "inadequate," and "none," according to the definitions of the Center for Disease Control[5] (Table 1).

Any person with a sore throat or other symptoms compatible with diphtheria and a positive culture for *C diphtheriae* organisms was classified as a "case." A person without symptoms but who had a positive throat culture for *C diphtheriae* organisms was classified as a "carrier." The term "infection" applied to anyone with a positive culture regardless of his clinical state and, therefore, included both cases and carriers.

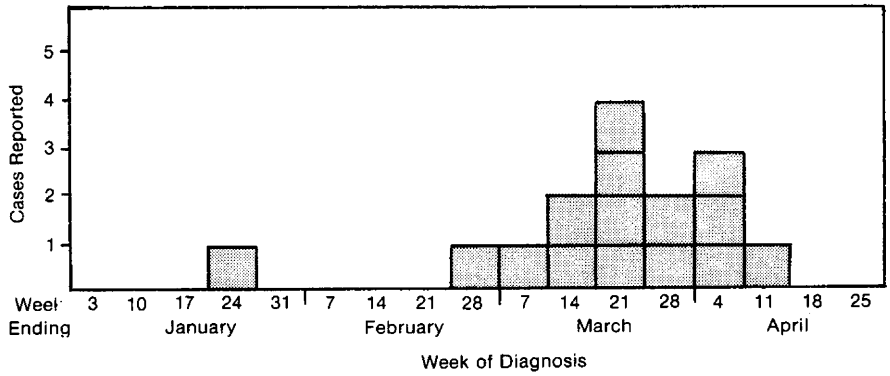
Results

When diphtheria was first diagnosed in the elementary school, 67% of the children and staff were already fully immunized, and 97% had had at least one dose of diphtheria toxoid. The first case in the elementary school population was diagnosed in late February 1970, and by April 8, 15 cases had occurred (Figure).

Throat cultures were done on 306 children and staff; toxigenic *C diphtheriae*, gravis type, was isolated from 104 (34%). Fifteen of these (14%) were cases, and 89 (86%) were carriers. There was *no* statistical difference in the risk of diphtheria infection among those with full, lapsed, inadequate, or no previous diphtheria immunization (Table 2). However, the risk of becoming a case was 30 times as great for those with no immunization and 11.5 times as great for those with inadequate immunizations as for those with full diphtheria immunization (Table 3). Among the 104 infected with *C diphtheriae*, the risk of being symptomatic was 13.3 times as great for those inadequately immunized and 37.0 times as great for those with no previous immunizations as for those who were fully immunized (Table 4).

Comment

The importance of carriers in the spread of diphtheria was well documented by Doull and Lara[6] in the



Diphtheria cases in Elgin, Tex, elementary school, spring 1970.

Table 2.—Immunization and Culture Status of Students and Staff, Elgin, Tex, Elementary School, Spring 1970

Immunization Status	Culture Status: Positive	Culture Status: Negative	Culture Status: Total	Diphtheria Infection Attack Rate (per 100)
Full	73	132	205	35.6
Lapsed	0	4	4	0
Inadequate	28	59	87	32.4
None	3	7	10	30.0
Total	104	202	306	34.0

Table 3.—Immunization Status of Diphtheria Cases, Elgin, Tex, Elementary School, Spring 1970

Immunization Status	Cases	No. at Risk	Diphtheria Case Attack Rate (per 100)
Full	2	205	1.0
Lapsed	0	4	0
Inadequate	10	87	11.5
None	3	10	30.0
Total	15	306	4.9

Table 4.—Risk of Symptoms and Immunization Status of Students and Staff With Positive Diphtheria Cultures, Elgin, Tex, Elementary School, Spring 1970

Immunization	Symptomatic Cases	Asymptomatic Carriers	Total Infected	Symptom Attack Rate (per 100 Positive Cultures)	Relative Risk
Full	2	71	73	2.7	. . .
Inadequate	10	18	28	35.8	13.3
None	3	0	3	100.0	37.0
Total	15	89	104	14.4	. . .

early 1920s. In very thorough investigations, only about 20% of diagnosed diphtheria cases could be traced to another suspected case, and the remaining 80% of the cases were attributed to asymptomatic carriers in the population. Recent epidemics in Austin[1] and Elgin,[5] Tex, provided ample evidence that carriers continue to play a very important role in the transmission of diphtheria.

When diphtheria toxoid became available, it was generally believed that it induced immunity that protected individuals from symptomatic illness but not from asymptomatic infection. This was based on the observation that immunity is related to the neutralization of toxin elaborated by *C diphtheriae* and not interference with diphtheria infection.

In 1936, Frost et al[7] alluded to a paucity of observations on record concerning antitoxic immunity and the carrier state. Nonetheless, he stated that the limited data suggested that there is little, if any, difference between those individuals with and those without antitoxic immunity in their risk of becoming infected.

More recently, Tasman and Lansberg[8] put forth the hypothesis that toxoid use reduces the number of carriers. This is based on surveys that showed a steady decline in the prevalence of carriers. Since toxoid immunization does prevent cases and since cases are more contagious than carriers,[6] the decline in carriers could be due to the decrease in contagious cases rather than to the direct effects of immunization.

The findings in Elgin corroborate the assumptions of Frost et al[7] and show that there is no difference in the risk of diphtheria acquisition among those with full, lapsed, inadequate, and no immunizations. However, they also demonstrate the value of immunization in reducing the risk of disease and show that the protection against symptomatic illness afforded those infected with *C diphtheriae* is directly related to their immunization status.

Some authors[9] have estimated that if 70% or 80% of the population were adequately immunized against diphtheria, spread of diphtheria would be prevented. However, diphtheria outbreaks have been described in populations with as much as 94% of the people being previously immunized.[2-4] These outbreaks, the known importance of carriers in the spread of diphtheria, and the demonstrated failure of toxoid to prevent the carrier state lead us to conclude that the concept of herd immunity is not applicable in the prevention of diphtheria. A high level of community immunization will not stop the transmission of diphtheria, but it will limit the number of contagious cases. At the first appearance of a diphtheria case, control activities should be directed toward identifying, isolating, and treating carriers, as well as toward immunizing persons with less than full immunization status. This dual approach will reduce or eliminate the spread of infection by reducing the number of carriers, and it will reduce the number of cases by improving the immunization status of exposed individuals.

Roy Morris, MD, Elgin city health officer, treated the majority of cases and arranged for treatment of carriers; Milton Saxon, Elgin school superintendent, and Eva C. Danklefs, Elgin school nurse helped arrange culture surveys; M.S. Dickerson, MD, coordinated federal, state, and local assistance and support; Will Callihan assisted in culture surveys, interviews, and immunization of patients; Jesse V. Irons, ScD, and Carl D. Heather, DVM, coordinated state laboratory assistance; H.D. Bredthauer and Lucie M. Hickman, Texas State Department of Health, processed bacteriological specimens; and Wallis Jones, PhD, Susan Bickham, Geraldine Wiggins, and Jane McLaughlin, Laboratory Division, Center for Disease Control, Atlanta, processed specimens and performed all typing of *C diphtheriae* organisms. All isolates from the initial throat cultures were typed by the Bacteria Immunology Unit, Center for Disease Control.

References

1. Zalma VM, Older JJ, Brooks GF: The Austin, Texas, diphtheria outbreak. *JAMA* **211**:2125-2129, 1970.
2. Murphy WF, Maley VH, Dick L: Continued high incidence of diphtheria in a well immunized community. *Public Health Rep* **71**:481-486, 1956.
3. Fanning J: An outbreak of diphtheria in a highly immunized community. *Brit Med J* **1**:371-373, 1947.
4. Corothers TE, Zatlin GS: An outbreak of diphtheria: A story of investigation and control. *Clin Pediat* **5**:29-33, 1966.
5. *Diphtheria Surveillance Report No. 9.* Atlanta, National Communicable Disease Center, 1969.
6. Doull JA, Lara H: The epidemiologic importance of diphtheria carriers. *Amer J Hyg* **5**:508-529, 1925.
7. Frost WH, Frobisher M Jr, VonVolkenburgh VA, et al: Diphtheria in Baltimore: A comparative study of morbidity, carrier prevalence and antitoxic immunity in 1921-1924 and 1933-1936. *Amer J Hyg* **24**:568-586, 1936.
8. Tasman A, Lansberg HP: Problems concerning the prophylaxis, pathogenesis and therapy of diphtheria. *Bull WHO* **16**:939-973, 1957.
9. Wilson GS, Miles AA: *Topley and Wilson's Principles of Bacteriology and Immunity.* Baltimore, Williams & Wilkins Co, 1957, pp 1587-1588.

Exhibit 5

Table 1

COVID-19 vaccination recommendations have changed. Find the latest recommendations at www.cdc.gov/covidschedule

Recommended Adult Immunization Schedule for ages 19 years or older, United States, 2023

Vaccine	19–26 years	27–49 years	50–64 years	≥65 years
COVID-19	2- or 3- dose primary series and booster (See Notes)			
Influenza inactivated (IIV4) or **Influenza recombinant** (RIV4)	1 dose annually			
or		or		
Influenza live, attenuated (LAIV4)	1 dose annually			
Tetanus, diphtheria, pertussis (Tdap or Td)	1 dose Tdap each pregnancy; 1 dose Td/Tdap for wound management (see notes)			
	1 dose Tdap, then Td or Tdap booster every 10 years			
Measles, mumps, rubella (MMR)	1 or 2 doses depending on indication (if born in 1957 or later)			For healthcare personnel, see notes
Varicella (VAR)	2 doses (if born in 1980 or later)		2 doses	
Zoster recombinant (RZV)	2 doses for immunocompromising conditions (see notes)		2 doses	
Human papillomavirus (HPV)	2 or 3 doses depending on age at initial vaccination or condition	27 through 45 years		
Pneumococcal (PCV15, PCV20, PPSV23)	1 dose PCV15 followed by PPSV23 OR 1 dose PCV20 (see notes)			See Notes
				See Notes
Hepatitis A (HepA)	2, 3, or 4 doses depending on vaccine			
Hepatitis B (HepB)	2, 3, or 4 doses depending on vaccine or condition			
Meningococcal A, C, W, Y (MenACWY)	1 or 2 doses depending on indication, see notes for booster recommendations			
Meningococcal B (MenB)	2 or 3 doses depending on vaccine and indication, see notes for booster recommendations			
	19 through 23 years			
***Haemophilus influenzae* type b** (Hib)	1 or 3 doses depending on indication			

Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection

Recommended vaccination for adults with an additional risk factor or another indication

Recommended vaccination based on shared clinical decision-making

No recommendation/ Not applicable

Exhibit 6

Vaccination Coverage among Adults in the United States, National Health Interview Survey, 2019–2020

Summary

The Centers for Disease Control and Prevention (CDC) recommends vaccinations for adults based on age, health conditions, prior vaccinations, and other considerations to prevent morbidity and mortality from vaccine-preventable diseases. Updated vaccination recommendations for adults from CDC are published annually, and Healthy People 2030 (HP2030) objectives include increasing the proportion of adults aged 19 years or older who receive recommended age-appropriate vaccines. Still, vaccination coverage among U.S. adults remains low for most vaccines.

To assess vaccination coverage among adults aged ≥19 years, CDC analyzed data from the National Health Interview Survey (NHIS). NHIS is a continuous, cross-sectional national household survey of the noninstitutionalized U.S. civilian population. In a probability sample of households, interviews are conducted over the course of the year and data are compiled and released on an annual basis. For this report, adult receipt of influenza, pneumococcal, herpes zoster, and Td/Tdap vaccines was assessed using data from 2019 and 2020. A composite adult vaccination quality measure (1), which tracks routinely recommended age-appropriate vaccination among adults, was assessed using 2019 data, and trends in adult vaccination were examined during 2010–2020 with a particular focus on vaccination coverage since 2016 to represent recent trends in adult vaccination.

Coverage for the age-appropriate composite adult vaccination measures for 2019 was low (<45%) for both versions of the composite measure among adults aged ≥19 years and among all race/ethnicity groups for adults aged ≥19 (<50%). Coverage for all vaccines differed by race/ethnicity with generally lower coverage among non-White adults compared with White adults. Linear trend tests since 2016 indicated that coverage increased for influenza, herpes zoster and Tdap vaccination and remained stable for pneumococcal and vaccination with any tetanus-containing vaccine.

Substantial improvement in adult vaccination uptake is needed to reduce the burden of vaccine-preventable diseases. Increasing the proportion of adults who receive recommended age-appropriate vaccines and assuring equitable access to and uptake of recommended vaccines is a high-priority public health issue.

Methods

The NHIS is a continuous, cross-sectional national household survey of the noninstitutionalized U.S. civilian population conducted by the U.S. Census Bureau for CDC's National Center for Health Statistics. Due to data collection difficulties posed by the COVID-19 pandemic, the 2020 NHIS shifted from in-person interviewing to all-telephone interviewing starting in late March and continuing through June 2020. From July through December 2020, data collection in select areas was opened for in-person interviewing, however, NHIS data collection remained predominantly by telephone during this period (2). NHIS's objective is to monitor the health of the U.S. population and provide estimates of health indicators, health care use and access, and health-related behaviors (3). Non-institutionalized adults aged ≥19 years with interviews conducted during August 2019–June 2020 (for influenza vaccination), January–December 2020 (for pneumococcal and herpes zoster vaccination), and January–December 2019 (for Td and Tdap vaccination) were included in this analysis. (Information on Td or Tdap vaccination was not collected in the 2020 NHIS.) The total sample of persons aged ≥19 years was 31,633 in 2019 and 31,360 in 2020. The final sample adult core response rate was 59.1% for the 2019 NHIS and 48.9% for the 2020 NHIS. Questions about receipt of vaccinations recommended for adults are asked of one randomly selected adult within each family in the household.

Weighted data were used to produce national vaccination coverage estimates. For non-influenza adult vaccination coverage estimates, the weighted proportion of respondents who reported receiving selected vaccinations was calculated. To better assess influenza vaccination coverage each season, the Kaplan-Meier survival analysis procedure was used. Race/ethnicity was categorized as follows: White, Black, Hispanic, Asian, and Other. In this report, persons categorized as White, Black, Asian, or Other race identified as non-Hispanic. Persons categorized as Hispanic might be of any race. Persons characterized as Other include those who identified as American Indian/Alaska Native and persons who identified multiple races. The five race/ethnicity categories are mutually exclusive.

For the adult vaccination composite measure, data from the 2019 NHIS were analyzed to determine estimates for a composite measure of vaccination coverage for select vaccines routinely recommended for all adults aged ≥19 years (Td, Tdap, and influenza vaccine) or indicated based on age (herpes zoster and pneumococcal vaccines), and for three age groups (19–59 years, 60–64 years, and ≥65 years) based on the vaccines recommended for those age groups. Estimates for composite measures were calculated to include any tetanus-toxoid containing vaccine in the past 10 years, with and without influenza vaccination in the past 12 months. Point estimates and 95% confidence intervals (CIs) were calculated by using SUDAAN software (Research Triangle Institute, Research Triangle Park, NC, version 11.0.1) to account for the complex sample design. T-tests were used for comparisons between data years and for comparisons of each level of each respondent characteristic to a chosen referent level (e.g., for race/ethnicity, White was the reference group). Statistical significance was defined as $p<0.05$. Coverage estimates are not reported for small sample size ($n<30$) or large relative standard errors (standard error/estimate >0.3).

Results

Pneumococcal Vaccination

- Pneumococcal vaccination coverage overall (≥1 dose of PPSV23 or PCV13) among adults aged 19–64 years at increased risk for pneumococcal disease was 23.9% in 2020, similar to the estimate for 2019.
  - Coverage among White adults aged 19–64 years at increased risk was higher (26.3%) compared with Hispanic (16.7%) and Asian (13.8%) adults.
- Coverage among adults aged ≥65 years was 67.5%, similar to the estimate for 2019.
  - Coverage among White adults aged ≥65 years (72.4%) was higher compared with Black (50.8%), Hispanic (48.1%), and Asian (54.9%) adults.

TABLE 1. Estimated proportion of adults aged ≥19 years who ever received pneumococcal vaccination by increased-risk status and race/ethnicity — National Health Interview Survey, United States, 2020

Herpes Zoster Vaccination

- Overall, herpes zoster vaccination coverage among adults aged ≥50 and ≥60 years in 2020 was 29.4% and 39.1%, respectively, higher than estimates for 2019.
  - White adults aged ≥50 and ≥60 years had higher coverage compared with Black, Hispanic, and Other adults.
- Zoster vaccine live (ZVL) coverage in 2020 was 17.8% among adults aged ≥50 years, 4.0% among adults aged 50–59 years, and 25.5% among adults aged ≥60 years, all lower than estimates for 2019.
- Recombinant zoster vaccine (RZV) coverage (≥1 dose) was 14.1% among adults aged ≥50 years, 7.3% among adults aged 50–59 years, and 17.9% among adults aged ≥60 years, all higher than estimates for 2019.
  - RZV coverage (at least 2 doses) was 10.8% among adults aged ≥50 years, 13.9% among adults aged ≥60 years, and 15.1% among adults aged ≥65 years, all higher than estimates for 2019.

TABLE 2. Estimated proportion of adults aged ≥50 years who ever received herpes zoster vaccination, by age and race/ethnicity — National Health Interview Survey, United States, 2020

Tetanus Vaccination Coverage (Td and Tdap)

- In 2019, the proportion of adults aged ≥19 years reporting having received any tetanus toxoid–containing vaccination during the past 10 years was 62.9%, similar to 2018.
  - White adults had higher coverage compared with Black, Hispanic, and Asian adults.
- Among adults aged ≥19 years for whom Tdap vaccination could be assessed specifically, overall coverage was 30.1%, similar to the estimate for 2018.

TABLE 3. Estimated proportion of adults aged ≥19 years who in the past 10 years received any tetanus vaccination and Tdap vaccination, by race/ethnicity and overall by age group — National Health Interview Survey, United States, 2019

Adult Vaccination Composite Measure

- In 2019, few adults aged ≥19 years had received all age-appropriate vaccines (including influenza vaccination) included in the composite measure (21.8%).
- Coverage for the composite adult vaccination quality measure was low in all age groups, ranging from 8.2% among adults aged 50–64 years to 27.6% among adults aged 19–49 years.
  - Low coverage with herpes zoster vaccine was the primary driver of low coverage among adults aged 50–64 years.
- Coverage for the composite adult vaccination quality measure (including influenza vaccination) was lower among Black (15.9%) and Hispanic (17.3%) adults compared with White (23.7%), Asian (23.5%) and Other (25.7%) adults aged ≥19 years.

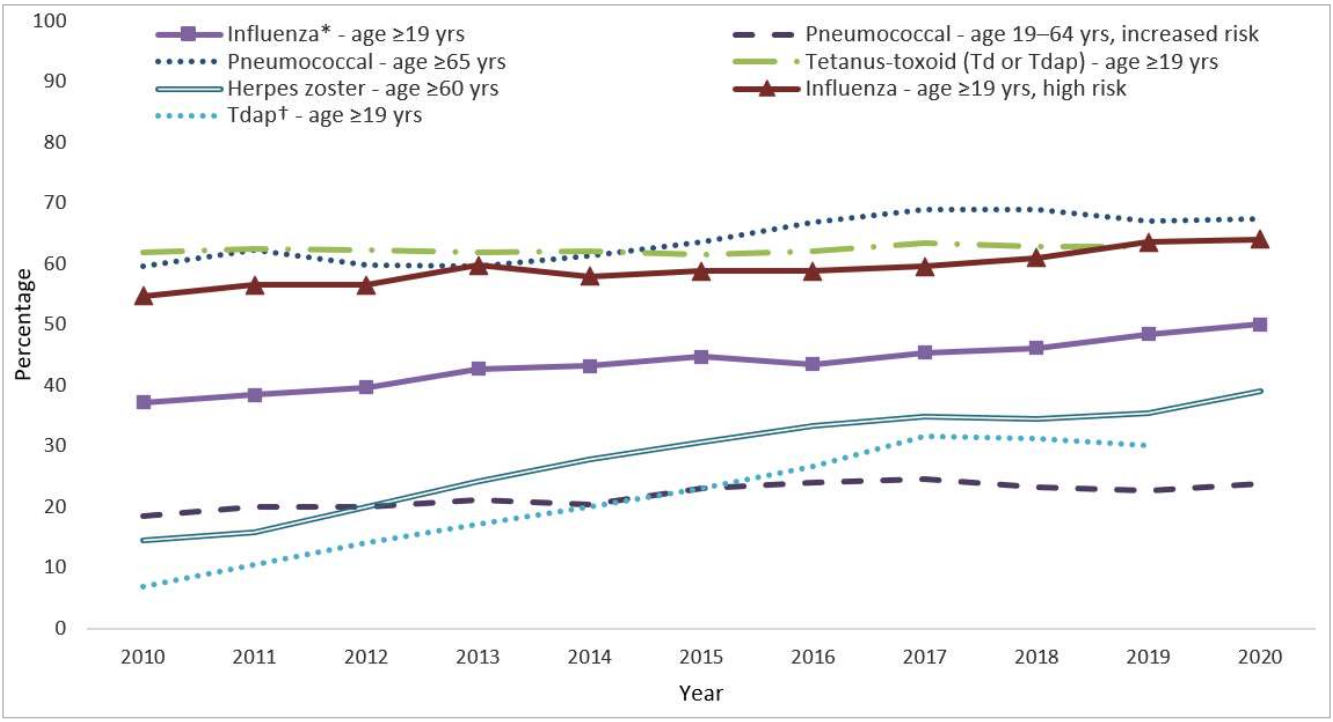
TABLE 4. Vaccination coverage estimates using an age-appropriate composite adult vaccination quality measure and individual component measures, by age group — National Health Interview Survey, United States, 2019

TABLE 4_1. Vaccination coverage estimates using an age-appropriate composite* adult vaccination quality measure and individual component measures, by race/ethnicity† — National Health Interview Survey, United States, 2019

Trends in Adult Vaccination Coverage

- Trends in coverage with select vaccines recommended for adults from 2010–2020 are shown in the Figure.
- While coverage for all vaccines except any tetanus-containing vaccine (Td or Tdap) increased since 2010, coverage for several vaccines has plateaued in recent years.
- From 2016–2020, increases in coverage were observed for influenza vaccination among adults aged ≥19 years (annual average percentage point increase: 1.6%, 95% CI 1.2, 2.0); herpes zoster vaccination among adults aged ≥60 years (annual average percentage point increase: 1.2%, 95% CI 0.8, 1.6); and Tdap vaccination among adults aged ≥19 years (annual average percentage point increase: 1.0%, 95% CI 0.4, 1.5). Coverage for pneumococcal vaccination and for any tetanus-containing vaccine (Td or Tdap) remained stable from 2016–2020.

FIGURE. Estimated proportion of adults aged ≥19 years who received selected vaccines, by age group and risk status — National Health Interview Survey, United States, 2010–2020



Abbreviations: Td = tetanus and diphtheria toxoids; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine.

* Estimates are season-specific. Year 2020 corresponds to the 2019-20 influenza season.

† Tdap vaccination coverage data among adults aged ≥65 years are available beginning in the NHIS 2012 survey.

Discussion

NHIS data from 2019 and 2020 indicate that many adults in the United States remained unprotected against vaccine-preventable diseases. Adult vaccination coverage remained similar to coverage in the year prior for most vaccines, with small increases observed for herpes zoster vaccination. Racial and ethnic differences in vaccination coverage persisted for all vaccinations, with generally lower coverage among non-White and Hispanic adults compared with White adults. Coverage for the age-appropriate composite measures was low in all age groups and in all race/ethnicity groups.

Many changes to Advisory Committee on Immunization Practices (ACIP) recommendations have occurred since 2010 for the vaccines assessed in this report. Since 1997, ACIP has recommended PPSV23 vaccination of all adults aged ≥65 years and younger adults with certain medical conditions (4). In 2012, ACIP recommended PCV13 to adults aged 19–64 years at increased risk and in 2014 recommended PCV13 in series with PPSV23 for all adults aged ≥65 years; the routine recommendation for PCV13 in adults aged ≥65 years was changed in 2019 to a recommendation for administration of PCV13 based on shared clinical decision-making for adults aged ≥65 years who do not have an immunocompromising condition, cerebrospinal fluid lead, or cochlear implant, and who have not previously received PCV13 (5–7). In 2021, ACIP recommended 15-valent or 20-valent PCV for PCV-naïve adults previously eligible for pneumococcal vaccine; when PCV15 is used, it should be followed by a dose of PPSV23 ≥1 year later (8). Despite many changes in recommendations, at least one dose of pneumococcal vaccine has been recommended for eligible adults throughout the period assessed in the report; since 2014, two doses of pneumococcal vaccine have been recommended for certain adults aged ≥65 years. In 2006, ACIP recommended ZVL for adults aged ≥60 years and in 2017, ACIP preferentially recommended RZV for use in immunocompetent adults aged ≥50 years over ZVL due to higher and longer-lasting efficacy (9, 10). In 2021, ACIP recommended two doses of RZV for use in immunodeficient or immunosuppressed adults aged ≥19 years (11). In 2012, ACIP recommended Tdap to all adults aged ≥19 years who have not yet received a dose of Tdap, regardless of interval since the last Td shot (12) and in 2019, updated its recommendations to allow either Td or Tdap to be used for the decennial Td booster, prophylaxis for wound management, and for catch-up doses (13).

The largest average annual changes in vaccination coverage since 2010 have occurred for herpes zoster (2.4%) and Tdap (2.8%) vaccination while smaller increases occurred for influenza and pneumococcal vaccination. Linear trend tests from 2016 indicate increases in coverage for these vaccines have diminished in recent years compared with increases from 2010. Since

the 2010–11 influenza season, ACIP has recommended annual influenza vaccination for all persons aged ≥6 months (14). Though influenza vaccination coverage has continued to increase among all adults since this universal recommendation, coverage remains low with only approximately half of adults vaccinated in the 2019–20 season.

The U.S. Department of Health and Human Services has proposed a developmental HP2030 objective to assess overall adult vaccination performance. This developmental measure targets increasing the proportion of adults aged ≥19 years who receive recommended age-appropriate vaccines. This objective is a high-priority public health issue supported by evidence-based interventions; NHIS data like those presented here are a possible source of the reliable baseline data needed for it to become a core HP2030 objective.

Limitations

The estimates in this report are subject to several limitations. First, all data rely on self-report and were not validated with medical records. However, adult self-reported vaccination status has been shown to be ≥70% sensitive in one or more studies for pneumococcal, tetanus toxoid-containing, herpes zoster, and hepatitis B vaccines and ≥70% specific in one or more studies for all except tetanus and hepatitis B vaccination (15–17). Second, the NHIS response rate was 59.1% in 2019 and 48.9% in 2020. Nonresponse bias can result if respondents and non-respondents differ in their vaccination rates, and if survey weighting does not fully correct for this. Third, NHIS data from 2020 at the start of the COVID-19 pandemic were obtained by telephone rather than in-person interviews and the impact of that change is unknown. While disruptions to certain vaccination services due to COVID-19 have been described (18, 19), vaccination coverage assessed in this report consider cumulative vaccination over time and for 2020 data, any disruptions in health care access or utilization would not be expected to show a substantial impact. Fourth, Tdap estimates are subject to considerable uncertainty and potential for bias. Respondents who reported tetanus vaccination but were unable to say whether Td or Tdap was used (19.1% of respondents reporting tetanus vaccination) were excluded from estimations of Tdap vaccination coverage. Finally, the NHIS sample excludes persons in the military and those residing in institutions, which might result in underestimation or overestimation of vaccination coverage levels.

Conclusion

Despite increases in vaccination coverage among all adults for influenza, herpes zoster and Tdap in recent years, few adults are fully vaccinated according to ACIP recommendations. Disparities in vaccination coverage by race/ethnicity were seen for all vaccines assessed. Increasing the proportion of adults who receive recommended age-appropriate vaccines and assuring equitable access to and uptake of recommended vaccines is a high-priority public health issue.

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References:

1. Shen AK, Williams WW, O'Halloran AC, et al. Promoting adult immunization using population-based data for a composite measure. Am J Prev Med 2018;55:517–23.
2. National Center for Health Statistics. Survey Description, National Health Interview Survey, 2020. Hyattsville, Maryland. 2021. Available at: https://ftp.cdc.gov/pub/Health_Statistics/NCHS/Dataset_Documentation/NHIS/2020/srvydesc-508.pdf .
3. National Center for Health Statistics. National Health Interview Survey, 2020. Public-use data file and documentation. Available at: NHIS – Data, Questionnaires and Related Documentation (cdc.gov)
4. Prevention of pneumococcal disease: Recommendations of the Advisory Committee on Immunization Practice (ACIP). MMWR Recomm Rep 1997;46(No. RR-8).
5. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP).

MMWR Morb Mortal Wkly Rep 2012;61:816–9.

6. Tomczyk S, Bennett NM, Stoecker C, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2014;63:822–5.
7. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: updated recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2019;68:1068–75.
8. Kobayashi M, Farrar JL, Gierke R, et al. Use of 15-Valent Pneumococcal Conjugate Vaccine and 20-Valent Pneumococcal Conjugate Vaccine Among U.S. Adults: Updated Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2022;71:109–17.
9. Hales CM, Harpaz R, Ortega-Sanchez I, Bialek SR. Update on recommendations for use of herpes zoster vaccine. MMWR Morb Mortal Wkly Rep 2014;63:729–31.
10. Dooling KL, Guo A, Patel M, et al. Recommendations of the Advisory Committee on Immunization Practices for use of herpes zoster vaccines. MMWR Morb Mortal Wkly Rep 2018;67:103–8.
11. Anderson TC, Masters NB, Guo A, et al. Use of Recombinant Zoster Vaccine in Immunocompromised Adults Aged ≥19 Years: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2022;71:80-4.
12. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine in adults aged 65 years and older—Advisory Committee on Immunization Practices (ACIP), 2012. MMWR Morb Mortal Wkly Rep 2012;61:468–70.
13. Havers FP, Moro PL, Hunter P, et al. Use of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccines: Updated Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2020;69:77-83.
14. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2010;59(No. RR-8).
15. Rolnick SJ, Parker ED, Nordin JD, et al. Self-report compared to electronic medical record across eight adult vaccines: do results vary by demographic factors? Vaccine 2013;31(37):3928-3935.
16. Donald RM, Baken L, Nelson A, Nichol KL. Validation of self-report of influenza and pneumococcal vaccination status in elderly outpatients. Am J Prev Med 1999;16:173-177.
17. Zimmerman RK, Raymund M, Janosky JE, et al. Sensitivity and specificity of patient self-report of influenza and pneumococcal polysaccharide vaccinations among elderly outpatients in diverse patient care strata. Vaccine 2003;21:1486-1491.
18. Hong K, Zhou F, Tsai Y, et al. Decline in Receipt of Vaccines by Medicare Beneficiaries During the COVID-19 Pandemic — United States, 2020. MMWR Morb Mortal Wkly Rep 2021;70:245-9.
19. Liow C, Payne H, Gillen M, et al. Declines in Routine Adult and Teen Vaccinations Continued in 2021. Avalere Health, January 10, 2022. Available at: Declines in Routine Adult and Teen Vaccinations Continued in 2021 | Avalere Health .

Last Reviewed: February 17, 2022

Exhibit 7

MMWR Weekly
January 21, 2000 / 49(02);35-38,47

Notice to Readers: Recommended Childhood Immunization Schedule -- United States, 2000

Each year, CDC's Advisory Committee on Immunization Practices (ACIP) reviews the recommended childhood immunization schedule to ensure it remains current with changes in manufacturers' vaccine formulations, revisions in recommendations for the use of licensed vaccines, and recommendations for newly licensed vaccines. This report presents the recommended childhood immunization schedule for 2000 (Figure 1) and explains the changes that have occurred since January 1999.

Since the publication of the immunization schedule in January 1999 (1), ACIP, the American Academy of Family Physicians, and the American Academy of Pediatrics have recommended removal of rotavirus vaccine from the schedule, endorsed an all-inactivated poliovirus vaccine (IPV) schedule for polio vaccination, recommended exclusive use of acellular pertussis vaccines for all doses of the pertussis vaccine series, and added hepatitis A vaccine (Hep A) to the schedule to reflect its recommended use in selected geographic areas (2). Detailed recommendations for using vaccines are available from the manufacturers' package inserts, ACIP statements on specific vaccines, and the 1997 Red Book (3). ACIP statements for each recommended childhood vaccine can be viewed, downloaded, and printed at CDC's National Immunization Program World-Wide Web site, http://www.cdc.gov/nip/publications/acip-list.htm.

Removal of Rotavirus Vaccine from the Schedule

On October 22, 1999, ACIP recommended that Rotashield®* (rhesus rotavirus vaccine-tetravalent [RRV-TV]) (Wyeth Laboratories, Inc., Marietta, Pennsylvania), the only U.S. licensed rotavirus vaccine, no longer be used in the United States (4). The decision was based on the results of an expedited review of scientific data presented to ACIP by CDC. Data from the review indicated a strong association between RRV-TV and intussusception among infants 1-2 weeks following vaccination. Vaccine use was suspended in July pending the ACIP data review. Parents should be reassured that children who received the rotavirus vaccine before July are not at increased risk for intussusception now. The manufacturer withdrew the vaccine from the market in October.

Inactivated Poliovirus Vaccine for All Four Doses

As the global eradication of poliomyelitis continues, the risk for importation of wild-type poliovirus into the United States decreases dramatically. To eliminate the risk for vaccine-associated paralytic poliomyelitis (VAPP), an all-IPV schedule is recommended for routine childhood vaccination in the United States (5). All children should receive four doses of IPV: at age 2 months, age 4 months, between ages 6 and 18 months, and between ages 4 and 6 years. Oral poliovirus vaccine (OPV), if available, may be used only for the following special circumstances:

1. Mass vaccination campaigns to control outbreaks of paralytic polio.
2. Unvaccinated children who will be traveling within 4 weeks to areas where polio is endemic or epidemic.
3. Children of parents who do not accept the recommended number of vaccine injections; these children may receive OPV only for the third or fourth dose or both. In this situation, health-care providers should administer OPV only after discussing the risk for VAPP with parents or caregivers.

OPV supplies are expected to be very limited in the United States after inventories are depleted. ACIP reaffirms its support for the global eradication initiative and use of OPV as the vaccine of choice to eradicate polio where it is endemic.

Acellular Pertussis Vaccine

ACIP recommends exclusive use of acellular pertussis vaccines for all doses of the pertussis vaccine series. The fourth dose may be administered as early as age 12 months, provided 6 months have elapsed since the third dose and the child is unlikely to return at 15-18 months.

Hepatitis A

Hepatitis A vaccine (Hep A) is listed on the schedule for the first time because it is recommended for routine use in some states and regions. Its appearance on the schedule alerts providers to consult with their local public health authority to learn the current recommendations for hepatitis A vaccination in their community. Additional information on the use of Hep A can be found in recently published guidelines (2).

Hepatitis B

Special considerations apply in the selection of hepatitis B vaccine products for the dose administered at birth (6).

Vaccine Information Statements

The National Childhood Vaccine Injury Act requires that all health-care providers, whether public or private, give to parents or patients copies of Vaccine Information Statements before administering each dose of the vaccines listed in this schedule (except Hep A). Vaccine Information Statements, developed by CDC, can be obtained from state health departments and CDC's World-Wide Web site, http://www.cdc.gov/nip/publications/VIS. Instructions on use of the Vaccine Information Statements are available from CDC's website or the December 17, 1999, Federal Register (64 FR 70914).

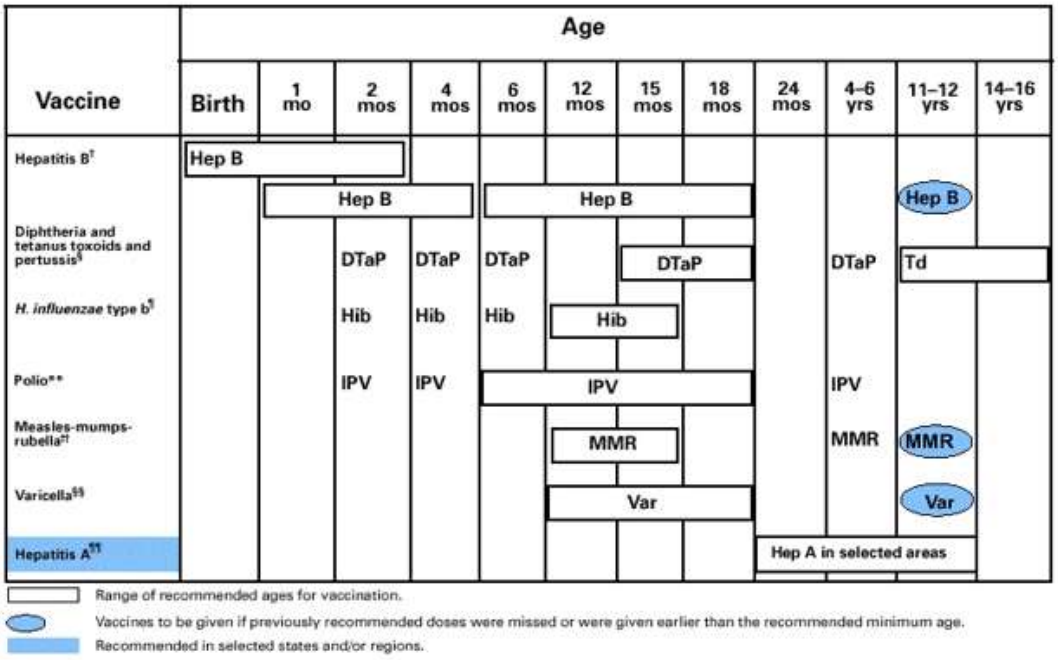
References

1. CDC. Recommended childhood immunization schedule--United States, 1999. MMWR 1999;48:12-6.
2. CDC. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1999;48(no. RR-12).
3. American Academy of Pediatrics. Active and passive immunization. In: Peter G, ed. 1997 Red book: report of the Committee on Infectious Diseases. 24th ed. Elk Grove Village, Illinois: American Academy of Pediatrics 1997:1-71.
4. CDC. Withdrawal of rotavirus vaccine recommendation. MMWR 1999;48:1007.
5. CDC. Recommendations of the Advisory Committee on Immunization Practices: revised recommendations for routine poliomyelitis vaccination. MMWR 1999;48:590.
6. CDC. Recommendations regarding the use of vaccines that contain thimerosal as a preservative. MMWR 1999;48:996-8.

* Use of trade names and commercial sources is for identification only and does not constitute or imply endorsement by CDC or the U.S. Department of Health and Human Services.

Figure 1

FIGURE 1. Recommended childhood immunization schedule* — United States, January–December 2000



On October 22, 1999, the Advisory Committee on Immunization Practices (ACIP) recommended that Rotashield® (rhesus rotavirus vaccine-tetravalent [RRV-TV]), the only U.S.-licensed rotavirus vaccine, no longer be used in the United States (*MMWR*, Vol. 48, No. 43, November 5, 1999). Parents should be reassured that children who received rotavirus vaccine before July 1999 are not now at increased risk for intussusception.

* This schedule indicates the recommended ages for routine administration of licensed childhood vaccines as of November 1, 1999. Any dose not given at the recommended age should be given as a "catch-up" vaccination at any subsequent visit when indicated and feasible. Additional vaccines may be licensed and recommended during the year. Licensed combination vaccines may be used whenever any components of the combination are indicated and the vaccine's other components are not contraindicated. Providers should consult the manufacturers' package inserts for detailed recommendations.

† **Infants born to hepatitis B surface antigen (HBsAg)-negative mothers** should receive the first dose of hepatitis B vaccine (Hep B) by age 2 months. The second dose should be administered at least 1 month after the first dose. The third dose should be administered at least 4 months after the first dose and at least 2 months after the second dose, but not before age 6 months. **Infants born to HBsAg-positive mothers** should receive Hep B and 0.5 mL hepatitis B immune globulin (HBIG) within 12 hours of birth at separate sites. The second dose is recommended at age 1–2 months and the third dose at age 6 months. **Infants born to mothers whose HBsAg status is unknown** should receive Hep B within 12 hours of birth. Maternal blood should be drawn at delivery to determine the mother's HBsAg status; if the HBsAg test is positive, the infant should receive HBIG as soon as possible (no later than age 1 week). **All children and adolescents (through age 18 years)** who have not been vaccinated against hepatitis B may begin the series during any visit. Providers should make special efforts to vaccinate children who were born in or whose parents were born in areas of the world where hepatitis B virus infection is moderately or highly endemic.

§ The fourth dose of diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) can be administered as early as age 12 months, provided 6 months have elapsed since the third dose and the child is unlikely to return at age 15–18 months. Tetanus and diphtheria toxoids (Td) is recommended at age 11–12 years if at least 5 years have elapsed since the last dose of diphtheria and tetanus toxoids and pertussis vaccine (DTP), DTaP, or diphtheria and tetanus toxoids (DT). Subsequent routine Td boosters are recommended every 10 years.

¶ Three *Haemophilus influenzae* type b (Hib) conjugate vaccines are licensed for infant use. If Hib conjugate vaccine (PRP-OMP) (PedvaxHIB® or ComVax® [Merck]) is administered at ages 2 months and 4 months, a dose at age 6 months is not required. Because clinical studies in infants have demonstrated that using some combination products may induce a lower immune response to the Hib vaccine component, DTaP/Hib combination products should not be used for primary vaccination in infants at ages 2, 4, or 6 months unless approved by the Food and Drug Administration for these ages.

** To eliminate the risk for vaccine-associated paralytic poliomyelitis (VAPP), an all-inactivated poliovirus vaccine (IPV) schedule is now recommended for routine childhood polio vaccination in the United States. All children should receive four doses of IPV: at age 2 months, age 4 months, between ages 6 and 18 months, and between ages 4 and 6 years. Oral poliovirus vaccine (OPV) (if available) may be used only for the following special circumstances: 1) mass vaccination campaigns to control outbreaks of paralytic polio; 2) unvaccinated children who will be traveling in <4 weeks to areas where polio is endemic or epidemic; and 3) children of parents who do not accept the recommended number of vaccine injections. Children of parents who do not accept the recommended number of vaccine injections may receive OPV only for the third or fourth dose or both; in this situation, health-care providers should administer OPV only after discussing the risk for VAPP with parents or caregivers. During the transition to an all-IPV schedule, recommendations for the use of remaining OPV supplies in physicians' offices and clinics have been issued by the American Academy of Pediatrics (*Pediatrics*, Vol. 104, No. 6, December 1999).

†† The second dose of measles, mumps, and rubella vaccine (MMR) is recommended routinely at age 4–6 years but may be administered during any visit, provided at least 4 weeks have elapsed since receipt of the first dose and that both doses are administered beginning at or after age 12 months. Those who previously have not received the second dose should complete the schedule no later than the routine visit to a health-care provider at age 11–12 years.

§§ Varicella (Var) vaccine is recommended at any visit on or after the first birthday for susceptible children, i.e., those who lack a reliable history of chickenpox (as judged by a health-care provider) and who have not been vaccinated. Susceptible persons aged ≥13 years should receive two doses given at least 4 weeks apart.

¶¶ Hepatitis A vaccine (Hep A) is recommended for use in selected states and regions. Information is available from local public health authorities and *MMWR*, Vol. 48, No. RR-12, October 1, 1999.

Use of trade names and commercial sources is for identification only and does not constitute or imply endorsement by CDC or the U.S. Department of Health and Human Services.

Source: Advisory Committee on Immunization Practices (ACIP), American Academy of Family Physicians (AAFP), and American Academy of Pediatrics (AAP).

Return to top.

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Exhibit 8

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

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

December 30, 2021

Elizabeth Brehm
Siri & Glimstad
200 Park Ave, 17th Floor
New York, NY 10166
Via email: foia@sirillp.com

Dear Ms. Brehm:

This letter is our final response to your Centers for Disease Control and Prevention and Agency for Toxic Substances and Disease Registry (CDC/ATSDR) Freedom of Information Act (FOIA) request of September 28, 2020, assigned #20-02418-FOIA, for:

> *"Documents sufficient to reflect that acellular pertussis vaccines, while reducing symptoms from pertussis, do not prevent infection and transmission."*

Published scientific literature was used to inform the sentence in question ("Acellular pertussis vaccines may not prevent colonization (carrying the bacteria in your body without getting sick or spread of the bacteria."). For administrative convenience and to fully respond to your request, program staff have provided examples of literature that support the content of this sentence below.

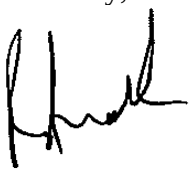
Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model.
https://pubmed.ncbi.nlm.nih.gov/24277828/

Pertussis Prevention: Reasons for Resurgence, and Differences in the Current Acellular Pertussis Vaccines
https://pubmed.ncbi.nlm.nih.gov/31333640/

Reduced Severity of Pertussis in Persons with Age-Appropriate Pertussis Vaccination-United States, 2010-2012
https://pubmed.ncbi.nlm.nih.gov/29017283/

If you need any further assistance or would like to discuss any aspect of the records provided please contact either our FOIA Requester Service Center at 770-488-6399 or our FOIA Public Liaison at 770-488-6277.

Sincerely,



Roger Andoh
CDC/ATSDR FOIA Officer
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Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model

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Edited by Rino Rappuoli, Novartis Vaccines and Diagnostics Srl, Siena, Italy, and approved October 22, 2013 (received for review August 5, 2013)

Pertussis is a highly contagious respiratory illness caused by the bacterial pathogen *Bordetella pertussis*. Pertussis rates in the United States have been rising and reached a 50-y high of 42,000 cases in 2012. Although pertussis resurgence is not completely understood, we hypothesize that current acellular pertussis (aP) vaccines fail to prevent colonization and transmission. To test our hypothesis, infant baboons were vaccinated at 2, 4, and 6 mo of age with aP or whole-cell pertussis (wP) vaccines and challenged with *B. pertussis* at 7 mo. Infection was followed by quantifying colonization in nasopharyngeal washes and monitoring leukocytosis and symptoms. Baboons vaccinated with aP were protected from severe pertussis-associated symptoms but not from colonization, did not clear the infection faster than naïve animals, and readily transmitted *B. pertussis* to unvaccinated contacts. Vaccination with wP induced a more rapid clearance compared with naïve and aP-vaccinated animals. By comparison, previously infected animals were not colonized upon secondary infection. Although all vaccinated and previously infected animals had robust serum antibody responses, we found key differences in T-cell immunity. Previously infected animals and wP-vaccinated animals possess strong *B. pertussis*-specific T helper 17 (Th17) memory and Th1 memory, whereas aP vaccination induced a Th1/Th2 response instead. The observation that aP, which induces an immune response mismatched to that induced by natural infection, fails to prevent colonization or transmission provides a plausible explanation for the resurgence of pertussis and suggests that optimal control of pertussis will require the development of improved vaccines.

whooping cough | T-cell memory | animal models | adaptive immunity | IL-17

Pertussis is a highly contagious, acute respiratory illness caused by the bacterial pathogen *Bordetella pertussis* (1, 2). Infection results in a wide spectrum of clinical manifestations ranging from mild respiratory symptoms to a severe cough illness accompanied by marked leukocytosis and the hallmark inspiratory whoop and posttussive emesis (3). Because acellular pertussis vaccines replaced whole-cell vaccines in the 1990s, pertussis has reemerged at a startling rate in the United States despite nationwide vaccine coverage in excess of 95% (4). With a 50-y high of 42,000 reported cases in the United States in 2012, pertussis is the most common of the vaccine-preventable diseases (5). This resurgence is mirrored throughout the industrial world despite similar high rates of vaccination (6–9). Two common hypotheses for the resurgence have been proposed: *i*) current acellular pertussis vaccines (aP) vaccines are less effective than the whole-cell pertussis (wP) vaccines they replaced and *ii*) aP-induced immunity wanes more quickly than anticipated (10–13). However, pertussis resurgence is not completely understood (14, 15).

Hampering our ability to counteract this resurgence is the fact that pertussis pathogenesis and immunity to natural infection have not been well studied in humans because typical pertussis is sporadic given high rates of vaccination in developed countries. Human challenge studies have been proposed but never conducted due to a variety of logistical and ethical problems including the potential for severe disease, the lack of an effective therapeutic for established disease, and the highly contagious nature of pertussis. Although a variety of small-animal models have been used to study pertussis, none of them adequately reproduce the human disease (16). To address this gap, we recently developed a nonhuman primate model of pertussis using baboons (*Papio anubis*) and found the disease is very similar to severe clinical pertussis. Upon challenge, baboons experience 2 wk of heavy respiratory colonization and leukocytosis peaking between 30,000–80,000 cells/mL, similar to the range in pertussis-infected infants (1, 17). In addition, baboons experience a paroxysmal cough illness characterized by repeated fits of 5–10 coughs. The coughing fits last on average >2 wk in the baboon, although this is less than some severely infected children, where the cough can last up to 12 wk (1, 17). We also characterized airborne transmission of *B. pertussis* from infected to naïve animals, which is the route of transmission postulated to occur between humans (18). Because this is the only model of pertussis to reproduce the cough illness and transmission of the human disease, we believe it provides the unique opportunity to test our hypothesis that aP vaccines fail to prevent *B. pertussis* colonization, thus enabling transmission among vaccinated individuals.

Using this model we have confirmed that, as in humans, aP vaccines provide excellent protection against severe disease in baboons. However, aP vaccines do not prevent colonization following direct challenge or infection by transmission. In addition, aP-vaccinated animals are capable of transmitting disease to naïve contacts. By comparison, wP-vaccinated animals cleared infection significantly more quickly than aP-vaccinated or naïve

Significance

Pertussis has reemerged as an important public health concern since current acellular pertussis vaccines (aP) replaced older whole-cell vaccines (wP). In this study, we show nonhuman primates vaccinated with aP were protected from severe symptoms but not infection and readily transmitted *Bordetella pertussis* to contacts. Vaccination with wP and previous infection induced a more rapid clearance compared with naïve and aP-vaccinated animals. While all groups possessed robust antibody responses, key differences in T-cell memory suggest that aP vaccination induces a suboptimal immune response that is unable to prevent infection. These data provide a plausible explanation for pertussis resurgence and suggest that attaining herd immunity will require the development of improved vaccination strategies that prevent *B. pertussis* colonization and transmission.

Author contributions: J.M.W. and T.J.M. designed research; J.M.W., L.I.Z., and T.J.M. performed research; J.M.W. and T.J.M. analyzed data; and J.M.W. and T.J.M. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

See Commentary on page 575.

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This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1314688110/-/DCSupplemental.

animals. We also found that aP vaccination induces T helper 2 (Th2) and T helper 1 (Th1) immune memory responses, whereas infection and—to a lesser extent—wP vaccination induce Th17 and Th1 memory. Our results suggest that in addition to the potential contribution of reduced efficacy and waning immunity of aP, the inability of aP to prevent colonization and transmission provides a plausible explanation for pertussis resurgence.

Results

Acellular Pertussis Vaccines Protect Against Disease but Fail to Prevent Infection. Several observational studies recently concluded that children primed with aP vaccine are at greater risk for pertussis diagnosis compared with wP-primed children (19–22). Although these data suggest aP vaccine is less effective than wP vaccine at preventing colonization, the rate of undiagnosed *B. pertussis* carriage in vaccinated individuals is unknown. To assess the ability of each vaccine to prevent colonization and clinical pertussis symptoms, baboons were vaccinated according to the US schedule at 2, 4, and 6 mo of age with human doses of combination diphtheria, tetanus, and pertussis vaccines containing aP or inactivated wP (Table 1 provides a list of the components of each vaccine). At 7 mo of age, vaccinated, naïve, and previously infected (convalescent) animals were challenged with D420, a *B. pertussis* clinical isolate that causes severe infection in humans and baboons (17). Naïve animals were heavily colonized with peak levels between 10^7–10^8 cfu/mL in nasopharyngeal washes (Fig. 1*A*). After 2 wk, colonization gradually decreased, and the infection cleared after 30 d. Consistent with our previous finding, none of the convalescent animals were colonized (17). Compared with naïve animals, aP-vaccinated animals had slightly reduced colonization for the first 10 d but remained consistently colonized before clearing after 35 d. In wP-vaccinated animals the initial colonization was similar to aP-vaccinated animals but the infection cleared after 18 d, significantly faster than naïve and aP-vaccinated animals (Fig. 1*B*).

To assess the efficacy of the vaccines in preventing the symptoms of severe pertussis, peripheral blood was drawn serially, and complete blood counts were performed to monitor leukocytosis, a significant marker of morbidity in pertussis-infected infants (23). Compared with preinfection levels, naïve animals had a significant increase in circulating white blood cells at each time point, peaking at over 40,000 cells per μL, an eightfold increase over preinfection levels (Fig. 1*C*). In contrast to the colonization data, aP vaccination, wP vaccination, and convalescence all prevented leukocytosis (Fig. 1*C*). In addition, wP-vaccinated, aP-vaccinated, and convalescent animals did not cough and showed no reduction of activity, loss of appetite, or other outward signs of disease.

Acellular Vaccines Fail to Prevent Infection Following Natural Transmission. To assess the ability of vaccination to prevent pertussis infection by transmission, two aP-vaccinated animals and one unvaccinated animal were cohoused with a directly challenged, unvaccinated animal. Similar to our previous findings (18), all animals became colonized 7–10 d after cohousing with the infected animal (Fig. 2). The peak levels and kinetics of colonization were indistinguishable between the naïve and aP-vaccinated animals.

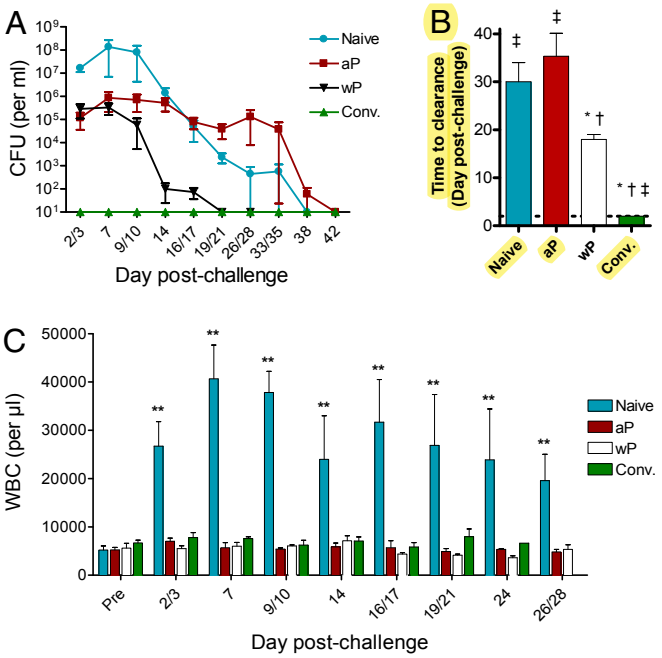

Fig. 1. The effect of vaccination or convalescence on colonization and leukocytosis. Naïve animals, aP-vaccinated animals, wP-vaccinated animals, and previously infected [convalescent conv.)] animals were directly challenged with *B. pertussis* ($n = 3$–4 per group). (*A*) Colonization was monitored by quantifying *B. pertussis* cfu per mL in biweekly nasopharyngeal washes with a limit of detection of 10 cfu per mL. For each animal the time to clearance is defined as the first day that no *B. pertussis* cfu were recovered from nasopharyngeal washes. (*B*) The mean time to clearance is shown for each group ($n = 3$ per group). Because no *B. pertussis* organisms were recovered from the conv. animals, the mean time to clearance was defined as the first day of sampling (day 2, indicated by the dashed line). *$P < 0.05$ vs. Naïve, †$P < 0.05$ vs. aP, ‡$P < 0.05$ vs. wP. (*C*) The mean circulating white blood cell counts before and after challenge are shown for each group of animals ($n = 3$–4 per group). **$P < 0.01$ vs. preinfection from same group.

Acellular-Vaccinated Animals Are Capable of Transmitting *B. pertussis* to Naïve Contacts. Because aP fails to prevent colonization we hypothesized that aP-vaccinated animals can transmit *B. pertussis* infection to contacts. To test this hypothesis, two aP-vaccinated animals were challenged with *B. pertussis* and placed in separate cages. After 24 h, a naïve animal was added to each cage, and all animals were followed for colonization. Both of the naïve animals were infected by transmission from their aP-vaccinated cage mates (Fig. 3).

Vaccination and Previous Infection Induce Robust Antibody Responses. Sera collected before vaccination or primary infection and again at 1 wk before challenge were analyzed for IgG antibodies against heat-killed *B. pertussis* and the vaccine antigens

Table 1. Components of aP and wP vaccines used in this study

Vaccine component	Daptacel	Infanrix	Triple antigen
Diphtheria toxoid	15 Lf	25 Lf	20–30 Lf
Tetanus toxoid	5 Lf	10 Lf	5–25 Lf
Whole-cell *Bordetella pertussis*	—	—	≥4 IU
Inactivated pertussis toxin	10 μg	25 μg	—
Filamentous hemagglutinin	5 μg	25 μg	—
Pertactin	3 μg	8 μg	—
Fimbriae types 2 and 3	5 μg	—	—
Aluminum (from aluminum phosphate)	0.33 mg	≤0.625 mg	≤1.25 mg

IU, international units; Lf, limit of flocculation units.

frontiers in Immunology

REVIEW
published: 03 July 2019
doi: 10.3389/fimmu.2019.01344

Pertussis Prevention: Reasons for Resurgence, and Differences in the Current Acellular Pertussis Vaccines

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Specialty section:
This article was submitted to Vaccines and Molecular Therapeutics, a section of the journal Frontiers in Immunology

Received: *24 February 2019*
Accepted: *28 May 2019*
Published: *03 July 2019*

Citation:
Esposito S, Stefanelli P, Fry NK, Fedele G, He Q, Paterson P, Tan T, Knuf M, Rodrigo C, Weil Olivier C, Flanagan KL, Hung I, Lutsar I, Edwards K, O'Ryan M and Principi N (2019) Pertussis Prevention: Reasons for Resurgence, and Differences in the Current Acellular Pertussis Vaccines. Front. Immunol. 10:1344. doi: 10.3389/fimmu.2019.01344

Pertussis is an acute respiratory disease caused by *Bordetella pertussis*. Due to its frequency and severity, prevention of pertussis has been considered an important public health issue for many years. The development of the whole-cell pertussis vaccine (wPV) and its introduction into the pediatric immunization schedule was associated with a marked reduction in pertussis cases in the vaccinated cohort. However, due to the frequency of local and systemic adverse events after immunization with wPV, work on a less reactive vaccine was undertaken based on isolated *B. pertussis* components that induced protective immune responses with fewer local and systemic reactions. These component vaccines were termed acellular vaccines and contained one or more pertussis antigens, including pertussis toxin (PT), filamentous haemagglutinin (FHA), pertactin (PRN), and fimbrial proteins 2 (FIM2) and 3 (FIM3). Preparations containing up to five components were developed, and several efficacy trials clearly demonstrated that the aPVs were able to confer comparable short-term protection than the most effective wPVs with fewer local and systemic reactions. There has been a resurgence of pertussis

were reported in another meta-analysis including studies of aPVs administered according to the USA schedule (46). VE was compared after the childhood series (five doses) and after an adolescent booster dose (sixth dose). Relative VE was defined as VE in the population given prior doses of an aPV and absolute VE was defined as VE in an aPV-naïve population. Absolute VE after the childhood series was 91% (95% CI 87–95%) but declined annually by 9.6% (46). Initial relative VE after adolescent boosting was 70% (95% CI: 54 to 86%) and declined by 45.3% annually. The absolute VE of the full six-dose aPV series was estimated to be 85% (95% CI: 84–86%) in the first year after series completion. However, it declined by 11.7% (95% CI: 11.1 to 12.3%) per year, and at 18 years of age, protection was limited to 28.2% of immunized patients (95% CI: 27 to 29%) (46).

Wang et al. (47) studied 279 children aged 5 to 15 years who presented to primary care with a persistent cough of 2 to 8 weeks duration. Evidence of recent *B. pertussis* infection based on a high oral fluid anti-pertussis toxin IgG titer was demonstrated in 215 children who had been fully vaccinated. Risk was higher in those who had been immunized ≥7 years earlier, but in 12% of these cases, chronic cough was demonstrated in patients given an aPV <7 years before. Further evidence of waning immunity after recent aPV immunization was reported by Principi et al. (48) who documented *B. pertussis* infection in 18.7% (95% CI 11.5–28.0) of children and adolescents with chronic cough who had been immunized with an aPV a few years previously (<2 years in some cases).

Immune Responses to Pertussis Vaccines and Natural Infection

Studies that have compared immune responses after natural *B. pertussis* infection and the administration of both wPVs and aPVs have clearly shown that the immune stimulation evoked by aPVs is different from that due to natural infection and wPVs (49–51). Natural infection evokes both mucosal and systemic immune responses, while aPVs induce only a systemic immune response. As *B.* pertussis is a mucosal pathogen and only exceptionally causes infection outside the respiratory tract, this difference is of particular importance in pertussis control. Mucosal immunity is essential to prevent colonization and transmission of *B. pertussis* organisms. Consequently, preventive measures such as aPVs that do not induce a valid mucosal response can prevent disease but cannot avoid infection and transmission. Animal studies have shown that natural infection is associated with a strong secretory IgA response in both the upper and lower airways and induction of resident memory T cells (TRM) (52, 53). Moreover, it has been recently reported (54) that IL-17 and IFN-γ-secreting CD69+CD4+ TRM cells were expanded in the respiratory tract after *B. pertussis* challenge of mice immunized with wP, but not aP vaccines. However, natural infection was associated with the most persistent protection against nasal colonization and this correlated with potent induction of nasal tissue TRM cells. These animal data suggest that the lack of mucosal immune response after aPV administration might explain its lower efficacy when compared to wPVs and the shorter duration of protection compared to both wPV vaccination and natural infection.

Clear differences between systemic immune response after natural infection and aP and wP vaccines. Natural infection and wPvs induce antibodies of the IgG1, IgG2, and IgG3 subclasses, with marginal production of IgG4 (55), suggesting a strong Th1 response. In contrast, the immune response after aPVs evoke a mixed Th2 and Th17 response (56). APVs evoke the production of IgG1 and IgG4 antibodies, which is consistent with a Th2 response. Furthermore, aPVs evoke CD4+ T-cells that produce high concentrations of IL-4 and IL-5 and low amounts of IFNγ, again consistent with a Th2 response (57).

Since Th1 cytokines play an important role in protection against pertussis (58, 59), this finding can further explain the better protection offered by wPVs and natural infection. Studies carried out in children who have received infant series of either wPV or aPVs have shown children given aPVs exhibited higher pertussis-specific antibody levels and higher memory B- and T-cell responses (5, 60–63). Although no correlates of antibody protection for pertussis have been established (64), the higher IgG levels in aPV-immunized children could lead to the conclusion that better humoral protection was afforded by the aP rather than wP vaccines. However, the antigens measured were only those included in the aPVs and not the additional antigens included in the wPs.

These differences in immune responses persist over time, even after booster aPVs (65, 66). The administration of aPV booster doses at 4 and 9 years of age was associated with an increase in the production of IgG4, regardless of the type of vaccine used for priming, but was significantly higher in aPV-primed children (66). IgG4 antibodies are unable to activate the complement system and lead to a suboptimal inflammatory response with impaired phagocytosis and antimicrobial defense, another potential mechanism for the lower efficacy of aPVs compared to wPVs (67). Moreover, the evidence that production of IgG4 after immunization with aPV increases with each dose seems to indicate that the protection offered by aPVs tends to be as shorter with each subsequent boosters (68, 69). Preadolescent booster vaccination with an aPV was found to induce lower B-cell and Th1 cell responses in aPV-primed compared with wPV-primed children, resulting in significantly lower Th1/Th2 ratios. Confirming this, it has been shown that wPv or aPV primary immunizations in infancy determines adolescent cellular immune profiles, showing a beneficial Th1-dominated response after wP-priming (69). These findings of a preferential Th1 response were also shown in the baboon model, with aPV vaccines preventing disease after natural pertussis challenge, but not preventing transmission of pertussis organisms (70). All these findings indicate that although aPVs are as individually protective as wPVs in the first years after priming, they induce shorter long-term protection than wPVs and a different profile of pertussis-specific immunity.

Finally, aPV pertussis vaccines do not prevent colonization. Consequently, they do not reduce the circulation of *B. pertussis* and do not exert any herd immunity effect.

These findings at least partly explain the resurgence of pertussis.

Genetic Modifications of *Bordetella pertussis*

Circulation of *B. pertussis* strains with modified or absent antigens included in the aPV have been reported in both the pre-vaccine era and the aPV era (71–73). Moreover, strains with polymorphisms of the PT gene resulting in the production of greater amounts of this protein have been detected (74–79). Although it cannot be excluded that this phenomenon might simply be derived from the natural evolutionary course of *B. pertussis*, it has been proposed that it might be a consequence of *B. pertussis* adaptation to aPV use (80).

Genes encoding antigens included in the aPV vaccines have evolved at higher rates than other non-vaccine surface protein-encoding genes soon after the introduction of aPVs into the pediatric immunization schedule (81). The most compelling data have been the evolution of PRN-negative *B. pertussis* strains according to the use of vaccines PRN-containing vaccines. With some exceptions (82–84), studies have demonstrated that the emergence of PRN-deficient strains has resulted as a consequence of aPV-induced selection pressure. The rate of PRN-negative isolates is significantly correlated with aPV use in the USA (85). In Denmark, where an aPV without PRN is used, no PRN-deficient isolates have been detected (86). In Japan where aPVs with PRN were administered for many years (87), consistent rates of PRN-negative strains have been demonstrated over time (2005–2007, 41%; 2008–2010, 35%; and 2011–2013, 25%) (88, 89). However, when these aPV vaccines were replaced with a preparation without PRN in November 2012, a marked reduction of PRN-deleted strains was observed (2014–2016, 8%) (90). The clinical relevance of PRN-deleted strains has not been precisely defined (80), but children infected with these strains do not have more severe pertussis (91, 92), In contrast, *B. pertussis* strains with the enhanced PT promoter allele PTP3, instead of the common PTP2 allele, were found to produce greater amounts of PT (74) and cause more severe disease in younger infants (92).

Interesting, *B. pertussis* strains lacking the *PRN* gene show increased fitness and/or prolonged infection times in animals immunized with ACVs (74, 93, 94). This finding suggests that loss of PRN could lead to a reduced immune response to aPVs and favor pertussis resurgence. However, clinical studies that have evaluated the effectiveness of aPVs containing PRN in the setting of PRN-deficient pertussis have produced conflicting results. One study in the US (80) assessed the VEs of a five-dose DTaP series among 4–10 year-olds and a Tdap booster among 11–19 year-olds in an area where >90% of *B. pertussis* strains were PRN deficient. It was found that overall DTaP VE was 84% (95% CI 58–94%) while that of TdaP was 70% (95% CI 54–81%), which do not substantially differ than rates reported during the circulation of PRN-positive strains. In contrast, a second US study revealed that in vaccinated persons, the likelihood of suffering from pertussis disease was greater if the infecting strain was PRN-negative than if it is PRN-positive (85).

In conclusion, aPV use seems to favor adaptation of *B. pertussis* strains with emergence of mutated strains. However, the role of genetic modification in reducing aPV protection remains unclear with future studies needed.

ROLE OF ANTIGENS INCLUDED IN PRESENTLY AVAILABLE VACCINES IN CONDITIONING PROTECTION

Although pertussis resurgence has been demonstrated to be independent of the type of aPV used, it is theoretically possible that the composition of vaccines and the immunization strategies may have played a role in modifying the pertussis incidence. However, estimates of aPV efficacy and comparisons between different aPVs are very problematic for several reasons. First, the criteria for the diagnosis of pertussis used in the various aPV effectiveness trials have not been uniform. In some cases, significant underestimations of the real pertussis incidence may have limited the reliability of final results. When the WHO's clinical case definition of pertussis as prolonged paroxysmal cough is used, it is highly likely that most of the mild cases are not included. Second, study designs, administration schedules, and duration of follow-up have not been consistent in the effectiveness trials. In many European countries, the primary series includes only two doses of an aPV with a booster dose at ∼1 year. In contrast, in other countries, including the US, the primary series is based on three doses within the first 6 months of life, with a booster dose given after the first birthday. Third, most, but not all, national immunization schedules include a booster before entering school and during adolescence. Fourth, the composition of the administered aPV can vary. Most of these studies have been carried out with vaccines containing three or five antigens, but in earlier studies vaccines with only PT have been included. In addition, the quantity of antigen can differ among the preparations. For example, GSK DTaP vaccines contain 25 μg PT, 25 μg FHA, and 8 μg PRN, while the Sanofi preparation also includes FIM2 and three different amounts of PT, FHA, and PRN for the primary and booster doses. Tdap contains 10 μg PT, 5 μg FHA, and 3 μg PRN when administered alone, but when Tdap is combined with polio, hepatitis B, and *Haemophilus influenzae* type b, the PT and FHA content is increased to 20 μg. In addition, the type of aluminum salt used as an adjuvant and its content vary slightly among between vaccines. Finally, there has been no single study that directly compares all aPV vaccines with different numbers and quantities of included antigens.

Role of the Number of Pertussis Antigens

In those studies that directly compared vaccines using similar vaccine schedules, similar definitions of pertussis disease, and comparable durations of follow-up, it can be concluded that the 3-component aPV (3aPV) and the 5-component aPV (5aPV) have comparable efficacy. Greco et al. evaluated two 3aPVs produced by different pharmaceutical companies (12), and Gustafsson et al. (13) studied a 5aPV, with both studies being conducted in children that had received three doses at ∼2, 4, and

a lack of perceived need for the vaccine, and concerns about its safety and effectiveness (115).

CONCLUSIONS

The resurgence of pertussis observed in recent years seems to be a complex but real phenomenon resulting from a number of cases, including the use of aPV in many locales. Lack of mucosal immune responses after aPV administration favor infection, persistent colonization, and transmission of the pathogen. Moreover, earlier waning of protective immunity and the circulation of *B. pertussis* variants depleted of vaccine-included antigens further favor the increase in pertussis disease. Several different aPVs are available, but it has yet to be determined which of them confers the highest and the most-prolonged protection. Further studies are needed to evaluate the importance of individual antigens included in aPVs in conferring protection against disease, colonization, and transmission. However, present knowledge seems to indicate that PT, particularly if genetically detoxified, represents the main antigen that ensures protection from disease even if not from infection. The contribution of FHA, PRN, and FIM2 and FIM3 in vaccine efficacy and long-lasting protection is still under discussion and needs further study.

The optimal pertussis vaccine would be one that induced both a mucosal and systemic responses similar to those occurring under natural infection, leading to a long-term protection against both disease and infection. Such a vaccine might increase public confidence and result in better vaccine uptake. Meanwhile, the identification of more efficacious vaccination strategies with currently available vaccines reaching high vaccination coverage rates is required, including the vaccination of pregnant women (50).

AUTHOR CONTRIBUTIONS

SE proposed the project, coordinated the Study Group, and wrote the first draft of the study. PS, NF, and GF coordinated the sections of the project on Vaccines, Microbiology, and Immunology, respectively, giving a substantial scientific contribution. QH, PP, TT, MK, CR, CW, KF, IH, IL, KE, and MO gave a substantial scientific contribution. NP co-wrote the first draft of the manuscript and supervised the project. All authors approved the final submitted version of the manuscript.

FUNDING

This study was supported by WAidid 2018_11 grant.

REFERENCES

1. Centers for Disease Control and Prevention. *Pertussis (whooping cough). Causes and Transmission.* (2017). Available online at: https://www.cdc.gov/pertussis/about/causes-transmission.html (accessed August 15, 2018).
2. Yeung KHT, Duclos P, Nelson EAS, Hutubessy RCW. An update of the global burden of pertussis in children younger than 5 years: a modelling study. *Lancet Infect Dis*. (2017) 17:974–80. doi: 10.1016/S1473-3099(17)30390-0
3. Cherry JD, Brunnel P, Golden G. Report of the task force on pertussis and pertussis immunization. *Pediatrics*. (1988) 81(Suppl.) 933–84.
4. Plotkin SA, Orenstein W, Offit PA. (editors). *Vaccines*. Philadelphia, PA: Elsevier Saunders (2013).
5. Berkovic SF, Harkin L, McMahon JM, Pelekanos JT, Zuberi SM, Wirrell EC, et al. *De-novo* mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study. *Lancet Neurol*. (2006) 5:488–92. doi: 10.1016/S1474-4422(06)70446-X
6. Reyes IS, Hsieh DT, Laux LC, Wilfong AA. Alleged cases of vaccine encephalopathy rediagnosed years later as Dravet syndrome. *Pediatrics*. (2011) 128:e699–702. doi: 10.1542/peds.2010-0887
7. Sato Y, Kimura M, Fukumi H. Development of a pertussis component vaccine in Japan. *Lancet*. (1984) 1:122–6. doi: 10.1016/S0140-6736(84)90061-8
8. Romanus V, Jonsell R, Bergquist SO. Pertussis in Sweden after the cessation of general immunization in 1979. *Pediatr Infect Dis J*. (1987) 6:364–71. doi: 10.1097/00006454-198704000-00005
9. Gangarosa EJ, Galazka AM, Wolfe CR, Phillips LM, Gangarosa RE, Miller E, et al. Impact of anti-vaccine movements on pertussis control: the untold story. *Lancet*. (1998) 351:356–61. doi: 10.1016/S0140-6736(97)04334-1
10. Trollfors B, Taranger J, Lagergard T, Lind L, Sundh V, Zackrisson G, et al. A placebo-controlled trial of a pertussis-toxoid vaccine. *N Engl J Med*. (1995) 333:1045–50. doi: 10.1056/NEJM199510193331604
11. Storsaeter J, Hallander H, Farrington CP, Olin P, M€ollby R, Miller E. Secondary analyses of the efficacy of two acellular pertussis vaccines evaluated in a Swedish phase III trial. *Vaccine*. (1990) 8:457–61. doi: 10.1016/0264-410X(90)90246-I
12. Greco D, Salmaso S, Mastrantonio P, Giuliano M, Tozzi AE, Anemona A, et al. A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. N Engl J Med (1996) 334:341–8. doi: 10.1056/NEJM199602083340601
13. Gustafsson L, Hallander HO, Olin P, Reizenstein E, Storsaeter J. A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. *N Engl J Med*. (1996) 334:349–55. doi: 10.1056/NEJM199602083340602
14. Edwards KM, Decker MD. Acellular pertussis vaccines for infants. *N Engl J Med*. (1996) 334:391. doi: 10.1056/NEJM199602083340609
15. Hallander HO, Gustafsson L. Efficacy and effectiveness of acellular pertussis vaccines: a 20-year Swedish experience. *Expert Rev Vacc*. (2009) 8:1303–7. doi: 10.1586/erv.09.88
16. European Centre for Disease Prevention and Control. *Vaccine Scheduler. Pertussis: Recommended Vaccinations*. Available online at: https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByDisease?SelectedDiseaseId=3&SelectedCountryIdByDisease=-1 (accessed August 15, 2018).
17. Centers for Disease Control and Prevention. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. Available online at: https://www.cdc.gov/vaccines/pubs/pinkbook/pert.html (accessed August 15, 2018).
18. McIntyre P, Gidding H, Gilmour R, Lawrence G, Hull B, Horby P, et al. Vaccine preventable diseases and vaccination coverage in Australia, 1993–1998. *Commun Dis Intell*. (2000) 24(Suppl):22–26.
19. Jajosky RA, Hall PA, Adams DA, Dawkins FJ, Sharp P, Anderson WJ, et al. Summary of notifiable diseases—United States, 2004. *MMWR Morb Mortal Wkly Rep*. (2006) 53:1–79.
20. McNabb SJ, Jajosky RA, Hall-Baker PA, Adams DA, Sharp P, Anderson WJ, et al. Summary of notifiable diseases—United States, 2005. *MMWR Morb Mortal Wkly Rep*. (2007) 54:1–92.
21. Adams DA, Gallagher KA, Jajosky RA, Ward J, Sharp P, Anderon WJ, et al. Summary of notifiable diseases—United States, 2010. *MMWR Morb Mortal Wkly Rep*. (2012) 59:1–111.
22. Adams DA, Jajosky RA, Ajani U, Kriseman J, Sharp P, Onwen DH, et al. Summary of notifiable diseases—United States, 2012. *MMWR Morb Mortal Wkly Rep*. (2014) 61:1–121.

Exhibit 9

Causes and How It Spreads

Whooping cough is a very contagious respiratory illness that spreads from person to person.

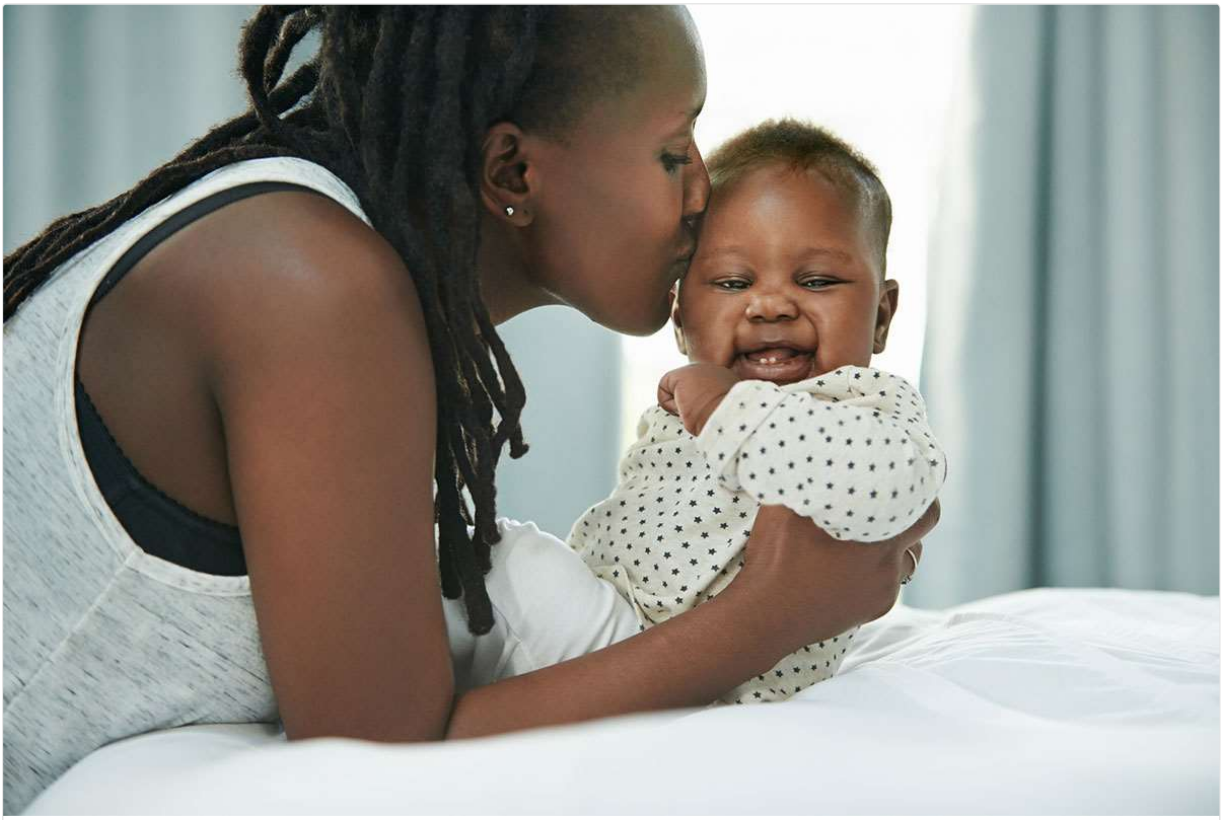
Causes

Whooping cough, also known as pertussis, is a very contagious respiratory illness caused by a type of bacteria called *Bordetella pertussis.* The disease is only found in humans.

Whooping cough bacteria attach to the cilia (tiny, hair-like extensions) that line part of the upper respiratory system. The bacteria release toxins (poisons), which damage the cilia and cause airways to swell.

How it spreads

The bacteria that cause whooping cough spread easily from person to person through the air. When a person who has whooping cough sneezes or coughs, they can release small particles with the bacteria in them. Other people then breathe in the bacteria. It also spreads when people spend a lot of time together or share breathing space, like when you hold a newborn on your chest.



Babies can get whooping cough from family or caregivers who don't know they have it.

People can be contagious for weeks

People can spread the bacteria from the start of the very first symptoms and for at least 2 weeks after coughing begins.

Taking antibiotics early in the illness may shorten the amount of time someone is contagious. Learn more about treatment.

People can spread the disease even if they don't know they have it

Some people have mild symptoms and don't know they have whooping cough, but they can still spread the bacteria to others.

Many babies who get whooping cough are infected by older siblings, parents, or caregivers who don't know they have it. Learn what you can do to protect babies from whooping cough.

Signs and Symptoms

Diagnosis and Treatment

Prevention

Complications

Last Reviewed: August 4, 2022
Source: National Center for Immunization and Respiratory Diseases, Division of Bacterial Diseases

Exhibit 10

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Recommendations and Reports / Vol. 67 / No. 2
April 27, 2018

Prevention of Pertussis, Tetanus, and Diphtheria with Vaccines in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP)

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Tdap Vaccines

Two Tdap products are licensed for use in adolescents and adults as a single-dose booster vaccination against tetanus, diphtheria, and pertussis: Boostrix (GlaxoSmithKline, Rixensart, Belgium), and Adacel (Sanofi Pasteur, Swiftwater, Pennsylvania). The age indication for approved use differs depending upon the specific Tdap product and licensure (Table 5). Both Tdap products consist of pertussis antigen and diphtheria and tetanus toxoids (Table 5). The pertussis antigen composition and amount differ, as does the amount of diphtheria toxoids between the two Tdap products. Summaries of the data on the immunogenicity and safety of each of these vaccines have been published (*4*,*5*).

Adacel (Sanofi Pasteur) is licensed by FDA as a single dose in persons aged 10–64 years (*141*). Adacel contains the same tetanus toxoid, diphtheria toxoid, and five pertussis antigens (PT, PRN, FHA, and FIM) as those in Daptacel (pediatric DTaP), but is formulated with reduced quantities of the toxoids and antigens (Table 5). Adacel contains no thimerosal or other preservative. Additional information is available in the package insert (https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142764.pdf).

Boostrix (GSK) is licensed by FDA as a single dose in persons aged ≥10 years (*142*). Boostrix contains the same tetanus toxoid, diphtheria toxoid, and three pertussis antigens (PT, PRN, and FHA) as those in Infanrix (pediatric DTaP), but is formulated with reduced quantities of the toxoids and antigens (Table 5). Boostrix contains no thimerosal or other preservative. Additional information is available in the package insert (https://www.fda.gov/downloads/BiologicsBloodVaccines/UCM152842.pdf).

Immunogenicity and Efficacy

Both Tdap products were licensed on the basis of clinical trials demonstrating immunogenicity not inferior to U.S.-licensed Td or pediatric DTaP products and an overall safety profile clinically comparable to U.S.-licensed Td products (*143*,*144*). Determining the efficacy of the tetanus and diphtheria toxoid components for each Tdap product was based on the comparison of the rates of protective immune response to these antigens as compared to U.S.-licensed Td and using established serologic correlates of protection (*45*,*72*). The percentage of persons achieving protective antitetanus and antidiphtheria antibody concentrations (>0.1 IU/mL) and the booster response to each of these antigens 1 month postvaccination were evaluated.

Because no well-accepted serologic or laboratory correlate of protection against pertussis has been established, clinical endpoint efficacy studies of acellular pertussis vaccines among adolescents or adults were not required for Tdap licensure. Instead, the efficacy of the pertussis components of Tdap vaccines was inferred using a serologic bridge to infants vaccinated with DTaP in efficacy trials with clinical endpoints (*145*). The immune response of adolescents and adults to each pertussis vaccine antigen after a single dose of Tdap was compared with the immune responses of infants who received 3 doses of pediatric DTaP that included the same pertussis components as the Tdap being assessed (*141*,*142*). The percentage of persons with an acceptable booster response to pertussis vaccine antigens according to predefined criteria also was evaluated. The predefined lower limit was defined as the lower limit of 95% CI for the GMC ratio of the Tdap/pediatric DTaP. Prelicensure Tdap vaccine efficacy was inferred using a serologic bridge to infants vaccinated with 3 doses of DTaP and ranged from 79% to 89% (*105*,*106*).

Postlicensure Tdap Effectiveness

Following the 2005 Tdap recommendation for adolescents and adults, postlicensure pertussis vaccine effectiveness estimates for Tdap in settings with similar vaccines and recommendation schedules have ranged from 66% to 78% among adolescents who received both DTP and DTaP as children (*146*–*148*). Among adolescents who received only DTaP as children, in a matched case-control study, the overall estimated vaccine effectiveness of Tdap against pertussis was 63.9% (95% CI = 50%–74%) (*29*). Initial vaccine effectiveness against pertussis within one year of Tdap vaccination was 73% (95% CI = 60%–82%), but after 2–4 years, postvaccination vaccine effectiveness decreased to 34% (95% CI = -0.03%–58%) (*29*). Another study that calculated Tdap vaccine effectiveness among adolescents found that, within the first year after vaccination, effectiveness was 68.8% (95% CI = 59.7%–75.9%); by ≥4 years after vaccination, vaccine effectiveness was 8.9% (95% CI = -30.6%–36.4%) (*149*). As observed with DTaP, Tdap vaccine effectiveness declines substantially with increasing time since vaccination (*29*,*149*,*150*). Although there are no studies estimating Tdap vaccine effectiveness in persons who received only DTP as infants, reported rates of pertussis have been observed to be significantly lower among children who had started their vaccination series with DTP than among those who had started with DTaP (*151*,*152*).

Prevention of Transmission: Indirect Protection ("Cocooning")

At the time Tdap was first recommended, it was anticipated that this vaccine would prevent pertussis in adolescents and adults and thereby result in preventing transmission

Exhibit 11

Meningococcal Vaccination: What Everyone Should Know

Key Facts

There are 2 types of meningococcal vaccines used in the United States:

- Meningococcal conjugate or MenACWY vaccines
- Serogroup B meningococcal or MenB vaccines

Who Should Get Meningococcal Vaccines?

CDC recommends meningococcal vaccination for all preteens and teens. In certain situations, CDC also recommends other children and adults get meningococcal vaccines. Below is more information about which meningococcal vaccines, including booster shots, CDC recommends for people by age.

Talk to your or your child's doctor about what is best for your specific situation.

Preteens and Teens

All 11 to 12 year olds **should get a MenACWY vaccine**, with a booster shot at 16 years old. Teens **may also get a MenB vaccine**, preferably at 16 through 18 years old.

> Taking a complement inhibitor such as eculizumab (Soliris®) or ravulizumab (Ultomiris®) increases your risk for meningococcal disease. Even if you received meningococcal vaccines, you could still get meningococcal disease.

While any teen **may** choose to get a MenB vaccine, certain preteens and teens **should** get it if they:

- Have a rare type of immune disorder called complement component deficiency
- Are taking a type of medicine called a complement inhibitor (for example, Soliris® or Ultomiris®)
- Have a damaged spleen or sickle cell disease, or their spleen has been removed
- Are part of a population identified to be at increased risk because of a serogroup B meningococcal disease outbreak

Get more information about meningococcal vaccine recommendations for teenagers: Meningococcal Vaccination for Preteens and Teens: Information for Parents. Talk to your child's doctor to find out if, and when, they will need MenACWY or MenB booster shots.

Meningococcal Vaccines for Preteens and Teens
This fact sheet answers general questions about meningococcal vaccines for preteens and teens.
English | Spanish

Babies and Children

CDC recommends MenACWY vaccination for children who are between 2 months and 10 years old if they:

- Have a rare type of immune disorder called complement component deficiency

- Are taking a type of medicine called a complement inhibitor (for example, Soliris® or Ultomiris®)
- Have a damaged spleen or sickle cell disease, or their spleen has been removed
- Have HIV
- Are traveling to or residing in countries in which serogroup A, C, W, or Y meningococcal disease is common
- Are part of a population identified to be at increased risk because of a serogroup A, C, W, or Y meningococcal disease outbreak

Helpful Terms

- ***Neisseria meningitidis*:** The bacteria that cause meningococcal disease.
- **Serogroup:** A group of bacteria that are closely related. There are 6 serogroups of *Neisseria meningitidis* that cause most meningococcal disease in the world — A, B, C, W, X, and Y.

CDC recommends MenB vaccination for children 10 years or older if they:

- Have a rare type of immune disorder called complement component deficiency
- Are taking a type of medicine called a complement inhibitor (for example, Soliris® or Ultomiris®)
- Have a damaged spleen or sickle cell disease, or their spleen has been removed
- Are part of a population identified to be at increased risk because of a serogroup B meningococcal disease outbreak

Talk to your child's doctor to find out if, and when, they will need MenACWY or MenB booster shots.

Adults

CDC recommends MenACWY vaccination for adults if they:

- Have a rare type of immune disorder called complement component deficiency
- Are taking a type of medicine called a complement inhibitor (for example, Soliris® or Ultomiris®)
- Have a damaged spleen or sickle cell disease, or their spleen has been removed
- Have HIV
- Are a microbiologist who is routinely exposed to *Neisseria meningitidis*
- Are traveling to or residing in countries in which serogroup A, C, W, or Y meningococcal disease is common
- Are part of a population identified to be at increased risk because of a serogroup A, C, W, or Y meningococcal disease outbreak
- Are not up to date with this vaccine and are a first-year college student living in a residence hall
- Are a military recruit

CDC recommends MenB vaccination for adults if they:

- Have a rare type of immune disorder called complement component deficiency
- Are taking a type of medicine called a complement inhibitor (for example, Soliris® or Ultomiris®)
- Have a damaged spleen or sickle cell disease, or their spleen has been removed
- Are a microbiologist who is routinely exposed to *Neisseria meningitidis*
- Are part of a population identified to be at increased risk because of a serogroup B meningococcal disease outbreak

Talk to your doctor to find out if, and when, you will need MenACWY or MenB booster shots.

Who Might Not Be Able to Get These Vaccines?

Because of age or health conditions, some people should not get certain vaccines or should wait before getting them. Read the guidelines below and ask your or your child's doctor for more information.

Tell the person who is giving you or your child a meningococcal vaccine if:

You or your child have had a life-threatening allergic reaction or have a severe allergy.

- If you have ever had a life-threatening allergic reaction after a previous dose of MenACWY or MenB vaccine, do not get another dose of that type of vaccine.
- Do not get a meningococcal vaccine if you have a severe allergy to any part of that vaccine. Your or your child's doctor can tell you about the vaccine's ingredients.

You are pregnant or breastfeeding.

- Pregnant women who are at increased risk for serogroup A, C, W, or Y meningococcal disease may get MenACWY vaccines.
- Pregnant or breastfeeding women who are at increased risk for serogroup B meningococcal disease may get MenB vaccines. However, they should talk with a doctor to decide if the benefits of getting the vaccine outweigh the risks.

You or your child are not feeling well.

- People who have a mild illness, such as a cold, can probably get these vaccines. People who have a moderate or severe illness should probably wait until they recover. Your or your child's doctor can advise you.

What Types of Meningococcal Vaccines Are There?

There are 2 types of meningococcal vaccines available in the United States:

- MenACWY (conjugate) vaccines (Menactra®, Menveo®, and MenQuadfi®)
- MenB (recombinant protein) vaccines (Bexsero® and Trumenba®)

MenACWY Vaccines

- Menactra® , Menveo® , and MenQuadfi® : Vaccine providers give 2 doses to preteens and teens. Vaccine providers also give it to certain people at increased risk of meningococcal disease. It helps protect against 4 types of the bacteria that cause meningococcal disease (serogroups A, C, W, and Y).

Helpful Terms

- **Conjugate:** A type of vaccine that joins a protein to an antigen in order to improve the protection the vaccine provides
- **Recombinant protein:** A type of vaccine that contains protein antigens

MenB Vaccines

- Bexsero® : Vaccine providers give a 2-dose series to people 16 through 23 years old who are not at increased risk of meningococcal disease. Vaccine providers also give a 2-dose series to people 10 years or older at increased risk of meningococcal disease. Bexsero® helps protect against serogroup B meningococcal disease.
- Trumenba® : Vaccine providers give a 2-dose series to people 16 through 23 years old who are not at increased risk of meningococcal disease. Vaccine providers give a 3-dose series to people 10 years or older at increased risk of meningococcal disease. Trumenba® helps protect against serogroup B meningococcal disease.

How Well Do These Vaccines Work?

Summary

Vaccines that help protect against meningococcal disease work well but cannot prevent all cases.

As part of the licensure process, MenACWY and MenB vaccines showed that they produce an immune response. This immune response suggests the vaccines provide protection, but data are limited on how well they work. Since meningococcal disease is uncommon, many people need to get these vaccines in order to measure their effectiveness.

Available data suggest that protection from MenACWY vaccines decreases in many teens within 5 years. Getting the 16-year-old MenACWY booster dose is critical so teens have protection when they are most at risk for meningococcal disease. Available data on MenB vaccines suggest that protective antibodies also decrease quickly (within 1 to 2 years) after vaccination.

In Depth

Rates of meningococcal disease have declined in the United States since the 1990s and remain low today. Much of the decline occurred before the routine use of MenACWY vaccines. In addition, serogroup B meningococcal disease declined even though MenB vaccines were not available until the end of 2014.

CDC first recommended preteens and teens get a MenACWY vaccine in 2005. Since then, rates of meningococcal disease in teens caused by serogroups C, Y, and W have decreased by over 90% (note: serogroup A meningococcal disease continues to be very rare in the United States). Other age groups that CDC does not recommend routine MenACWY vaccination for did not see this large of a percent decline. These

data suggest MenACWY vaccines have provided protection to those vaccinated, but probably not to the larger, unvaccinated community (population or herd immunity). Experts also believe MenB vaccines do not provide protection to unvaccinated people through population immunity.

What Are the Possible Side Effects of Meningococcal Vaccines?

Most people who get a meningococcal vaccine do not have any serious problems with it. With any medicine, including vaccines, there is a chance of side effects. These are usually mild and go away on their own within a few days, but serious reactions are possible.

Mild Problems

MenACWY Vaccines

Mild problems following MenACWY vaccination can include:

- Reactions where the shot was given
  - Redness
  - Soreness
- Muscle pain
- Headache
- Feeling tired

If these problems occur, they usually last for 1 or 2 days.

MenB Vaccines

Mild problems following a MenB vaccination can include:

- Reactions where the shot was given
  - Soreness
  - Redness
  - Swelling
- Feeling tired
- Headache
- Muscle or joint pain
- Fever or chills
- Nausea or diarrhea

If these problems occur, they can last up to 3 to 5 days.

Problems that Could Happen After Getting Any Injected Vaccine

- People sometimes faint after medical procedures, including vaccination. Sitting or lying down for about 15 minutes can help prevent fainting, and injuries caused by a fall. Tell the provider if you or your child feel dizzy, have vision changes, or have ringing in the ears.
- As with any medicine, there is a very remote chance of a vaccine causing a severe allergic reaction, other serious injury, or death.

Where Can I Find These Vaccines?

Your doctor is usually the best place to receive recommended vaccines for you or your child. These vaccines are part of the routine childhood immunization schedule. Therefore, vaccines for children and teens are regularly available at

- Pediatric and family practice offices
- Community health clinics
- Public health departments

If your doctor does not have these vaccines for adults, ask for a referral.

Vaccines may also be available at

- Pharmacies

- Workplaces
- Community health clinics
- Health departments
- Other community locations, such as schools and religious centers

You can also contact your state health department to learn more about where to get vaccines in your community.

When receiving any vaccine, ask the provider to record the vaccine in the state or local vaccine registry, if available. This helps providers at future visits know what vaccines you or your child have already received.

How Can I Get Help Paying for These Vaccines?

People can pay for meningococcal vaccines in several ways:

Private Health Insurance

Most private health insurance plans cover these vaccines. Check with your insurance provider for details on whether there is any cost to you. Ask your insurance provider for a list of in-network vaccine providers.

Vaccines for Children Program

Most health insurance plans cover routine vaccinations. The Vaccines for Children (VFC) program also provides vaccines for children 18 years and younger who are uninsured, underinsured, Medicaid-eligible, American Indian, or Alaska Native.

Related Pages

CDC's Meningococcal Disease Website

Educational Materials on Meningococcal Disease

- Adult Vaccine Assessment Tool: What Vaccines Do You Need?
- Meningococcal Vaccination for Preteens and Teens: Information for Parents

Immunization Schedules

- Recommended Vaccinations for Children (7 through 18 Years Old)
- Recommended Adult Immunization Schedule for Ages 19 Years or Older

Meningococcal Vaccine Information Statements

- MenACWY (English / Other Languages)
- MenB (English / Other Languages)

Vaccine Safety

- CDC's Vaccine Safety Website
- Meningococcal Vaccine Safety Website: A Closer Look at the Safety Data
- Frequently Asked Questions about Vaccine Safety

Meningococcal ACWY State Mandates for Elementary and Secondary Schools
Find out the MenACWY vaccination mandates for elementary and secondary schools in your state

Vaccines for Children Program

Information for the General Public: Cochlear Implants and Vaccination Recommendations

Last Reviewed: October 12, 2021

Exhibit 12

Meningococcal Vaccination for Adolescents: Information for Healthcare Professionals

CDC recommends meningococcal vaccination for all adolescents. Follow the recommended immunization schedule to ensure that your patients get the meningococcal vaccines that they need.

- All 11 to 12 year olds **should** receive a single dose of meningococcal conjugate (MenACWY) vaccine.
- Since protection wanes, CDC recommends a booster dose at age 16 years. The booster dose provides protection during the ages when adolescents are at highest risk of meningococcal disease.
- Adolescents and young adults (16 through 23 years of age) **may** also receive a serogroup B meningococcal (MenB) vaccine. The preferred age at which to administer MenB vaccine is 16 through 18 years.
- CDC recommends that certain adolescents and young adults **should** receive a MenB vaccine. They include those at increased risk because of a serogroup B meningococcal disease outbreak and people with certain medical conditions.

Adolescents are at increased risk for meningococcal disease.

Anyone can get meningococcal disease. However, adolescents and young adults 16 through 23 years of age are at increased risk for meningococcal disease. In addition, college students have a slightly higher risk than other teens and young adults who are not attending college. Meningococcal bacteria can cause severe disease, including meningitis, bacteremia, and septicemia, resulting in permanent disabilities and even death.

Meningococcal Vaccines

Meningococcal conjugate (MenACWY) vaccines

- Menactra®
- Menveo® (one- and two-vial presentations)
- MenQuadfi®

Serogroup B meningococcal (MenB) vaccines

- Bexsero®
- Trumenba®

There are 2 types of meningococcal vaccines available in the United States. Each type helps protect against different serogroups of meningococcal disease.

MenACWY vaccines provide protection against 4 serogroups: A, C, W, and Y. MenB vaccines provide protection against serogroup B. Currently no meningococcal vaccine offers protection in a single shot against these 5 serogroups.

You can administer MenACWY and MenB vaccines at the same time. You can also administer them with other vaccines recommended for adolescents.

Vaccine providers may administer meningococcal and other vaccines during the same visit, but at different injection sites if feasible.

CDC recommends meningococcal vaccination for people identified as being at increased risk during outbreaks.

CDC supports state and local health departments in investigating outbreaks and implementing outbreak control measures. During a serogroup A, C, W, or Y meningococcal disease outbreak, CDC recommends MenACWY vaccination for people at increased risk because of the outbreak. During a serogroup B meningococcal disease outbreak, CDC recommends MenB

vaccination for people at increased risk because of the outbreak. People who have previously received MenACWY or MenB vaccine and become at increased risk because of an outbreak may be recommended to receive a booster dose depending on how long it has been since they previously received the vaccine.

MenACWY Vaccines

Report Adverse Events

Adverse events occurring after administration of any vaccine should be reported to the Vaccine Adverse Event Reporting System (VAERS). Reports can be submitted to VAERS online, by fax, or by mail. Additional information about VAERS is available by telephone (1-800-822-7967) or on the VAERS website .

A MenACWY booster dose helps protect adolescents during the ages they are at highest risk.

Protection from MenACWY vaccination wanes in most adolescents within 5 years. Based on that information, adolescents need a booster dose at age 16 years. The booster dose provides protection during the years when they are at highest risk of meningococcal disease.

MenACWY vaccines are safe.

CDC continually monitors the safety of all vaccines. For information about side effects, see the MenACWY Vaccine Information Statement.

Many colleges require proof of MenACWY vaccination within 5 years before starting school.

CDC recommends that students receive a MenACWY vaccine within 5 years prior to starting college. This vaccination is required to attend many colleges.

The minimum booster dose interval is 8 weeks for MenACWY vaccines.

The minimum interval between doses is 8 weeks. However, healthy adolescents do not need a booster if the initial dose is given at or after age 16 years.

People with certain medical conditions need a 2-dose primary series of MenACWY vaccine and routine booster doses.

Vaccinate people with the following medical conditions with a 2-dose primary series of MenACWY vaccine administered 8 weeks apart:

- Complement component deficiency (e.g., C5-C9, properdin, factor H, factor D, or are taking a complement inhibitor such as Soliris® or Ultomiris®)
- Functional or anatomic asplenia (including sickle cell disease)
- HIV

Administer routine booster doses every 5 years throughout life to people with these medical conditions. Booster doses will help these patients maintain protection against meningococcal disease.

Exhibit 13

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

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

November 30, 2020

Elizabeth Brehm
Siri & Glimstad
200 Park Ave, 17th Floor
New York, NY 10166
Via email: foia@sirillp.com

Dear Ms. Brehm:

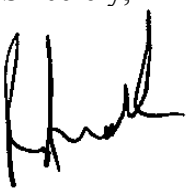
This letter is in response to your Centers for Disease Control and Prevention and Agency for Toxic Substances and Disease Registry (CDC/ATSDR) Freedom of Information Act (FOIA) request of November 9, 2020, for 'documentation sufficient to reflect any case(s) of transmission of Hepatitis B in an elementary, middle, or high school setting.'

A search of our records failed to reveal any documents pertaining to your request.

You may contact our FOIA Public Liaison at 770-488-6277 for any further assistance and to discuss any aspect of your request. Additionally, you may contact the Office of Government Information Services (OGIS) at the National Archives and Records Administration to inquire about the FOIA mediation services they offer. The contact information for OGIS is as follows: Office of Government Information Services, National Archives and Records Administration, 8601 Adelphi Road-OGIS, College Park, Maryland 20740-6001, e-mail at ogis@nara.gov; telephone at 202-741-5770; toll free at 1-877-684-6448; or facsimile at 202-741-5769.

If you are not satisfied with the response to this request, you may administratively appeal by writing to the Deputy Agency Chief FOIA Officer, Office of the Assistant Secretary for Public Affairs, U.S. Department of Health and Human Services, Hubert H. Humphrey Building, 200 Independence Avenue, Suite 729H, Washington, D.C. 20201. You may also transmit your appeal via email to FOIARequest@psc.hhs.gov. Please mark both your appeal letter and envelope "FOIA Appeal." Your appeal must be postmarked or electronically transmitted by February 28, 2021.

Sincerely,



Roger Andoh
CDC/ATSDR FOIA Officer
Office of the Chief Operating Officer
(770) 488-6399
Fax: (404) 235-1852

#21-00200-FOIA

Exhibit 14

VIRAL HEPATITIS IN WEST VIRGINA

2020 Surveillance Summary

May 2022

WEST VIRGINIA Department of Health & Human Resources
BUREAU FOR PUBLIC HEALTH

Division of STD, HIV, Hepatitis and Tuberculosis
Office of Epidemiology and Prevention Services
350 Capitol Street, Room 125
Charleston, West Virginia 25301

Hepatitis B Virus (HBV)

Disease Overview

Like hepatitis A, hepatitis B is a vaccine-preventable liver disease. It is caused by the hepatitis B virus (HBV) and can be transmitted through direct contact with contaminated blood, semen, or other bodily fluids. Transmission of the HBV can occur through sexual contact, sharing needles, syringes, or other drug use equipment, or perinatally from mother to baby at birth. Unlike hepatitis A, hepatitis B can be short-term (acute) or long-term (chronic), affecting some for a few months and others for years. The long-term effects of chronic hepatitis B can include cirrhosis of the liver, liver cancer, and even death. Although there is no cure, those who are chronically infected with the HBV can be treated to reduce the risk of developing more serious liver disease. The best way to prevent HBV infection is to be vaccinated.

HBV in West Virginia

For several years West Virginia reported one of the highest incidence rates of acute hepatitis B in the nation. The rate in West Virginia has declined steadily since 2016, falling to 3.2 cases per 100,000 population in 2020 (Figure 2.1); however, the rate in 2020 could be artificially low due to the increased demand for public health response to the COVID-19 outbreak and fewer case-patients being contacted for interview. Most acute hepatitis B cases were male (63%), reported their race as White (88%), and were between the ages of 30-59 (76%). The most frequently reported risk factors for acute hepatitis B cases in 2020 were injection and non-injection drug use (Table 2.4). A similar demographic profile was found among chronic hepatitis B cases.

Exhibit 15

VACCINE INFORMATION STATEMENT

MMR (Measles, Mumps, and Rubella) Vaccine: *What You Need to Know*

Many Vaccine Information Statements are available in Spanish and other languages. See www.immunize.org/vis

Hojas de información sobre vacunas están disponibles en español y en muchos otros idiomas. Visite www.immunize.org/vis

1 Why get vaccinated?

Measles, **mumps**, and **rubella** are viral diseases that can have serious consequences. Before vaccines, these diseases were very common in the United States, especially among children. They are still common in many parts of the world.

Measles

- Measles virus causes symptoms that can include fever, cough, runny nose, and red, watery eyes, commonly followed by a rash that covers the whole body.
- Measles can lead to ear infections, diarrhea, and infection of the lungs (pneumonia). Rarely, measles can cause brain damage or death.

Mumps

- Mumps virus causes fever, headache, muscle aches, tiredness, loss of appetite, and swollen and tender salivary glands under the ears on one or both sides.
- Mumps can lead to deafness, swelling of the brain and/or spinal cord covering (encephalitis or meningitis), painful swelling of the testicles or ovaries, and, very rarely, death.

Rubella (also known as German Measles)

- Rubella virus causes fever, sore throat, rash, headache, and eye irritation.
- Rubella can cause arthritis in up to half of teenage and adult women.
- If a woman gets rubella while she is pregnant, she could have a miscarriage or her baby could be born with serious birth defects.

These diseases can easily spread from person to person. Measles doesn't even require personal contact. You can get measles by entering a room that a person with measles left up to 2 hours before.

Vaccines and high rates of vaccination have made these diseases much less common in the United States.

2 MMR vaccine

Children should get 2 doses of MMR vaccine, usually:

- First dose: 12 through 15 months of age
- Second dose: 4 through 6 years of age

Infants who will be traveling outside the United States when they are between 6 and 11 months of age should get a dose of MMR vaccine before travel. This can provide temporary protection from measles infection, but will not give permanent immunity. The child should still get 2 doses at the recommended ages for long-lasting protection.

Adults might also need MMR vaccine. Many adults 18 years of age and older might be susceptible to measles, mumps, and rubella without knowing it.

A third dose of MMR might be recommended in certain mumps outbreak situations.

There are no known risks to getting MMR vaccine at the same time as other vaccines.

There is a combination vaccine called MMRV that contains both chickenpox and MMR vaccines. MMRV is an option for some children 12 months through 12 years of age. There is a separate Vaccine Information Statement for MMRV. Your health care provider can give you more information.

3 Some people should not get this vaccine

Tell your vaccine provider if the person getting the vaccine:

- **Has any severe, life-threatening allergies.** A person who has ever had a life-threatening allergic reaction after a dose of MMR vaccine, or has a severe allergy to any part of this vaccine, may be advised not to be vaccinated. Ask your health care provider if you want information about vaccine components.
- **Is pregnant, or thinks she might be pregnant.** Pregnant women should wait to get MMR vaccine until after they are no longer pregnant. Women should avoid getting pregnant for at least 1 month after getting MMR vaccine.
- **Has a weakened immune system** due to disease (such as cancer or HIV/AIDS) or medical treatments (such as radiation, immunotherapy, steroids, or chemotherapy).
- **Has a parent, brother, or sister with a history of immune system problems.**
- **Has ever had a condition that makes them bruise or bleed easily.**
- **Has recently had a blood transfusion or received other blood products**. You might be advised to postpone MMR vaccination for 3 months or more.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

- **Has tuberculosis**.
- **Has gotten any other vaccines in the past 4 weeks**. Live vaccines given too close together might not work as well.
- **Is not feeling well**. A mild illness, such as a cold, is usually not a reason to postpone a vaccination. Someone who is moderately or severely ill should probably wait. Your doctor can advise you.

4 Risks of a vaccine reaction

With any medicine, including vaccines, there is a chance of reactions. These are usually mild and go away on their own, but serious reactions are also possible.

Getting MMR vaccine is much safer than getting measles, mumps, or rubella disease. Most people who get MMR vaccine do not have any problems with it.

After MMR vaccination, a person might experience:

Minor events:

- Sore arm from the injection
- Fever
- Redness or rash at the injection site
- Swelling of glands in the cheeks or neck

If these events happen, they usually begin within 2 weeks after the shot. They occur less often after the second dose.

Moderate events:

- Seizure (jerking or staring) often associated with fever
- Temporary pain and stiffness in the joints, mostly in teenage or adult women
- Temporary low platelet count, which can cause unusual bleeding or bruising
- Rash all over body

Severe events occur very rarely:

- Deafness
- Long-term seizures, coma, or lowered consciousness
- Brain damage

Other things that could happen after this vaccine:

- People sometimes faint after medical procedures, including vaccination. Sitting or lying down for about 15 minutes can help prevent fainting and injuries caused by a fall. Tell your provider if you feel dizzy or have vision changes or ringing in the ears.
- Some people get shoulder pain that can be more severe and longer-lasting than routine soreness that can follow injections. This happens very rarely.
- Any medication can cause a severe allergic reaction. Such reactions to a vaccine are estimated at about 1 in a million doses, and would happen within a few minutes to a few hours after the vaccination.

As with any medicine, there is a very remote chance of a vaccine causing a serious injury or death.

The safety of vaccines is always being monitored. For more information, visit: **www.cdc.gov/vaccinesafety/**

5 What if there is a serious problem?

What should I look for?

- Look for anything that concerns you, such as signs of a severe allergic reaction, very high fever, or unusual behavior.

  Signs of a **severe allergic reaction** can include hives, swelling of the face and throat, difficulty breathing, a fast heartbeat, dizziness, and weakness. These would usually start a few minutes to a few hours after the vaccination.

What should I do?

- If you think it is a **severe allergic reaction** or other emergency that can't wait, call 9-1-1 and get to the nearest hospital. Otherwise, call your health care provider.

  Afterward, the reaction should be reported to the Vaccine Adverse Event Reporting System (VAERS). Your doctor should file this report, or you can do it yourself through the VAERS web site at **www.vaers.hhs.gov**, or by calling **1-800-822-7967**.

VAERS does not give medical advice.

6 The National Vaccine Injury Compensation Program

The National Vaccine Injury Compensation Program (VICP) is a federal program that was created to compensate people who may have been injured by certain vaccines.

Persons who believe they may have been injured by a vaccine can learn about the program and about filing a claim by calling **1-800-338-2382** or visiting the VICP website at **www.hrsa.gov/vaccinecompensation**. There is a time limit to file a claim for compensation.

7 How can I learn more?

- Ask your healthcare provider. He or she can give you the vaccine package insert or suggest other sources of information.
- Call your local or state health department.
- Contact the Centers for Disease Control and Prevention (CDC):
  - Call **1-800-232-4636** (**1-800-CDC-INFO**) or
  - Visit CDC's website at **www.cdc.gov/vaccines**

Vaccine Information Statement

MMR Vaccine

Office use only

2/12/2018 42 U.S.C. § 300aa-26

Exhibit 16

March 27, 2019

Siri & Glimstad LLP
Aaron Siri, Esq.
200 Park Ave
17th Floor
New York, NY 101066

In reply refer to file: **2018-6847**

Dear Mr. Siri,

This is in reply to your Freedom of Information Act (FOIA) request dated August 20, 2018 in which you requested "a copy of the report for each clinical trial relied upon by the FDA when approving M-M-R II in 1978." Your request was received in the Center for Biologics Evaluation and Research (CBER) on August 21, 2018.

Enclosed are the documents responsive to your request.

We have withheld portions of pages under Exemption (b)(4), 5 U.S.C. § 522(b)(4). That exemption permits the withholding of trade secrets and commercial or financial information that was obtained from a person outside the government and that is privileged or confidential. The withholding of such information is permitted if disclosure is likely to cause substantial competitive harm to the person who submitted the information.

In addition, we have withheld portions of pages under Exemption (b)(6), 5 U.S.C. § 522(b)(6). That exemption protects information from disclosure when its release would cause a clearly unwarranted invasion of personal privacy. FOIA Exemption 6 is available to protect information in personnel or medical files and similar files. This requires a balancing of the public's right to disclosure against the individual's right to privacy.

You have the right to appeal this determination. By filing an appeal, you preserve your rights under FOIA and give the agency a chance to review and reconsider your request and the agency's decision.

Your appeal must be mailed within 90 days from the date of this response to:

Ms. Catherine Teti
Deputy Agency Chief FOIA Officer
U.S. Department of Health and Human Services
Office of the Assistant Secretary for Public Affairs
Room 729H
200 Independence Avenue, S.W.
Washington, DC 20201

Please clearly mark both the envelope and your letter "FDA Freedom of Information Act Appeal."

If you would like to discuss our response before filing an appeal to attempt to resolve your dispute without going through the appeals process, please contact:

Beth Brockner-Ryan, Branch Chief
Center for Biologics Evaluation and Research (CBER)
Access Litigation and Freedom of Information Branch
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Building 71, Room 1114
Silver Spring, MD 20993-0002
Email:beth.brocknerryan@fda.hhs.gov
Main Line 240-402-7800
FOI Line 240-402-8008

You also have the right to contact:

FDA FOIA Public Liaison
Office of the Executive Secretariat
5630 Fishers Lane
Room-1050
Rockville, MD 20857
Email: FDAFOIA@fda.hhs.gov

If you are unable to resolve your FOIA dispute through our FOIA Public Liaison, the Office of Government Information Services (OGIS), the Federal FOIA Ombudsman's office, offers mediation services to help resolve disputes between FOIA requesters and Federal agencies. The contact information for OGIS is:

Office of Government Information Services
National Archives and Records Administration
8601 Adelphi Road–OGIS
College Park, MD 20740-6001
Telephone: 202-741-5770
Toll-Free: 1-877-684-6448
E-mail: ogis@nara.gov
Fax: 202-741-5769

If you have any questions or if we can be of further assistance, please let us know by referencing the above file number. You can contact John Hyder by phone at 240-402-8079 or by e-mail at John.Hyder@fda.hhs.gov.

Sincerely,

Beth A. Brockner Ryan -S

Digitally signed by Beth A. Brockner Ryan -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300052489, cn=Beth A. Brockner Ryan -S
Date: 2019.03.27 10:26:33 -04'00'

Beth Brockner Ryan
Chief, Access Litigation and Freedom of Information Branch

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
BETHESDA, MARYLAND 20014

SEP 15 1978

Our Reference Nos. 76-316, 77-303 and 77-304

Alan Gray, Ph.D.
Merck Sharp & Dohme
Division of Merck and Co., Inc.
West Point, Pennsylvania 19486

Dear Dr. Gray:

This is to inform you that the amendments to your product license applications to include the use of the RA27/3 strain rubella virus grown in human diploid cells have been accepted for manufacture of the following products:

Rubella Virus Vaccine, Live
Measles, Mumps and Rubella Virus Vaccine, Live
Measles and Rubella Virus Vaccine, Live

We agree that the results of stability testing of vaccines prepared with the buffered sorbitol-gelatin diluent support your request for a longer dating period. Accordingly, your license applications for the three products are also amended to include the use of the diluent and a dating period of two years at 2°-8°C from date of issue.

Please continue to submit stability data as they become available.

Sincerely yours,

Paul Parkman

for Harry M. Meyer, Jr., M.D.
Director
Bureau of Biologics

Summary of Clinical Tests of Combined Live
Measles-Mumps-Rubella (RA 27/3) Virus Vaccine

Study No.	Investigator	Lot No.	Age		No. Vacc.	Antibody Responses among Triple Seronegatives								Re.
						Measles			Mumps			RA 27/3 Rubella		
			Range	Mean (Yrs.)		No. Conv./ No. Seroneg. (%)		GMT	No. Conv./ No. Seroneg. (%)		GMT	No. Conv./ No. Seroneg. (%)		GMT	
442	Villarejos	621	10m- 7y	3.7	199	23/23	(100)	99	22/23	(96)	7	23/23	(100)	149	1
443	Weibel	621	11m- 8y	1.7	105	65/69	(94)	56	66/69	(96)	8	69/69	(100)	133	2
459	Lerman	60664	14m- 4y	1.6	41	13/14	(93)	62	13/14	(93)	17	14/14	(100)	269	3
467	Weibel	621	11m- 7y	1.9	137	55/58	(95)	71	57/58	(98)	7	58/58	(100)	146	4
473	McCollum	621													5
484	Gershon	621	13m-15y		39										6
511	Villarejos	60664	8m-11y	3.3	50	9/11	(82)	20	10/11	(91)	5	11/11	(100)	226	7
		60665	11m- 7y	3.3	50	4/5	(80)	25	4/5	(80)	11	5/5	(100)	169	
		60666	11m-11y	4.2	50	2/2	(100)	28	2/2	(100)	8	2/2	(100)	256	
513	Weibel	60664	12m- 7y	1.7	53	28/30	(93)	70	29/30	(97)	19	30/30	(100)	256	8
		60665	12m- 4y	1.5	54	33/34	(97)	70	33/34	(97)	23	33/34	(97)	200	
		60666	11m- 4y	1.4	56	32/33	(97)	66	32/33	(97)	26	32/33	(97)	251	
		Totals			834	264/279	(95)	63	268/279	(96)	11	277/279	(99)	178	

4/24/78

Table 10

Clinical Complaints Reported Among Children Who Received Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot No. 621/C-D763 (Study #442)

Clinical Complaint	Total Vaccinees (199 Children)						Initially Seronegative to: Measles, Mumps and Rubella (23 Children)					
	Days Post-Vaccination					No. with Complaint	Days Post Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Irritability	32 (16.1%)	9 (4.5)	2 (1.0)	4 (2.1)		39	5 (21.7)			1 (5.0)		5
Malaise	30 (15.1)	14 (7.0)	3 (1.5)	7 (3.6)	1 (0.5)	43	5 (21.7)	1 (4.3)		2 (10.0)		7
Headache		1 (0.5)	2 (1.0)			2						0
Upper Respiratory Illness	9 (4.5)	11 (5.5)	5 (2.5)	8 (4.1)	5 (2.6)	23	1 (4.3)	1 (4.3)	1 (4.3)	2 (10.0)	1 (5.0)	3
Otitis			2 (1.0)	3 (1.5)		3			1 (4.3)	1 (5.0)		1
Ophthalmopathy		1 (0.5)				1						0
Gastrointestinal Illness	13 (6.5)	7 (3.5)	2 (1.0)	5 (2.6)	1 (0.5)	22		1 (4.3)				1
Anorexia	5 (2.5)	3 (1.5)	2 (1.0)	5 (2.6)		13				1 (5.0)		1
Mild Dermatitis		1 (0.5)				1						0
Persons with Complaints:	49 (24.6)	22 (11.1)	11 (5.5)	19 (9.8)	6 (3.1)	73	6 (26.1)	2 (8.7)	1 (4.3)	4 (20.0)	1 (5.0)	10
Persons with No Complaints:	150 (75.4)	177 (88.9)	188 (94.5)	175 (90.2)	187 (96.9)	123	17 (73.9)	21 (91.3)	22 (95.7)	16 (80.0)	19 (95.0)	12
Negative Physician Surveillance				5	6					3	3	

10/3/77

Table 10

Clinical Complaints Reported Among Children Who Received a 0.5 Ml Dose of Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot No. 621/C-D763 (Study #443)

Clinical Complaint	Total Vaccinees (102 Children)						Initially Seronegative to: Measles, Mumps and Rubella (68 Children)					
	Days Post-Vaccination					No. with Complaint	Days Post-Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Soreness at Injection Site	4 (4.2%)			1 (1.0)		5	2 (3.0)					2
Lymphadenopathy	2 (2.1)	3 (3.1)		2 (2.1)	2 (2.1)	6	1 (1.5)	1 (1.5)		2 (3.0)	2 (3.0)	3
Measles-Like Rash	1 (1.0)	9 (9.4)	6 (6.2)	1 (1.0)		11	1 (1.5)	7 (10.4)	5 (7.5)	1 (1.5)		9
Arthralgia			1 (1.0)	1 (1.0)		1			1 (1.5)	1 (1.5)		1
Myalgia		1 (1.0)				1		1 (1.5)				1
Irritability	3 (3.0)	3 (3.0)	1 (1.0)	1 (1.0)	1 (1.0)	4	2 (2.9)	2 (2.9)	1 (1.5)	1 (1.5)		3
Headache	2 (2.1)	2 (2.1)				2	2 (3.0)	2 (3.0)				2
Upper Respiratory Illness	38 (39.6)	37 (38.5)	24 (25.0)	35 (36.5)	32 (33.3)	64	28 (41.8)	27 (40.3)	20 (29.8)	25 (37.3)	20 (29.8)	46
Otitis	1 (1.0)	7 (7.3)	2 (2.1)	5 (5.2)	4 (4.2)	14	1 (1.5)	4 (6.0)	2 (3.0)	3 (4.5)	2 (3.0)	9
Ophthalmopathy	2 (2.1)	3 (3.1)	2 (2.1)	4 (4.2)	2 (2.1)	6	2 (3.0)	3 (4.5)	2 (3.0)	4 (6.0)	2 (3.0)	6
Gastrointestinal Illness	18 (18.7)	24 (25.0)	9 (9.4)	17 (17.7)	15 (15.6)	43	14 (20.9)	19 (28.4)	9 (13.4)	14 (20.9)	11 (16.4)	35
Anorexia	13 (13.5)	19 (19.8)	8 (8.3)	10 (10.4)	13 (13.5)	28	10 (14.9)	12 (17.9)	6 (9.0)	9 (13.4)	11 (16.4)	20
Fatigue				1 (1.0)		1				1 (1.5)		1
Rash-Chafing, Diaper, Heat, Herpes	4 (4.2)	4 (4.2)	1 (1.0)	4 (4.2)	5 (5.2)	12	3 (4.5)	4 (6.0)	1 (1.5)	3 (4.5)	3 (4.5)	9
Allergy, Asthma	1 (1.0)	2 (2.1)	3 (3.1)	2 (2.1)	3 (3.1)	6		1 (1.5)	2 (3.0)	1 (1.5)		3
Fever	1 (1.0)	1 (1.0)		2 (2.1)	1 (1.0)	4		1 (1.5)		1 (1.5)		2
Sudoresis	1 (1.0)					1	1 (1.5)					1
Teething	3 (3.0)			1 (1.0)	3 (3.0)	6	3 (4.4)			1 (1.5)	3 (4.4)	6
Persons with Complaints:	50 (52.1)	50 (52.1)	23 (34.4)	43 (44.8)	44 (45.8)	78	38 (56.7)	38 (56.7)	29 (43.3)	32 (47.8)	30 (44.8)	58
Persons with No Complaints:	46 (47.9)	46 (47.9)	63 (65.6)	53 (55.2)	52 (54.2)	18	29 (43.3)	29 (43.3)	38 (56.7)	35 (52.2)	37 (55.2)	9
Negative Physician Surveillance	6	6	6	6	6	6	1	1	1	1	1	1

5/6/77

Table 9

Clinical Complaints Reported Among Children Who Received Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60664/C-E810 (Study #459)

Clinical Complaint	Total Vaccinees (41 Children)						Initially Seronegatives (16 Children)					
	Days Post Vaccination					No. with Complaint	Days Post Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Injection Site:												
Soreness	2 (4.9%)					2						0
Systemic:												
Measles-Like Rash		4 (9.8)	2 (4.9)			5			1 (6.3)			1
Irritability	1 (2.4)	3 (7.3)	2 (4.9)		3 (7.5)	6	1 (6.3)				1 (6.7)	2
Anorexia	8 (19.5)	5 (12.2)	8 (19.5)	9 (22.0)	7 (17.5)	20	3 (18.8)	1 (6.3)	2 (12.5)	3 (18.8)	3 (20.0)	6
Disturbed Sleep		1 (2.4)				1		1 (6.3)				1
Upper Respiratory Illness	16 (39.0)	17 (41.5)	10 (24.4)	11 (26.8)	16 (40.0)	28	5 (31.3)	5 (31.3)	2 (12.5)	6 (37.5)	7 (46.7)	10
Otitis		2 (4.9)	1 (2.4)	3 (7.3)	3 (7.5)	8		1 (6.3)	1 (6.3)	2 (12.5)	1 (6.7)	4
Ophthalmopathy	3 (7.3)	1 (2.4)			3 (7.5)	7		1 (6.3)				1
Gastrointestinal Illness	9 (22.0)	9 (22.0)	6 (14.6)	10 (24.4)	9 (22.5)	24	3 (18.8)	1 (6.3)	2 (12.5)	5 (31.3)	3 (20.0)	10
Nonspecific Rash	2 (4.9)	4 (9.8)	2 (4.9)	3 (7.3)	3 (7.5)	5	1 (6.3)	2 (12.5)	2 (12.5)	2 (12.5)	1 (6.7)	3
Varicella				1 (2.4)		1				1 (6.3)		1
Allergy		1 (2.4)				1		1 (6.3)				1
Teething	1 (2.4)	3 (7.3)	1 (2.4)	1 (2.4)	2 (5.0)	4	1 (6.3)	1 (6.3)	1 (6.3)	1 (6.3)	1 (6.7)	1
Herpes-Type Rash	1 (2.4)					1						0
Persons with Complaint:	20 (48.8)	26 (63.4)	18 (43.9)	16 (39.0)	22 (55.0)	34	7 (43.8)	8 (50.0)	6 (37.5)	8 (50.0)	9 (60.0)	14
Persons with No Complaint:	21 (51.2)	15 (36.6)	23 (56.1)	25 (61.0)	18 (45.0)	7	9 (56.3)	8 (50.0)	10 (62.5)	8 (50.0)	6 (40.0)	2
Negative Surveillance					1						1	

4/21/78

Table 11

Clinical Complaints Reported Among Children Who Received a 0.5 ml Dose of Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #621/C-D763 (Study #467)

Clinical Complaint	Total Vaccinees (117 Children)						Initially Seronegatives (61 Children)					
	Days Post Vaccination					No. with Complaint	Days Post Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Soreness at Injection Site	2 (2.2%)	1 (1.1)	1 (1.1)			3	1 (2.1)	1 (2.1)	1 (2.1)			2
Lymphadenopathy		2 (2.2)		1 (1.1)		3		2 (4.3)		1 (2.1)		3
Measles-Like Rash	1 (1.1)	5 (5.6)	3 (3.4)			7	1 (2.1)	4 (8.5)	1 (2.1)			5
Headache		1 (1.1)		1 (1.1)	1 (1.1)	3		1 (2.1)				1
Irritability	4 (4.4)	4 (4.5)		1 (1.1)		8	3 (6.3)	1 (2.1)				4
Fever-Temperature Not Reported	1 (1.1)	1 (1.1)				2		1 (2.1)				1
Anorexia	10 (11.1)	12 (13.5)	6 (6.7)	7 (8.0)	6 (6.8)	23	5 (10.4)	7 (14.9)	4 (8.3)	2 (4.3)	1 (2.1)	11
Flush					1 (1.1)	1						0
Disturbed Sleep	2 (2.2)					2						0
Myalgia	1 (1.1)					1	1 (2.1)					1
Upper Respiratory Illness	15 (16.7)	29 (32.6)	17 (19.1)	20 (22.7)	31 (35.2)	53	6 (12.5)	13 (27.7)	9 (18.8)	9 (19.1)	10 (21.3)	22
Otitis	1 (1.1)	2 (2.2)	2 (2.2)	1 (1.1)	1 (1.1)	2		1 (2.1)	1 (2.1)			1
Ophthalmopathy		5 (5.6)	4 (4.5)	3 (3.4)	4 (4.5)	9		3 (6.4)	3 (6.3)	2 (4.3)	1 (2.1)	4
Gastrointestinal Illness	9 (10.0)	15 (16.9)	10 (11.2)	12 (13.6)	13 (14.8)	31	4 (8.3)	12 (25.5)	6 (12.5)	7 (14.9)	4 (8.5)	16
Nonspecific Rash	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)	4 (4.5)	6		1 (2.1)				1
Poison Ivy		1 (1.1)	1 (1.1)			1						0
Allergy		1 (1.1)		1 (1.1)		2		1 (2.1)		1 (2.1)		2
Teething	1 (1.1)	4 (4.5)	4 (4.5)	2 (2.3)	2 (2.3)	10	1 (2.1)	2 (4.3)	2 (4.2)			5
Negative Surveillance	27	28	28	29	29	27	13	14	13	14	14	13
Persons with Complaint:	30 (33.3)	44 (49.4)	28 (31.5)	30 (34.1)	37 (42.0)	56	12 (25.0)	21 (44.7)	14 (29.2)	14 (29.8)	13 (27.7)	25
Persons with No Complaint:	60 (66.7)	45 (50.6)	61 (68.5)	58 (65.9)	51 (58.0)	33	36 (75.0)	26 (55.3)	34 (70.8)	33 (70.2)	34 (72.3)	23

8/24/77

Table 12

Clinical Complaints Reported Among Children Who Received a 1.0 ml Dose of Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #621/C-D763 (Study #467)

Clinical Complaint	Total Vaccinees (20 Children)						Initially Seronegatives (11 Children)					
	Days Post Vaccination					No. with Complaint	Days Post Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Soreness at Injection Site	1 (5.9%)					1	1 (10.0)					1
Lymphadenopathy	1 (5.9)					1	1 (10.0)					1
Arthralgia			1 (5.9)			1						0
Measles-Like Rash			1 (5.9)			1			1 (10.0)			1
Irritability	1 (5.9)	1 (5.9)				1	1 (10.0)	1 (10.0)				1
Fever - Temperature Not Reported				1 (5.9)		1				1 (10.0)		1
Anorexia			1 (5.9)	1 (5.9)		2			1 (10.0)			1
Upper Respiratory Illness	4 (23.5)	5 (29.4)	2 (11.8)	4 (23.5)	1 (5.9)	8	1 (10.0)	1 (10.0)		2 (20.0)		4
Otitis			1 (5.9)	1 (5.9)	1 (5.9)	1			1 (10.0)	1 (10.0)	1 (10.0)	1
Gastrointestinal Illness	3 (17.6)		1 (5.9)	1 (5.9)		4	2 (20.0)		1 (10.0)			2
Impetigo				1 (5.9)		1				1 (10.0)		1
Negative Surveillance	3	3	3	3	3	3	1	1	1	1	1	1
Persons with Complaint:	7 (41.2)	6 (35.3)	5 (29.4)	5 (29.4)	2 (11.8)	9	3 (30.0)	2 (20.0)	2 (20.0)	3 (30.0)	1 (10.0)	5
Persons with No Complaint:	10 (58.8)	11 (64.7)	12 (70.6)	12 (70.6)	15 (88.2)	8	7 (70.0)	8 (80.0)	8 (80.0)	7 (70.0)	9 (90.0)	5

8/24/77

Table 13

Clinical Complaints Reported Among Children Who Received a 0.5 ml Dose of Combined Live Measles-Mumps-Rubella (HPV-77) Virus Vaccine, M-M-R (Study #467)

Clinical Complaint	Total Vaccinees (138 Children)						Initially Seronegatives (70 Children)					
	Days Post Vaccination					No. with Complaint	Days Post Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Injection Site:	7 (6.9%)					7	3 (5.7)					3
Soreness	6					6	2					2
Soreness and Induration	1					1	1					1
Systemic:												
Measles-Like Rash		5 (5.0)	2 (2.0)			5		1 (1.9)				1
Headache	1 (1.0)		1 (1.0)		2 (2.0)	2					1 (1.9)	1
Irritability	3 (3.0)	4 (4.0)	2 (2.0)	3 (3.0)		9	2 (3.8)	1 (1.9)		1 (1.9)		4
Anorexia	11 (10.9)	17 (16.8)	5 (5.0)	6 (5.9)	4 (4.0)	24	6 (11.3)	9 (17.0)	1 (1.9)	3 (5.7)	3 (5.7)	14
Flush	1 (1.0)					1						0
Disturbed Sleep		1 (1.0)				1						0
Myalgia	2 (2.0)					2	1 (1.9)					1
Upper Respiratory Illness	18 (17.8)	19 (18.8)	15 (14.9)	18 (17.8)	24 (23.8)	45	10 (18.9)	9 (17.0)	6 (11.3)	7 (13.2)	8 (15.1)	20
Otitis	1 (1.0)	4 (4.0)	2 (2.0)	1 (1.0)	1 (1.0)	7	1 (1.9)	2 (3.8)				3
Ophthalmopathy	2 (2.0)	3 (3.0)		1 (1.0)	2 (2.0)	6	2 (3.8)	2 (3.8)				4
Gastrointestinal Illness	15 (14.9)	12 (11.9)	5 (5.0)	5 (5.0)	6 (5.9)	27	7 (13.2)	3 (5.7)	3 (5.7)	2 (3.8)	4 (7.5)	11
Rash-Nonspecific	1 (1.0)	3 (3.0)	5 (5.0)	3 (3.0)	4 (4.0)	12	1 (1.9)	1 (1.9)	4 (7.5)	1 (1.9)	1 (1.9)	6
Varicella				1 (1.0)	1 (1.0)	1						0
Other*	1 (1.0)	1 (1.0)				2	1 (1.9)					1
Genitourinary Infection				1 (1.0)	1 (1.0)	1						0
Allergy	2 (2.0)	2 (2.0)		1 (1.0)		3	2 (3.8)	2 (3.8)				2
Teething		2 (2.0)	4 (4.0)	5 (5.0)	2 (2.0)	8		1 (1.9)		1 (1.9)	2 (3.8)	3
Negative Surveillance	37	37	37	37	37	37	17	17	17	17	17	17
Persons with Complaint:	36 (35.6)	41 (40.6)	24 (23.8)	26 (25.7)	30 (29.7)	57	20 (37.7)	18 (34.0)	9 (17.0)	10 (18.9)	12 (22.6)	27
Persons with No Complaints	65 (64.4)	60 (59.4)	77 (76.2)	75 (74.3)	71 (70.3)	44	33 (62.3)	35 (66.0)	44 (83.0)	43 (81.1)	41 (77.4)	26

* Includes ingested lighter fluid and bloody nose.

Table 10

Clinical Complaints Reported Among Children Who Received Combined
Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60664/C-E810 (Study #511)

Clinical Complaint	Total Vaccinees (50 Children)						Initially Seronegatives (13 Children)					
	Days Post Vaccination					No. with Complaint	Days Post Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Headache	1 (2.0%)	1 (2.0)	1 (2.0)	1 (2.0)		4						0
Irritability	5 (10.0)	8 (16.0)	6 (12.0)	5 (10.0)		18	2 (15.4)	3 (23.1)	3 (23.1)	1 (7.7)		7
Malaise	7 (14.0)	9 (18.0)	4 (8.0)	4 (8.0)		17	3 (23.1)	3 (23.1)	3 (23.1)	2 (15.4)		7
Anorexia		1 (2.0)		1 (2.0)		2				1 (7.7)		1
Upper Respiratory Illness	2 (4.0)	6 (12.0)	3 (6.0)	1 (2.0)		9			2 (15.4)			2
Lower Respiratory Illness	1 (2.0)	1 (2.0)				1	1 (7.7)	1 (7.7)				1
Gastrointestinal Illness	1 (2.0)	3 (6.0)	1 (2.0)	4 (8.0)	2 (4.0)	7			1 (7.7)	2 (15.4)	1 (7.7)	3
Persons with Complaint:	7 (14.0)	9 (18.0)	7 (14.0)	8 (16.0)	2 (4.0)	21	3 (23.1)	3 (23.1)	4 (30.8)	2 (15.4)	1 (7.7)	8
Persons with No Complaint:	43 (86.0)	41 (82.0)	43 (86.0)	42 (84.0)	48 (96.0)	29	10 (76.9)	10 (76.9)	9 (69.2)	11 (84.6)	12 (92.3)	5

1/31/78

Table 11

Clinical Complaints Reported Among Children Who Received Combined
Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60665/C-E811 (Study #511)

Clinical Complaint	Total Vaccinees (50 Children)						Initially Seronegatives (6 Children)					
	Days Post Vaccination					No. with Complaint	Days Post Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Headache	2 (4.0%)	1 (2.0)	4 (8.0)	2 (4.0)		8			1 (16.7)			1
Irritability	2 (4.0)	9 (18.0)	4 (8.0)	5 (10.0)	3 (6.1)	18		1 (16.7)		1 (16.7)		2
Malaise	2 (4.0)	7 (14.0)	2 (4.0)	3 (6.0)		12		1 (16.7)		1 (16.7)		2
Anorexia		1 (2.0)				1						0
Upper Respiratory Illness	2 (4.0)	4 (8.0)				4						0
Lower Respiratory Illness		1 (2.0)	1 (2.0)			1						0
Gastrointestinal Illness	1 (2.0)	3 (6.0)	2 (4.0)	1 (2.0)		5						0
Persons with Complaint:	2 (4.0)	11 (22.0)	7 (14.0)	6 (12.0)	3 (6.1)	20	0	1 (16.7)	1 (16.7)	1 (16.7)	0	3
Persons with No Complaint:	48 (96.0)	39 (78.0)	43 (86.0)	44 (88.0)	46 (93.9)	30	6 (100)	5 (83.3)	5 (83.3)	5 (83.3)	5 (100)	3
Negative Surveillance	0	0	0	0	1	0	0	0	0	0	1	0

1/31/78

Table 12

Clinical Complaints Reported Among Children Who Received Combined
Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60666/C-E812 (Study #511)

Clinical Complaint	Total Vaccinees (50 Children)						Initially Seronegatives (2 Children)					
	Days Post Vaccination					No. with Complaint	Days Post Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Headache		2 (4.0%)	4 (8.0)			6			1 (50.0)			1
Irritability	1 (2.0)	9 (18.0)	3 (6.0)	1 (2.0)	2 (4.0)	12						0
Malaise	2 (4.0)	6 (12.0)	4 (8.0)		3 (6.0)	13			1 (50.0)			1
Anorexia	1 (2.0)	3 (6.0)	1 (2.0)			5						0
Upper Respiratory Illness	1 (2.0)	2 (4.0)				2						0
Lower Respiratory Illness		1 (2.0)				1						0
Otitis	1 (2.0)					1						0
Gastrointestinal Illness	1 (2.0)	1 (2.0)	1 (2.0)			2						0
Persons with Complaint:	2 (4.0)	11 (22.0)	6 (12.0)	1 (2.0)	3 (6.0)	17	0	0	1 (50.0)	0	0	1
Persons with No Complaint:	48 (96.0)	39 (78.0)	44 (88.0)	49 (98.0)	47 (94.0)	33	2 (100)	2 (100)	1 (50.0)	2 (100)	2 (100)	1

1/31/78

Table 10

Clinical Complaints Reported Among Children Who Received Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60664/C-E810 (Study #513)

Clinical Complaint	Total Vaccinees (53 Children)						Initially Seronegatives (30 Children)					
	Days Post Vaccination					No. with Complaint	Days Post Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Injection Site:	2 (3.9%)					2	1 (3.3)					1
Soreness	2					2	1					1
Systemic:												
Arthralgia	1 (2.0)	1 (2.0)				1						0
Measles-Like Rash		6 (11.8)	1 (2.0)	1 (2.0)		6		4 (13.3)	1 (3.3)	1 (3.3)		4
Headache		1 (2.0)				1						0
Irritability	4 (7.8)	2 (3.9)	1 (2.0)	2 (3.9)	2 (3.9)	8	4 (13.3)	2 (6.7)	1 (3.3)	2 (6.7)	1 (3.3)	7
Anorexia	4 (7.8)	3 (5.9)	1 (2.0)	2 (3.9)	5 (9.8)	10	2 (6.7)	2 (6.7)		2 (6.7)	3 (10.0)	7
Disturbed Sleep			1 (2.0)		1 (2.0)	1						0
Fatigue		1 (2.0)			1 (2.0)	1		1 (3.3)			1 (3.3)	1
Myalgia	1 (2.0)	1 (2.0)				1						0
Upper Respiratory Illness	9 (17.6)	12 (23.5)	7 (13.7)	12 (23.5)	11 (21.6)	25	4 (13.3)	7 (23.3)	6 (20.0)	7 (23.3)	8 (26.7)	14
Otitis				1 (2.0)		1				1 (3.3)		1
Ophthalmopathy	1 (2.0)	1 (2.0)		1 (2.0)	1 (2.0)	2		1 (3.3)		1 (3.3)	1 (3.3)	1
Gastrointestinal Illness	12 (23.5)	11 (21.6)	2 (3.9)	4 (7.8)	5 (9.8)	18	9 (30.0)	9 (30.0)	1 (3.3)	3 (10.0)	4 (13.3)	15
Nonspecific Rash	5 (9.8)	4 (7.8)	4 (7.8)	6 (11.8)	8 (15.7)	15	2 (6.7)	4 (13.3)	4 (13.3)	5 (16.7)	5 (16.7)	10
Sores on Face		1 (2.0)				1		1 (3.3)				1
Allergy	1 (2.0)		1 (2.0)			2	1 (3.3)		1 (3.3)			2
Teething	2 (3.9)	4 (7.8)	1 (2.0)	2 (3.9)	3 (5.9)	9	1 (3.3)	4 (13.3)	1 (3.3)	2 (6.7)	1 (3.3)	7
Herpes-Type Rash		1 (2.0)		1 (2.0)		2		1 (3.3)		1 (3.3)		2
Persons with Complaint:	24 (47.1)	27 (52.9)	12 (23.5)	18 (35.3)	19 (37.3)	39	14 (46.7)	19 (63.3)	9 (30.0)	12 (40.0)	13 (43.3)	25
Persons with No Complaint:	27 (52.9)	24 (47.1)	39 (76.5)	33 (64.7)	32 (62.7)	12	16 (53.3)	11 (36.7)	21 (70.0)	18 (60.0)	17 (56.7)	5
Negative Surveillance	2	2	2	2	2	2	0	0	0	0	0	0

1/27/78

Table 11

Clinical Complaints Reported Among Children Who Received Combined
Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60665/C-E811 (Study #513)

Clinical Complaint	Total Vaccinees (54 Children)						Initially Seronegatives (34 Children)					
	Days Post Vaccination					No. with	Days Post Vaccination					No. with
	0-4	5-12	13-18	19-28	29-42	Complaint	0-4	5-12	13-18	19-28	29-42	Complaint
Injection Site:	2 (3.8%)					2	2 (5.9)					2
Soreness	1					1	1					1
Erythema and Soreness	1					1	1					1
Systemic:												
Lymphadenopathy	2 (3.8)	1 (1.9)				3	1 (2.9)	1 (2.9)				2
Measles-Like Rash		5 (9.6)	4 (7.7)	1 (1.9)		7		3 (8.8)	2 (5.9)			4
Irritability	4 (7.7)	6 (11.5)	1 (1.9)	1 (1.9)	2 (3.8)	9	4 (11.8)	4 (11.8)		1 (2.9)	2 (5.9)	7
Malaise	1 (1.9)	1 (1.9)				1	1 (2.9)	1 (2.9)				1
Anorexia	5 (9.6)	5 (9.6)	3 (5.8)	2 (3.8)	4 (7.7)	13	3 (8.8)	4 (11.8)	2 (5.9)	1 (2.9)	3 (8.8)	9
Disturbed Sleep	1 (1.9)	1 (1.9)	1 (1.9)			2	1 (2.9)	1 (2.9)				1
Fatigue	2 (3.8)					2	2 (5.9)					2
Upper Respiratory Illness	10 (19.2)	9 (17.3)	5 (9.6)	10 (19.2)	11 (21.2)	25	4 (11.8)	6 (17.6)	4 (11.8)	6 (17.6)	7 (20.6)	15
Otitis	2 (3.8)	2 (3.8)	2 (3.8)	1 (1.9)	1 (1.9)	4	2 (5.9)	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)	2
Ophthalmopathy	1 (1.9)	3 (5.8)		1 (1.9)	1 (1.9)	5	1 (2.9)	2 (5.9)		1 (2.9)	1 (2.9)	4
Gastrointestinal Illness	9 (17.3)	10 (19.2)	5 (9.6)	4 (7.7)	6 (11.5)	18	6 (17.6)	7 (20.6)	3 (8.8)	3 (8.8)	5 (14.7)	11
Nonspecific Rash	4 (7.7)	3 (5.8)		2 (3.8)	2 (3.8)	7	3 (8.8)	3 (8.8)		2 (5.9)	2 (5.9)	6
Allergy	1 (1.9)					1	1 (2.9)					1
Teething	1 (1.9)	1 (1.9)	1 (1.9)	3 (5.8)	3 (5.8)	4	1 (2.9)	1 (2.9)		1 (2.9)	1 (2.9)	2
Persons with Complaint:	24 (46.2)	26 (50.0)	18 (34.6)	21 (40.4)	18 (34.6)	36	16 (47.1)	18 (52.9)	11 (32.4)	13 (38.2)	12 (35.3)	23
Persons with No Complaint:	28 (53.8)	26 (50.0)	34 (65.4)	31 (59.6)	34 (65.4)	16	18 (52.9)	16 (47.1)	23 (67.6)	21 (61.8)	22 (64.7)	11
Negative Surveillance:	2	2	2	2	2	2	0	0	0	0	0	0

1/27/78

Table 12

Clinical Complaints Reported Among Children Who Received Combined
Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60666/C-E812 (Study #513)

Clinical Complaint	Total Vaccinees (56 Children)						Initially Seronegatives (33 Children)					
	Days Post Vaccination					No. with Complaint	Days Post Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Injection Site:	4 (7.4%)					4	3 (9.1)					3
Soreness	4					4	3					3
Systemic:												
Lymphadenopathy				1 (1.9)		1				1 (3.0)		1
Measles-Like Rash		6 (11.1)	2 (3.7)	1 (1.9)		8		4 (12.1)	2 (6.1)	1 (3.0)		6
Headache	1 (1.9)					1						0
Irritability	4 (7.4)	4 (7.4)	3 (5.6)	3 (5.6)	2 (3.7)	8	2 (6.1)	3 (9.1)	2 (6.1)	3 (9.1)	2 (6.1)	5
Anorexia	6 (11.1)	9 (16.7)	1 (1.9)	2 (3.7)	11 (20.4)	20	4 (12.1)	5 (15.2)			9 (27.3)	13
Disturbed Sleep	1 (1.9)	2 (3.7)				2	1 (3.0)	2 (6.1)				2
Fatigue		1 (1.9)		1 (1.9)		1		1 (3.0)		1 (3.0)		1
Myalgia				1 (1.9)	2 (3.7)	2				1 (3.0)	1 (3.0)	1
Upper Respiratory Illness	13 (24.1)	19 (35.2)	13 (24.1)	14 (25.9)	15 (27.8)	30	10 (30.3)	12 (36.4)	9 (27.3)	11 (33.3)	12 (36.4)	20
Otitis	1 (1.9)	2 (3.7)		2 (3.7)	2 (3.7)	5		1 (3.0)		2 (6.1)	2 (6.1)	3
Ophthalmopathy	2 (3.7)	1 (1.9)		1 (1.9)	1 (1.9)	4	1 (3.0)			1 (3.0)	1 (3.0)	2
Gastrointestinal Illness	6 (11.1)	4 (7.4)	4 (7.4)	5 (9.3)	7 (13.0)	18	4 (12.1)		3 (9.1)	4 (12.1)	3 (9.1)	12
Nonspecific Rash	4 (7.4)	8 (14.8)	6 (11.1)	7 (13.0)	6 (11.1)	19	3 (9.1)	5 (15.2)	4 (12.1)	4 (12.1)	4 (12.1)	13
Sore from Venipuncture	1 (1.9)					1	1 (3.0)					1
Teething		3 (5.6)	2 (3.7)	3 (5.6)	3 (5.6)	5		3 (9.1)	2 (6.1)	3 (9.1)	2 (6.1)	4
Herpes-Type Rash		1 (1.9)				1		1 (3.0)				1
Persons with Complaint:	27 (50.0)	33 (61.1)	22 (40.7)	24 (44.4)	25 (46.3)	41	20 (60.6)	22 (66.7)	16 (48.5)	19 (57.6)	17 (51.5)	27
Persons with No Complaint:	27 (50.0)	21 (38.9)	32 (59.3)	30 (55.6)	29 (53.7)	13	13 (39.4)	11 (33.3)	17 (51.5)	14 (42.4)	16 (48.5)	6
Negative Surveillance	2	2	2	2	2	2	0	0	0	0	0	0

1/27/78

Table 11

Clinical Complaints Reported Among Children Who Received Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot No. 621/C-D763 (Study #442)

Clinical Complaint	Total Vaccinees (199 Children)						Initially Seronegative to: Measles, Mumps and Rubella (23 Children)					
	Days Post-Vaccination					No. with Complaint	Days Post Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Irritability	32 (16.1%)	9 (4.5)	2 (1.0)	4 (2.1)		39	5 (21.7)			1 (5.0)		5
Malaise	30 (15.1)	14 (7.0)	3 (1.5)	7 (3.6)	1 (0.5)	43	5 (21.7)	1 (4.3)		2 (10.0)		7
Headache		1 (0.5)	2 (1.0)			2						0
Upper Respiratory Illness	9 (4.5)	11 (5.5)	5 (2.5)	8 (4.1)	5 (2.6)	23	1 (4.3)	1 (4.3)	1 (4.3)	2 (10.0)	1 (5.0)	3
Otitis			2 (1.0)	3 (1.5)		3			1 (4.3)	1 (5.0)		1
Ophthalmopathy		1 (0.5)				1						0
Gastrointestinal Illness	13 (6.5)	7 (3.5)	2 (1.0)	5 (2.6)	1 (0.5)	22		1 (4.3)				1
Anorexia	5 (2.5)	3 (1.5)	2 (1.0)	5 (2.6)		13				1 (5.0)		1
Mild Dermatitis		1 (0.5)				1						0
Persons with Complaints:	49 (24.6)	22 (11.1)	11 (5.5)	19 (9.8)	6 (3.1)	73	6 (26.1)	2 (8.7)	1 (4.3)	4 (20.0)	1 (5.0)	10
Persons with No Complaints:	150 (75.4)	177 (88.9)	188 (94.5)	175 (90.2)	187 (96.9)	123	17 (73.9)	21 (91.3)	22 (95.7)	16 (80.0)	19 (95.0)	12
Negative Physician Surveillance				5	6					3	3	

10/3/77

Exhibit 17

TABLE 1. Recommended schedule for active immunization of normal infants and children (See individual ACIP recommendations for details.)

Recommended age*	Vaccine(s)†	Comments
2 mo.	DTP-1,§ OPV-1¶	Can be given earlier in areas of high endemicity
4 mo.	DTP-2, OPV-2	6-wks-2-mo. interval desired between OPV doses to avoid interference
6 mo.	DTP-3	An additional dose of OPV at this time is optional for use in areas with a high risk of polio exposure
15 mo.**	MMR††	
18 mo.**	DTP-4, OPV-3	Completion of primary series
4-6 yr.§§	DTP-5, OPV-4	Preferably at or before school entry
14-16. yr	Td¶¶	Repeat every 10 years throughout life

*These recommended ages should not be construed as absolute, i.e. 2 mos. can be 6-10 weeks, etc.

†For all products used, consult manufacturer's package enclosure for instructions for storage, handling, and administration. Immunobiologics prepared by different manufacturers may vary, and those of the same manufacturer may change from time to time. The package insert should be followed for a specific product.

§DTP—Diphtheria and tetanus toxoids and pertussis vaccine.

¶OPV—Oral, attenuated poliovirus vaccine contains poliovirus types 1, 2, and 3.

**Simultaneous administration of MMR, DTP, and OPV is appropriate for patients whose compliance with medical care recommendations cannot be assured.

††MMR—Live measles, mumps, and rubella viruses in a combined vaccine (see text for discussion of single vaccines versus combination).

§§Up to the seventh birthday.

¶¶Td—Adult tetanus toxoid and diphtheria toxoid in combination, which contains the same dose of tetanus toxoid as DTP or DT and a reduced dose of diphtheria toxoid.

Exhibit 18

Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please call 800-835-4709 or 240-402-8010, extension 1. CBER Consumer Affairs Branch or send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use M-M-R II safely and effectively. See full prescribing information for M-M-R II.

M-M-R® II (Measles, Mumps, and Rubella Virus Vaccine Live)
Suspension for intramuscular or subcutaneous injection
Initial U.S. Approval: 1978

----------RECENT MAJOR CHANGES----------
Dosage and Administration
Dose and Schedule (2.1) ---------- ----------03/2023
Administration (2.2) ---------- ----------03/2023

----------INDICATIONS AND USAGE----------
M-M-R II is a vaccine indicated for active immunization for the prevention of measles, mumps, and rubella in individuals 12 months of age and older. (1)

----------DOSAGE AND ADMINISTRATION----------
For intramuscular or subcutaneous injection only. (2.1, 2.2).
A single dose is approximately 0.5 mL.
- The first dose is administered at 12 to 15 months of age. (2.1)
- The second dose is administered at 4 to 6 years of age. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Suspension for injection (approximately 0.5-mL dose) supplied as a lyophilized vaccine to be reconstituted using accompanying sterile diluent. (3)

----------CONTRAINDICATIONS----------
- Hypersensitivity to any component of the vaccine. (4.1)
- Immunosuppression. (4.2)
- Moderate or severe febrile illness. (4.3)
- Active untreated tuberculosis. (4.4)
- Pregnancy. (4.5, 8.1)

---------- WARNINGS AND PRECAUTIONS----------
- Use caution when administering M-M-R II to individuals with a history of febrile seizures. (5.1)
- Use caution when administering M-M-R II to individuals with anaphylaxis or immediate hypersensitivity following egg ingestion. (5.2)
- Use caution when administering M-M-R II to individuals with a history of thrombocytopenia. (5.3)
- Evaluate individuals for immune competence prior to administration of M-M-R II if there is a family history of congenital or hereditary immunodeficiency. (5.4)
- Immune Globulins (IG) and other blood products should not be given concurrently with M-M-R II. (5.5, 7.2)

---------- ADVERSE REACTIONS ----------
See full prescribing information for adverse reactions occurring during clinical trials or the post-marketing period. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov .

----------DRUG INTERACTIONS----------
- Administration of immune globulins and other blood products concurrently with M-M-R II vaccine may interfere with the expected immune response. (7.2)
- M-M-R II vaccination may result in a temporary depression of purified protein derivative (PPD) tuberculin skin sensitivity. (7.3)

---------- USE IN SPECIFIC POPULATIONS ----------
- Pregnancy: Do not administer M-M-R II to females who are pregnant. Pregnancy should be avoided for 1 month following vaccination with M-M-R II. (4.5, 8.1, 17)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

M-M-R II is a vaccine indicated for active immunization for the prevention of measles, mumps, and rubella in individuals 12 months of age and older.

2 DOSAGE AND ADMINISTRATION

Intramuscular or Subcutaneous administration only.

2.1 Dose and Schedule

A single dose of M-M-R II is approximately 0.5 mL.

The first dose is administered at 12 to 15 months of age. A second dose is administered at 4 to 6 years of age.

The second dose may be administered prior to 4 years of age, provided that there is a minimum interval of one month between the doses of measles, mumps and rubella virus vaccine, live {1-2}.

Children who received an initial dose of measles, mumps and rubella vaccine prior to their first birthday should receive additional doses of vaccine at 12-15 months of age and at 4-6 years of age to complete the vaccination series *[see Clinical Studies (14.2)]*.

For post-exposure prophylaxis for measles, administer a dose of M-M-R II vaccine within 72 hours after exposure.

2.2 Administration

Use a sterile syringe free of preservatives, antiseptics, and detergents for each injection and/or reconstitution of the vaccine because these substances may inactivate the live virus vaccine. To reconstitute, use only the diluent supplied with the vaccine since it is free of preservatives or other antiviral substances which might inactivate the vaccine.

Withdraw the entire volume of the supplied diluent from its vial and inject into lyophilized vaccine vial. Agitate to dissolve completely. Discard if the lyophilized vaccine cannot be dissolved.

Withdraw the entire volume of the reconstituted vaccine and inject the vaccine intramuscularly or subcutaneously.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Visually inspect the vaccine before and after reconstitution prior to administration. Before reconstitution, the lyophilized vaccine is a light yellow compact crystalline plug, when reconstituted, is a clear yellow liquid. Discard if particulate matter or discoloration are observed in the reconstituted vaccine.

To minimize loss of potency, administer M-M-R II as soon as possible after reconstitution. If not used immediately, the reconstituted vaccine may be stored between 36°F to 46°F (2°C to 8°C), protected from light, for up to 8 hours. Discard reconstituted vaccine if it is not used within 8 hours.

3 DOSAGE FORMS AND STRENGTHS

M-M-R II vaccine is a suspension for injection supplied as a single dose vial of lyophilized vaccine to be reconstituted using the accompanying sterile diluent *[see Dosage and Administration (2.2) and How Supplied/Storage and Handling (16)]*. A single dose after reconstitution is approximately 0.5 mL.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Do not administer M-M-R II vaccine to individuals with a history of hypersensitivity to any component of the vaccine (including gelatin) {3} or who have experienced a hypersensitivity reaction following administration of a previous dose of M-M-R II vaccine or any other measles, mumps and rubella-containing vaccine. Do not administer M-M-R II vaccine to individuals with a history of anaphylaxis to neomycin *[see Description (11)]*.

4.2 Immunosuppression

Do not administer M-M-R II vaccine to individuals who are immunodeficient or immunosuppressed due to disease or medical therapy. Measles inclusion body encephalitis {4} (MIBE), pneumonitis {5} and death as a direct consequence of disseminated measles vaccine virus infection have been reported in

immunocompromised individuals inadvertently vaccinated with measles-containing vaccine. In this population, disseminated mumps and rubella vaccine virus infection have also been reported.

4.3 Moderate or Severe Febrile Illness

Do not administer M-M-R II vaccine to individuals with an active febrile illness with fever >101.3°F (>38.5°C).

4.4 Active Untreated Tuberculosis

Do not administer M-M-R II vaccine to individuals with active untreated tuberculosis (TB).

4.5 Pregnancy

Do not administer M-M-R II to individuals who are pregnant or who are planning on becoming pregnant within the next month *[see Use in Specific Populations (8.1) and Patient Counseling Information (17)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Febrile Seizure

There is a risk of fever and associated febrile seizure in the first 2 weeks following immunization with M-M-R II vaccine. For children who have experienced a previous febrile seizure (from any cause) and those with a family history of febrile seizures there is a small increase in risk of febrile seizure following receipt of M-M-R II vaccine *[see Adverse Reactions (6)]*.

5.2 Hypersensitivity to Eggs

Individuals with a history of anaphylactic, anaphylactoid, or other immediate reactions (e.g., hives, swelling of the mouth and throat, difficulty breathing, hypotension, or shock) subsequent to egg ingestion may be at an enhanced risk of immediate-type hypersensitivity reactions after receiving M-M-R II vaccine. The potential risks and known benefits should be evaluated before considering vaccination in these individuals.

5.3 Thrombocytopenia

Transient thrombocytopenia has been reported within 4-6 weeks following vaccination with measles, mumps and rubella vaccine. Carefully evaluate the potential risk and benefit of vaccination in children with thrombocytopenia or in those who experienced thrombocytopenia after vaccination with a previous dose of measles, mumps, and rubella vaccine {6-8} *[see Adverse Reactions (6)]*.

5.4 Family History of Immunodeficiency

Vaccination should be deferred in individuals with a family history of congenital or hereditary immunodeficiency until the individual's immune status has been evaluated and the individual has been found to be immunocompetent.

5.5 Immune Globulins and Transfusions

Immune Globulins (IG) and other blood products should not be given concurrently with M-M-R II *[see Drug Interactions (7.2)]*. These products may contain antibodies that interfere with vaccine virus replication and decrease the expected immune response.

The Advisory Committee on Immunization Practices (ACIP) has specific recommendations for intervals between administration of antibody containing products and live virus vaccines.

6 ADVERSE REACTIONS

The following adverse reactions include those identified during clinical trials or reported during post-approval use of M-M-R II vaccine or its individual components.

Body as a Whole

Panniculitis; atypical measles; fever; headache; dizziness; malaise; irritability.

Cardiovascular System

Vasculitis.

Digestive System

Pancreatitis; diarrhea; vomiting; parotitis; nausea.

Hematologic and Lymphatic Systems

Thrombocytopenia; purpura; regional lymphadenopathy; leukocytosis.

Immune System

Anaphylaxis, anaphylactoid reactions, angioedema (including peripheral or facial edema) and bronchial spasm.

Musculoskeletal System

Arthritis; arthralgia; myalgia.

Nervous System

Encephalitis; encephalopathy; measles inclusion body encephalitis (MIBE) subacute sclerosing panencephalitis (SSPE); Guillain-Barré Syndrome (GBS); acute disseminated encephalomyelitis (ADEM); transverse myelitis; febrile convulsions; afebrile convulsions or seizures; ataxia; polyneuritis; polyneuropathy; ocular palsies; paresthesia; syncope.

Respiratory System

Pneumonia; pneumonitis; sore throat; cough; rhinitis.

Skin

Stevens-Johnson syndrome; acute hemorrhagic edema of infancy; Henoch-Schönlein purpura; erythema multiforme; urticaria; rash; measles-like rash; pruritus; injection site reactions (pain, erythema, swelling and vesiculation).

Special Senses — Ear

Nerve deafness; otitis media.

Special Senses — Eye

Retinitis; optic neuritis; papillitis; conjunctivitis.

Urogenital System

Epididymitis; orchitis.

In a randomized open-label clinical trial (NCT00432523), conducted in France and Germany, 752 children 12 months through 18 months of age received M-M-R II concomitantly administered with VARIVAX at a separate site, by either the intramuscular (n=374) or subcutaneous (n=378) route. In the overall population, 55.3% were male and the median age was 13.2 months. Local and systemic solicited adverse reactions were recorded by parents or guardians using standardized diary cards. Local solicited reactions were recorded for 4 days after vaccination, and systemic solicited adverse reactions were recorded for 42 days after vaccination. In the event that a participant experienced a rash or a mumps-like illness, parents and/or guardians were instructed to contact the investigator for an examination as soon as possible and no later than 72 hours following onset of symptoms. The nature of any rash was characterized by principal investigator either as a measles-like, rubella-like, varicella-like or “other.” Study investigators reviewed the diary card with the participant or participant’s legal guardian 42 days vaccination to ensure consistency with protocol definitions. Table 1 below presents the frequency of solicited adverse reactions based on the final assessment by the study investigators.

Table 1: Proportion of Participants Reporting Solicited Adverse Reactions Following Vaccination with M-M-R II, Concomitantly Administered with VARIVAX, by the Intramuscular or Subcutaneous Route

	INTRAMUSCULAR N=374 %	SUBCUTANEOUS N=376 %
Solicited injection-site reactions at MMR injection-site (Days 0 to 4)*		
Erythema†	10.4	16.2
Mild	8.8	13.0
Moderate	0.8	3.2
Severe	0	0
Missing	0.8	0
Pain‡	7.0	7.2
Mild	5.1	5.9
Moderate	1.9	1.3
Severe	0	0

Swelling[†]	1.9	5.3
Mild	1.1	2.9
Moderate	0.5	1.1
Severe	0	0
Missing	0.3	1.3
Solicited systemic reactions (Days 0 to 42)		
Measles-like rash[§]	2.9	2.7
Rubella-like rash[§]	2.7	2.7
Varicella-like rash[§]	0.5	3.2
Mumps-like illness	0	0.3
Fever (temperature ≥38.0°C)[¶, #]	66.5	66.8
38.0-38.5°C	20.4	22.2
>38.5-39.0°C	17.4	16.6
>39.0-39.5°C	14.2	13.4
>39.5-40.0°C	11.8	11.0
>40.0°C	2.7	3.7

N=total number of participants in the group

* During the post vaccination monitoring period (0-42 days), 3 participants experienced a varicella-like injection-site rash at the M-M-R II injection site. All were reported in the subcutaneous group.
† Intensity of injection site reaction: mild or ≤2.5 cm; moderate or >2.5 to ≤5.0 cm; severe or >5.0 cm
‡ Intensity of pain: mild: awareness of symptom but easily tolerated; moderate: definitely acting like something is wrong; severe: extremely distressed or unable to do usual activities.
§ Testing to distinguish between rash caused by wild-type or vaccine virus was not performed. Reports of measles-, rubella- and varicella-like rash included 3 reports of measles, 1 report of rubella, and 1 report of varicella, all with onset within 15 days post-vaccination.
¶ The percentage of fever is defined within the population who had valid temperature measurements. One participant in IM group and two participants in SC group did not have temperature measurements and were excluded from the denominator; resulting in N=373 and N=374, respectively.
# In the IM Group 92.3% of fevers were documented using the rectal route of measurement and 7.7% of fevers were documented only by the axillary route of measurement. In the SC Group 89.6% of fevers were documented using the rectal route of measurement and 10.4% of fevers were documented only by the axillary route of measurement.

Unsolicited adverse events that occurred within 42 days following vaccination were recorded using diary cards supplemented by medical review. Data on unsolicited adverse events were transcribed into the study database during an on-site visit at day 42. The rates and types of reported adverse events (AEs) across groups were similar and included common clinical events that are often reported in the evaluated populations. Serious adverse events occurred at rates of 0.3% and 1% in the intramuscular and subcutaneous groups, respectively. One moderate intensity case of otitis media occurred in a participant in the subcutaneous group was considered related to the study vaccination.

7 DRUG INTERACTIONS

7.1 Corticosteroids and Immunosuppressive Drugs

M-M-R II vaccine should not be administered to individuals receiving immunosuppressive therapy, including high dose corticosteroids. Vaccination with M-M-R II vaccine can result in disseminated disease due to measles vaccine in individuals on immunosuppressive drugs *[see Contraindications (4.2)].*

7.2 Immune Globulins and Transfusions

Administration of immune globulins and other blood products concurrently with M-M-R II vaccine may interfere with the expected immune response {9-11} *[see Warnings and Precautions (5.5)].* The ACIP has specific recommendations for intervals between administration of antibody containing products and live virus vaccines.

7.3 Tuberculin Skin Testing

It has been reported that live attenuated measles, mumps and rubella virus vaccines given individually may result in a temporary depression of tuberculin skin sensitivity. Therefore, if a tuberculin skin test with tuberculin purified protein derivative (PPD) is to be done, it should be administered before, simultaneously with, or at least 4 to 6 weeks after vaccination with M-M-R II vaccine.

7.4 Use with Other Live Viral Vaccines

M-M-R II vaccine can be administered concurrently with other live viral vaccines. If not given concurrently, M-M-R II vaccine should be given one month before or one month after administration of other live viral vaccines to avoid potential for immune interference.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

M-M-R II vaccine is contraindicated for use in pregnant women because infection during pregnancy with the wild-type viruses has been associated with maternal and fetal adverse outcomes.

Increased rates of spontaneous abortion, stillbirth, premature delivery and congenital defects have been observed following infection with wild-type measles during pregnancy. {12,13} Wild-type mumps infection during the first trimester of pregnancy may increase the rate of spontaneous abortion.

Infection with wild-type rubella during pregnancy can lead to miscarriage or stillbirth. If rubella infection occurs during the first trimester of pregnancy, it can result in severe congenital defects, Congenital Rubella Syndrome (CRS). Congenital Rubella Syndrome in the infant includes but is not limited to eye manifestations (cataracts, glaucoma, retinitis), congenital heart defects, hearing loss, microcephaly, and intellectual disabilities. M-M-R II vaccine contains live attenuated measles, mumps and rubella viruses. It is not known whether M-M-R II vaccine can cause fetal harm when administered to pregnant woman. There are no adequate and well-controlled studies of M-M-R II vaccine administration to pregnant women.

All pregnancies have a risk of birth defect, loss or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Available data suggest the rates of major birth defects and miscarriage in women who received M-M-R II vaccine within 30 days prior to pregnancy or during pregnancy are consistent with estimated background rates *(see Data)*.

Data

Human Data

A cumulative assessment of post-marketing reports for M-M-R II vaccine from licensure 01 April 1978 through 31 December 2018, identified 796 reports of inadvertent administration of M-M-R II vaccine occurring 30 days before or at any time during pregnancy with known pregnancy outcomes. Of the prospectively followed pregnancies for whom the timing of M-M-R II vaccination was known, 425 women received M-M-R II vaccine during the 30 days prior to conception through the second trimester. The outcomes for these 425 prospectively followed pregnancies included 16 infants with major birth defects, 4 cases of fetal death and 50 cases of miscarriage. No abnormalities compatible with congenital rubella syndrome have been identified in patients who received M-M-R II vaccine. Rubella vaccine virus can cross the placenta, leading to asymptomatic infection of the fetus. Mumps vaccine virus has also been shown to infect the placenta {14}, but there is no evidence that it causes congenital malformations or disease in the fetus or infant.

The CDC established the Vaccine in Pregnancy registry (1971-1989) of women who had received rubella vaccines within 3 months before or after conception. Data on 1221 inadvertently vaccinated pregnant women demonstrated no evidence of an increase in fetal abnormalities or cases of Congenital Rubella Syndrome (CRS) in the enrolled women {15}.

8.2 Lactation

Risk Summary

It is not known whether measles or mumps vaccine virus is secreted in human milk. Studies have shown that lactating postpartum women vaccinated with live attenuated rubella vaccine may secrete the virus in breast milk and transmit it to breast-fed infants. {16,17} In the breast-fed infants with serological evidence of rubella virus vaccine strain antibodies, none exhibited severe disease; however, one exhibited mild clinical illness typical of acquired rubella. {18,19}

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for M-M-R II, and any potential adverse effects on the breastfed child from M-M-R II or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

M-M-R II vaccine is not approved for individuals less than 12 months of age. Safety and effectiveness of measles vaccine in infants below the age of 6 months have not been established *[see Clinical Studies (14)]*. Safety and effectiveness of mumps and rubella vaccine in infants less than 12 months of age have not been established.

8.5 Geriatric Use

Clinical studies of M-M-R II did not include sufficient numbers of seronegative subjects aged 65 and over to determine whether they respond differently from younger subjects.

11 DESCRIPTION

M-M-R II vaccine is a sterile lyophilized preparation of (1) Measles Virus Vaccine Live, an attenuated line of measles virus, derived from Enders' attenuated Edmonston strain and propagated in chick embryo cell culture; (2) Mumps Virus Vaccine Live, the Jeryl Lynn™ (B level) strain of mumps virus propagated in chick embryo cell culture; and (3) Rubella Virus Vaccine Live, the Wistar RA 27/3 strain of live attenuated rubella virus propagated in WI-38 human diploid lung fibroblasts. {20,21} The cells, virus pools, recombinant human serum albumin and fetal bovine serum used in manufacturing are tested and determined to be free of adventitious agents.

After reconstitution, each approximately 0.5 mL dose contains not less than 3.0 $\log_{10}$ $TCID_{50}$ (tissue culture infectious doses) of measles virus; 4.1 $\log_{10}$ $TCID_{50}$ of mumps virus; and 3.0 $\log_{10}$ $TCID_{50}$ of rubella virus.

Each dose is calculated to contain sorbitol (14.5 mg), sucrose (1.9 mg), hydrolyzed gelatin (14.5 mg), recombinant human albumin (≤0.3 mg), fetal bovine serum (<1 ppm), approximately 25 mcg of neomycin and other buffer and media ingredients. The product contains no preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

M-M-R II vaccination induces antibodies to measles, mumps, and rubella associated with protection which can be measured by neutralization assays, hemagglutination-inhibition (HI) assays, or enzyme linked immunosorbent assay (ELISA) tests. Results from efficacy studies or effectiveness studies that were previously conducted for the component vaccines of M-M-R II were used to define levels of serum antibodies that correlated with protection against measles, mumps, and rubella *[see Clinical Studies (14)].*

12.4 Persistence of Antibody Responses After Vaccination

Neutralizing and ELISA antibodies to measles, mumps, and rubella viruses are still detectable in 95-100%, 74-91%, and 90-100% of individuals respectively, 11 to 13 years after primary vaccination. {22-28}

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

M-M-R II vaccine has not been evaluated for carcinogenic or mutagenic potential or impairment of fertility.

14 CLINICAL STUDIES

14.1 Clinical Efficacy

Efficacy of measles, mumps, and rubella vaccines was established in a series of double-blind controlled trials. {29-34} These studies also established that seroconversion in response to vaccination against measles, mumps and rubella paralleled protection. {35-38}

14.2 Immunogenicity

Clinical studies enrolling 284 triple seronegative children, 11 months to 7 years of age, demonstrated that subcutaneously administered M-M-R II vaccine is immunogenic. In these studies, a single subcutaneous injection of the vaccine induced measles HI antibodies in 95%, mumps neutralizing antibodies in 96%, and rubella HI antibodies in 99% of susceptible individuals.

A study of 6-month-old and 15-month-old infants born to mothers vaccinated with a measles vaccine in childhood, demonstrated that, following infant and toddler vaccination subcutaneously with Measles Virus Vaccine, Live (previously US-licensed, manufactured by Merck), 74% of the 6-month-old infants developed detectable neutralizing antibody titers while 100% of the 15-month-old infants vaccinated with Measles Virus Vaccine, Live or M-M-R II vaccine developed neutralizing antibodies {39}. When the 6-month-old infants of immunized mothers were revaccinated at 15 months with M-M-R II vaccine, they developed antibody titers similar to those of toddlers who were vaccinated previously at 15-months of age.

In an open label clinical trial (NCT00432523) 752 children 12 through 18 months of age received M-M-R II either intramuscularly (n=374) or subcutaneously (n=378), concomitantly with VARIVAX. Antibody responses to measles, mumps, and rubella viruses were measured by ELISAs using sera obtained 6 weeks postvaccination. For anti-measles virus, anti-mumps virus and anti-rubella virus, seroresponse rates were defined as the percentage of children seronegative at baseline who achieved antibody titers above the respective seroresponse threshold for each assay 6 weeks post vaccination. Seroresponse thresholds were defined as 255 mIU/mL, 10 EU/mL, and 10 IU/mL for anti-measles virus, anti-mumps virus, and anti-rubella virus antibodies, respectively. For each vaccine antigen at least 89% of enrolled children were seronegative at baseline. In a post hoc analysis, seroresponse rates to mumps and rubella viruses were noninferior for the intramuscular group compared to the subcutaneous group (the lower bound of the 95% confidence interval for the difference in seroresponse rates [intramuscular group minus subcutaneous group] ≥-5%). While the seroresponse rate to measles virus narrowly missed meeting the post hoc criterion of -5% for noninferiority (lower bound of the 95% CI for the difference in seroresponse rate -5.28%), it met the pre-specified criterion using a -10% noninferiority margin. For measles, mumps and rubella antigens the lower bound of the 95% CI of the seroresponse rates was >90% after intramuscular administration. The point estimates of the proportions of children achieving antibody titers above the seroresponse thresholds for measles, mumps, and rubella viruses were as follows: 94.3%, 97.7%, and 98.1%, respectively, in the intramuscular group and 96.1%, 98.1%, and 98.1%, respectively, in the subcutaneous group.

15 REFERENCES

1. General Recommendations on Immunization, Recommendations of the Advisory Committee on Immunization Practices, MMWR 43(RR-1): 1-38, January 28, 1994.
2. Measles, Mumps, and Rubella — Vaccine Use and Strategies for Elimination of Measles, Rubella, and Congenital Rubella Syndrome and Control of Mumps: Recommendations of the Advisory Committee on Immunization Practices (ACIP), MMWR 47(RR-8): May 22, 1998.
3. Kelso, J.M.; Jones, R.T.; Yunginger, J.W.: Anaphylaxis to measles, mumps, and rubella vaccine mediated by IgE to gelatin, J. Allergy Clin. Immunol. 91: 867-872, 1993.
4. Bitnum, A.; et al: Measles Inclusion Body Encephalitis Caused by the Vaccine Strain of Measles Virus. Clin. Infect. Dis. 29: 855-861, 1999.
5. Angel, J.B.; et al: Vaccine Associated Measles Pneumonitis in an Adult with AIDS. Annals of Internal Medicine, 129: 104-106, 1998.
6. Cecinati V, et al. Vaccine administration and the development of immune thrombocytopenic purpura in children. Human Vaccines & Immunotherapeutics 9:5, 2013.
7. Mantadakis E, Farmaki E, Buchanan GR. Thrombocytopenic Purpura after Measles-Mumps-Rubella Vaccination: A Systematic Review of the Literature and Guidance for Management. J Ped 156(4): 2010.

8. Andrews N, Stowe J, Miller E, Svanstrom H, Johansen K, Bonhoeffer J, et al. A collaborative approach to investigating the risk of thrombocytopenic purpura after measles-mumps-rubella vaccination in England and Denmark. Vaccine. 2012;30:3042-6.

9. Rubella Prevention: Recommendation of the Immunization Practices Advisory Committee (ACIP), MMWR 39(RR-15): 1-18, November 23, 1990.

10. Peter, G.; et al (eds): Report of the Committee on Infectious Diseases, Twenty-fourth Edition, American Academy of Pediatrics, 344-357, 1997.

11. Measles Prevention: Recommendations of the Immunization Practices Advisory Committee (ACIP), MMWR 38(S-9): 5-22, December 29, 1989.

12. Eberhart-Phillips, J.E.; et al: Measles in pregnancy: a descriptive study of 58 cases. Obstetrics and Gynecology, 82(5): 797-801, November 1993.

13. Jespersen, C.S.; et al: Measles as a cause of fetal defects: A retrospective study of ten measles epidemics in Greenland. Acta Paediatr Scand. 66: 367-372, May 1977.

14. Yamauchi T, Wilson C, Geme JW Jr. Transmission of live, attenuated mumps virus to the human placenta. N Engl J Med. 1974;290(13):710-712.

15. Rubella Vaccination during Pregnancy —United States, 1971-1988. JAMA. 1989;261(23):3374–3383.

16. Losonsky, G.A.; Fishaut, J.M.; Strussenber, J.; Ogra, P.L.: Effect of immunization against rubella on lactation products. II. Maternal-neonatal interactions, J. Infect. Dis. 145: 661-666, 1982.

17. Losonsky, G.A.; Fishaut, J.M.; Strussenber, J.; Ogra, P.L.: Effect of immunization against rubella on lactation products. I. Development and characterization of specific immunologic reactivity in breast milk, J. Infect. Dis. 145: 654-660, 1982.

18. Landes, R.D.; Bass, J.W.; Millunchick, E.W.; Oetgen, W.J.: Neonatal rubella following postpartum maternal immunization, J. Pediatr. *97*: 465-467, 1980.

19. Lerman, S.J.: Neonatal rubella following postpartum maternal immunization, J. Pediatr. *98*: 668, 1981. (Letter)

20. Plotkin, S.A.; Cornfeld, D.; Ingalls, T.H.: Studies of immunization with living rubella virus: Trials in children with a strain cultured from an aborted fetus, Am. J. Dis. Child. 110: 381-389, 1965.

21. Plotkin, S.A.; Farquhar, J.; Katz, M.; Ingalls, T.H.: A new attenuated rubella virus grown in human fibroblasts: Evidence for reduced nasopharyngeal excretion, Am. J. Epidemiol. 86: 468-477, 1967.

22. Weibel, R.E.; Carlson, A.J.; Villarejos, V.M.; Buynak, E.B.; McLean, A.A.; Hilleman, M.R.: Clinical and Laboratory Studies of Combined Live Measles, Mumps, and Rubella Vaccines Using the RA 27/3 Rubella Virus, Proc. Soc. Exp. Biol. Med. 165: 323-326, 1980.

23. Watson, J.C.; Pearson, J.S.; Erdman, D.D.; et al: An Evaluation of Measles Revaccination Among School-Entry Age Children, 31st Interscience Conference on Antimicrobial Agents and Chemotherapy, Abstract #268, 143, 1991.

24. Unpublished data from the files of Merck Research Laboratories.

25. Davidkin, I.; Jokinen, S.; Broman, M. et al.: Persistence of Measles, Mumps, and Rubella Antibodies in an MMR-Vaccinated Cohort: A 20-Year Follow-up, JID 197:950–6, April 2008.

26. LeBaron, W.; Beeler J.; Sullivan, B.; et al.: Persistence of Measles Antibodies After 2 Doses of Measles Vaccine in a Postelimination Environment, Arch Pediatr Adolesc Med. 161:294-301, March 2007.

27. LeBaron, C.; Forghani, B.; Beck, C. et al.: Persistence of Mumps Antibodies after 2 Doses of Measles-Mumps-Rubella Vaccine, JID 199:552– 60 , February 2009.

28. LeBaron, W.; Forghani, B.; Matter, L. et al.: Persistence of Rubella Antibodies after 2 Doses of Measles-Mumps-Rubella Vaccine, JID 200:888–99, September 2009.

29. Hilleman, M.R.; Buynak, E.B.; Weibel, R.E.; et al: Development and Evaluation of the Moraten Measles Virus Vaccine, JAMA 206(3): 587-590, 1968.

30. Weibel, R.E.; Stokes, J.; Buynak, E.B.; et al: Live, Attenuated Mumps Virus Vaccine 3. Clinical and Serologic Aspects in a Field Evaluation, N. Engl. J. Med. 276: 245-251, 1967.

31. Hilleman, M.R.; Weibel, R.E.; Buynak, E.B.; et al: Live, Attenuated Mumps Virus Vaccine 4. Protective Efficacy as Measured in a Field Evaluation, N. Engl. J. Med. 276: 252-258, 1967.

32. Cutts, F.T.; Henderson, R.H.; Clements, C.J.; et al: Principles of measles control, Bull WHO 69(1): 1-7, 1991.

33. Weibel, R.E.; Buynak, E.B.; Stokes, J.; et al: Evaluation Of Live Attenuated Mumps Virus Vaccine, Strain Jeryl Lynn, First International Conference on Vaccines Against Viral and Rickettsial Diseases of Man, World Health Organization, No. 147, May 1967.

34. Leibhaber, H.; Ingalls, T.H.; LeBouvier, G.L.; et al: Vaccination With RA 27/3 Rubella Vaccine, Am. J. Dis. Child. 123: 133-136, February 1972.

35. Rosen, L.: Hemagglutination and Hemagglutination-Inhibition with Measles Virus, Virology 13: 139-141, January 1961.

36. Brown, G.C.; et al: Fluorescent-Antibody Marker for Vaccine-Induced Rubella Antibodies, Infection and Immunity 2(4): 360-363, 1970.

37. Buynak, E.B.; et al: Live Attenuated Mumps Virus Vaccine 1. Vaccine Development, Proceedings of the Society for Experimental Biology and Medicine, 123: 768-775, 1966.

38. Hilleman M.R., Studies of Live Attenuated Measles Virus Vaccine in Man: II. Appraisal of Efficacy. Amer. J. of Public Health, 52(2):44-56, 1962.

39. Johnson, C.E.; et al: Measles Vaccine Immunogenicity in 6- Versus 15-Month-Old Infants Born to Mothers in the Measles Vaccine Era, Pediatrics, 93(6): 939-943, 1994.

16 HOW SUPPLIED/STORAGE AND HANDLING

No. 4681 — M-M-R II vaccine is supplied as follows:
(1) a box of 10 single-dose vials of lyophilized vaccine (package A), NDC 0006-4681-00
(2) a box of 10 vials of diluent (package B)
Exposure to light may inactivate the vaccine viruses.

To maintain potency, M-M-R II must be stored between -58°F and +46°F (-50°C to +8°C). Use of dry ice may subject M-M-R II to temperatures colder than -58°F (-50°C).

Before reconstitution, refrigerate the lyophilized vaccine at 36°F to 46°F (2°C to 8°C).

Store accompanying diluent in the refrigerator (36°F to 46°F, 2°C to 8°C) or at room temperature (68°F to 77°F, 20°C to 25°C). **Do not freeze the diluent**.

Administer M-M-R II vaccine as soon as possible after reconstitution. If not administered immediately, reconstituted vaccine may be stored between 36°F to 46°F (2°C to 8°C), protected from light, for up to 8 hours. Discard reconstituted vaccine if it is not used within 8 hours.

For information regarding the product or questions regarding storage conditions, call 1-800-MERCK-90 (1-800-637-2590).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Package Insert).

Discuss the following with the patient:

- Provide the required vaccine information to the patient, parent, or guardian.
- Inform the patient, parent, or guardian of the benefits and risks associated with vaccination.
- Question the patient, parent, or guardian about reactions to a previous dose of M-M-R II vaccine or other measles-, mumps-, or rubella-containing vaccines.
- Question females of reproductive potential regarding the possibility of pregnancy. Inform female patients to avoid pregnancy for 1 month following vaccination *[see Contraindications (4.5) and Use in Specific Populations (8.1)]*.
- Inform the patient, parent, or guardian that vaccination with M-M-R II may not offer 100% protection from measles, mumps, and rubella infection.
- Instruct patients, parents, or guardians to report any adverse reactions to their health-care provider. The U.S. Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986. For information or a copy of the vaccine reporting form, call the VAERS toll-free number at 1-800-822-7967, or report online at **https://www.vaers.hhs.gov** .

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For patent information: **www.merck.com/product/patent/home.html**

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Exhibit 19

Immunogenicity and safety of a measles-mumps-rubella vaccine administered as a first dose to children 12–15 months of age: a phase III, randomized, non-inferiority, lot-to-lot consistency study

Authors: Nicola P Klein et al.

Running title: Immunogenicity and safety of MMR vaccine

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Supplementary Material

Supplementary Methods

This study is registered in ClinicalTrials.gov (NCT01702428) and a summary of the study protocol is available at https://www.gsk-clinicalstudyregister.com/study/115648?search=study&study_ids=115648#ps.

Other eligibility criteria

We only enrolled children who were in stable health, as established by medical history and clinical exam, and for whom the investigator believed that their parent(s)/legally acceptable representative(s) could comply with protocol requirements. In the United States (US), we only included children who had previously received a 3-dose primary series of a 13-valent pneumococcal conjugate vaccine (PCV13) with the last dose ≥60 days prior to study entry, and we excluded any child who had previously received a dose of 7-valent pneumococcal conjugate vaccine (*Prevnar/Prevenar*, Pfizer) or a fourth dose of any other pneumococcal conjugate vaccine.

Supplementary Table 6. Incidence of unsolicited adverse events (Day 0–42), serious adverse events, AEs prompting emergency room visits and NOCDs (Day 0–180) (total vaccinated cohort).

n (%)	MMR-RIT (N=3714)	MMR II (N=1289)
Unsolicited AEs (≥1 symptom)	1857 (50.0)	618 (47.9)
Grade 3	225 (6.1)	85 (6.6)
SAEs (any, ≥1 SAE)	77 (2.1)	25 (1.9)
AEs prompting ER visit	375 (10.1)	134 (10.4)
NOCDs (any, ≥1 NOCD)	128 (3.4)	48 (3.7)

AE, adverse event; ER, emergency room; N, number of children with the documented dose; n (%), number (percentage) of children reporting the AE at least once; NOCDs, new onset chronic diseases (see definition in Patients and methods); SAE, serious AE.
Grade 3 unsolicited AEs were those preventing normal, everyday activities.

Exhibit 20

BLA Clinical Review Memorandum

Application Type	Biologics License Application
STN	125748/0
CBER Received Date	June 4, 2021
PDUFA Goal Date	June 4, 2022
Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	No
Reviewer Name(s)	Robin Wisch, MD, Nadine Peart Akindele, MD
Review Completion Date / Stamped Date	June 3, 2022
Supervisory Concurrence	Anuja Rastogi, MD, MHS 1st Level Supervisory Review Clinical Review Staff, Immediate Office of Director DVRPA, OVRR, CBER Douglas Pratt, MD, MPH 2nd Level Supervisory Review Associate Director, Medical Affairs DVRPA, OVRR, CBER
Applicant	GlaxoSmithKline Biologicals, SA
Established Name	Combined Measles, Mumps, and Rubella (MMR) Live (Attenuated) Viral Vaccine
(Proposed) Trade Name	PRIORIX
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants	Each dose (approximately 0.5 mL) contains not less than 3.4 log10 Cell Culture Infective Dose 50% (CCID50) of measles virus, 4.2 log10 CCID50 of mumps virus, and 3.3 log10 CCID50 of rubella virus. Each dose also contains 32 mg of anhydrous lactose, 9 mg of sorbitol, 9 mg of amino acids, and 8 mg of mannitol. Each dose may also contain residual amounts of neomycin sulphate (≤25 µg) from the manufacturing process.
Dosage Form(s) and Route(s) of Administration	Dosage form: Suspension Route of Administration: Subcutaneous
Dosing Regimen	The first dose is administered at 12 through 15 months of age. The second dose is administered at 4 through 6 years of age. If PRIORIX is not administered according to this schedule and 2 doses of measles-, mumps- and rubella-virus vaccine are recommended for an individual, there should be a minimum of 4 weeks between the first and second dose. PRIORIX may be administered as a second dose to individuals who have received a first dose of another measles, mumps and rubella virus-containing vaccine.
Indication(s) and Intended Population(s)	Active immunization for the prevention of measles, mumps, and rubella in individuals 12 months of age and older.
Orphan Designated (Yes/No)	No

5.3 Table of Studies/Clinical Trials

Table 3: Clinical Trials Submitted in Support of Safety and Efficacy

Study Number	Region	Description	Population (Schedule)	Study Groups: # Enrolled (# Exposed)
Trial # 1: MMR-160 Lot Consistency Immunogenicity Safety (NCT01702428)	US (including Puerto Rico) Estonia Finland Mexico Spain	Phase 3, observer-blind, randomized, controlled, consistency and non-inferiority study to evaluate the immunogenicity and safety of PRIORIX vs. MMR-II, as a first dose	Healthy children 12 through 15 months (1 dose at Day 0 with VV and HAV, and PCV13 in US only)	PRIORIX: 3,719 (3,714) Lot 1: 1,239 (1,239) Lot 2: 1,234 (1,232) Lot 3: 1,246 (1,243) M-M-R II: 1,291 (1,289)
Trial # 2: MMR-158 Immunogenicity Safety (NCT01621802)	US Republic of Korea Taiwan	Phase 3, observer-blind, randomized, controlled study to evaluate non-inferiority PRIORIX as a second dose vs. M-M-R II as a second dose	Healthy children 4 through 6 years (1 dose at Day 0 with VV and DTaP-IPV in a US-only sub-cohort)	PRIORIX: 2,918 (2,917) Sub-cohort 1: 802 (802) Sub-cohort 2: 796 (796) Sub-cohort 3: 1,320 (1,319) M-M-R II: 1,091 (1,090) Sub-cohort 1: 299 (298) Sub-cohort 2: 303 (303) Sub-cohort 3: 489 (489)
Trial # 3: MMR-161 Immunogenicity Safety (NCT01681992)	US (including Puerto Rico) Czech Republic Finland Malaysia Spain Thailand	Phase 3, observer-blind, randomized, controlled study to evaluate the immunogenicity and safety of PRIORIX at an end of shelf-life potency (established for each antigen) vs. MMR-II	Healthy children 12 through 15 months (2 doses: 1 at Day 0 with VV and HAV, and PCV13 in US only and 1 at Day 42)	PRIORIX: 2998 (2990) Min: 1497 (1493) Med: 1501 (1497) M-M-R II: 1530 (1526)
Trial # 4: MMR-162 Safety Immunogenicity (NCT02184572)	US (including Puerto Rico) Estonia Finland Taiwan	Phase 3, observer-blind, randomized, controlled study to evaluate the safety and immunogenicity of PRIORIX (at a potency used to define maximum release limits) vs. MMR-II, as a first dose	Healthy children 12 through 15 months (1 dose at Day 0 with VV and HAV, and PCV13 in US only)	PRIORIX: 1165 (1164) M-M-R II: 575 (572)
Trial # 5: MMR-159 Immunogenicity Safety (NCT02058563)	US Estonia Slovakia	Phase 3, observer-blind, randomized, controlled study to evaluate non-inferiority of PRIORIX as a second dose vs. M-M-R II as a second dose	Healthy children, adolescents, and adults ≥ 7 years primed with at least 1 dose of an MMR vaccine (1 dose at Day 0)	PRIORIX: 497 (454) M-M-R II: 497 (457)

mIU/mL and White: 2831.4 mIU/mL). Otherwise, the immune responses by country, gender, and race were similar to those reported in the primary immunogenicity analyses.

6.1.11.4 Dropouts and/or Discontinuations

Approximately 95% of enrolled participants completed the study. Missing or non-evaluable immunogenicity measurements were not replaced. Immunogenicity analyses therefore excluded participants with missing or non-evaluable measurements. See Section 6.1.10.1.2.

6.1.11.5 Exploratory and Post Hoc Analyses

Not applicable.

6.1.12 Safety Analyses

6.1.12.1 Methods

Safety data surveillance is described in Section 6.1.7 above and shown in Table 16. Participant compliance with returning symptom sheets for collection of local and systemic solicited AEs following administered vaccines was ≥95.4%.

6.1.12.2 Overview of Adverse Events

Safety Overview

Safety data were collected for PRIORIX groups (by lot and pooled) and the M-M-R II group (pooled lots). Safety data were overall similar between individual lots and pooled lots for PRIORIX groups. Table 16 provides an overview of the rates of adverse events in the pooled PRIORIX lots compared to the pooled M-M-R II lots during the study period.

Table 16. Proportion of Participants Reporting at Least One Adverse Event Following MMR Vaccination, TVC, Study MMR-160

AE Type: Monitoring Period[a]	PRIORIX % (n/N)	M-M-R II % (n/N)
Immediate AE: 30 minutes	0.1% (3/3714)	0.2% (3/1289)
Solicited local at injection site[b]: 0-3 days	39.8% (1416/3555)	41.5% (515/1242)
Solicited systemic[c]: 0-14 days	71.8% (2560/3566)	74.7% (929/1243)
Fever (temperature ≥38.0 ºC): 0-42 days	34.7% (1239/3566)	33.1% (411/1243)
Rash: 0-42 days	29.2% (1043/3566)	30.4% (378/1243)
varicella-like rash	7.0% (250/3566)	6.8% (85/1243)
Measles/rubella-like rash	6.6% (235/3566)	6.2% (77/1243)
Other rash	19.0% (679/3566)	20.8% (259/1243)
Parotid/salivary gland swelling: 0-42 days	0	0
Meningism[d]: 0-42 days	0.3% (10/3566)	0.2% (3/1243)
Unsolicited: 0-42 days	50.0% (1857/3714)	47.9% (618/1289)
AEs leading to study w/d: Entire study period	<0.01% (2/3714)	0
SAEs: Entire study period	2.1% (77/3714)	1.9% (25/1289)

AE Type: Monitoring Period[a]	PRIORIX % (n/N)	M-M-R II % (n/N)
AEs of specific interest[e]: Entire study period	12.9% (478/3714)	13.1% (169/1289)
Deaths: Entire study period	0	0

Source: Adapted from STN 125748/0, MMR-160 Clinical Study Report Amendment 2, Section 8.2.1, Table 23, Table 24, Tables 47-50, Table 8.44, and MMR (RIT) Analysis #16 Table 6
Abbreviations: AE=adverse event; N=number of participants in population; n=number of participants who experienced the event; SAE=serious adverse event; TVC=Total Vaccinated Cohort was used as the analyses set for safety; w/d=withdrawal
Temperature 38.0 C =100.4 F
Note: For unsolicited events, the N is the number of participants in the TVC; For solicited local events, the N is the number of participants from the TVC with documented local events; For solicited systemic events, the N is the number of participants from the TVC with documented systemic events.
Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.
Data from the three PRIORIX lots were pooled for this summary.
a. Monitoring Period: time interval that the relevant type of AE was monitored for post-vaccination
b. Solicited local included pain, redness, and swelling at injection site
c. Solicited systemic included any systemic symptom including drowsiness, loss of appetite, or irritability
d. Signs or symptoms indicative of meningism (i.e., neck stiffness with or without light intolerance [photophobia] and headache; or convulsion/seizure) and included febrile convulsions
e. AEs of specific interest included new onset chronic disease (NOCD, e.g., autoimmune disorders, asthma, type I diabetes, vasculitis, celiac disease, conditions associated with sub-acute or chronic thrombocytopenia and allergies) and AEs prompting emergency room (ER) visit

The rates for any reported AE, including local and systemic solicited reactions, unsolicited AEs, and SAEs, were similar between the PRIORIX and M-M-R II pooled groups. Overall, 87.1% and 88.3% of participants, respectively, reported at least one solicited or unsolicited symptom during the 43-day post-vaccination period. There were two AEs in the PRIORIX group that led to study withdrawal and no deaths throughout the entire study period for either group.

Subpopulation Analyses

Descriptive summary safety data were reported by country, gender, and race if there were at least 50 participants per treatment group. In general, findings were similar to those reported in the safety analyses for the overall group. No clinically meaningful differences between vaccine groups in incidence of solicited local or systemic symptoms were observed in females and males or in any race group.

Solicited Adverse Reactions

Table 17 includes the percentages of PRIORIX and M-M-R II participants who reported any solicited adverse reactions, which are stratified by grade.

Table 17. Proportion of Participants With Solicited Reactions Post-Vaccination, TVC, Study MMR-160

Solicited Adverse Reaction	PRIORIX N=3555-3566	M-M-R II N=1242-1243
Local (injection site)	--	--
Pain[a], % (n/N)	--	--
Any	25.9% (919/3555)	28.1% (349/1242)
Grade 0	0.1% (2/3555)	0.0% (0/1242)
Grade 1	19.6% (697/3555)	20.9% (260/1242)
Grade 2	5.5% (196/3555)	6.2% (77/1242)
Grade 3	0.7% (24/3555)	1% (12/1242)
Erythema, % (n/N)	--	--
Any	24.5% (870/3555)	25.2% (313/1242)
Grade 0 (none)	0.1% (2/3555)	0.0% (0/1242)
Grade 1 (>0 to ≤5 mm)	20.5% (728/3555)	21.9% (272/1242)
Grade 2 (>5 to ≤20 mm)	3.5% (126/3555)	2.7% (33/1242)
Grade 3 (>20 mm)	0.4% (14/3555)	0.6% (8/1242)

Table 29. Proportion of Participants Reporting at Least One Adverse Event Following MMR Vaccination, TVC, Study MMR-158

AE Type: Monitoring Period[a], % (n/N)	PRIORIX Sub-cohort 1	M-M-R II Sub-cohort 1	PRIORIX Sub-cohort 2	M-M-R II Sub-cohort 2	PRIORIX Sub-cohort 3	M-M-R II Sub-cohort 3
Immediate AE: 30 minutes	0	0	0	0	0	0
Solicited local at injection site[b]: 0-3 days	48.3% (351/727)	48.7% (130/267)	29.8% (228/766)	30.4% (88/289)	33.0% (426/1289)	36.9% (177/480)
Solicited systemic[c]: 0-3 days	33.5% (245/731)	33.2% (89/268)	NA	NA	NA	NA
Fever (Any): 0-42 days	24.2% (177/731)	25.0% (67/268)	19.0% (146/767)	19.9% (58/291)	19.9% (257/1291)	20.0% (96/481)
Rash: 0-42 days	--	--	--	--	--	--
Any rash	8.3% (61/731)	10.4% (28/268)	4.8% (37/767)	4.1% (12/291)	4.3% (56/1291)	4.8% (23/481)
varicella-like rash[d]	0.5% (4/731)	1.1% (3/268)	NA	NA	NA	NA
Measles/rubella-like rash	1.9% (14/731)	1.9% (5/268)	0.4% (3/767)	0.7% (2/291)	0.3% (4/1291)	0.4% (2/481)
Other rash (not measles/rubella-like)	6.2% (45/731)	7.5% (20/268)	4.4% (34/767)	3.4% (10/291)	4.0% (52/1291)	4.4% (21/481)
Parotid/salivary gland swelling: 0-42 days	0	0	0	0.3% (1/291)	0.1% (1/1291)	0.2% (1/481)
Meningism[e]: 0-42 days	0	0.7% (2/268)	0.1% (1/767)	0	0	0
Unsolicited: 0-42 days	34.4% (276/802)	30.2% (90/298)	39.4% (314/796)	37.0% (112/303)	38.5% (508/1319)	38.0% (186/489)
AEs leading to study w/d: Entire study period	0	0	0	0	0	0
SAEs: Entire study period	0.5% (4/802)	0	1.8% (14/796)	0.3% (1/303)	1.9% (25/1319)	1.8% (9/489)

AE Type: Monitoring Period[a], % (n/N)	PRIORIX Sub-cohort 1	M-M-R II Sub-cohort 1	PRIORIX Sub-cohort 2	M-M-R II Sub-cohort 2	PRIORIX Sub-cohort 3	M-M-R II Sub-cohort 3
AEs of specific interest[f]: Entire study period	8.5% (68/802)	10.7% (32/298)	8.5% (68/796)	7.3% (22/303)	8.4% (111/1319)	7.8% (38/489)
Deaths: Entire study period	0	0	0	0	0	0

Source: Adapted from STN 125748/0, MMR-158 Clinical Study Report Amendment 2 Section 8.2.1 and Tables 24, 25, 26, 27, 28, 29, 69, 70, 71, 72, 73, 74, 75, 85, 8.67, 8.71, 8.72, 8.73, 8.77, 8.78, and 8.79; MMR (RIT) Analysis #16 Tables 1, 2, and 3.
Abbreviations: AE=adverse event; N=number of participants in cohort; n=number of participants who experienced the event; SAE=serious adverse event; TVC=Total Vaccinated Cohort was used as the analyses set for safety; w/d=withdrawal
Temperature 38.0 C =100.4 F
Note: For unsolicited events, the N is the number of participants in the TVC; For solicited local events, the N is the number of participants from the TVC with documented local events; For solicited systemic events, the N is the number of participants from the TVC with documented systemic events.
Note: Sub-cohort 1 (co-administration) = GSK PRIORIX or Merck M-M-R II concomitantly administered with varicella vaccine and DTaP-IPV and analyzed for immunogenicity and safety.
Sub-cohort 2 (immunogenicity) = GSK PRIORIX or Merck M-M-R II alone and analyzed for immunogenicity and safety.
Sub-cohort 3 (safety) = GSK PRIORIX or Merck M-M-R II alone and analyzed for safety only.
a. Monitoring Period: time interval that the relevant type of AE was monitored for post-vaccination
b. Solicited local includes pain, redness, and swelling at injection site
c. Drowsiness and loss of appetite are standard solicited symptoms in clinical trials evaluating DTaP-IPV vaccine recipients
d. Only collected for participants who received varicella vaccine
e. Signs or symptoms indicative of meningism (i.e., neck stiffness with or without light intolerance [photophobia] and headache; or convulsion/seizure) and includes febrile convulsions
f. AEs of specific interest includes new onset chronic disease (NOCD, e.g., autoimmune disorders, asthma, type I diabetes, vasculitis, celiac disease, conditions associated with sub-acute or chronic thrombocytopenia and allergies) and AEs prompting emergency room (ER) visit

Table 40. Proportion of Participants Reporting at Least One Adverse Event Following MMR Vaccination, TVC, Study MMR-161

AE Type: Monitoring Period[a], % (n/N)	Medium Potency PRIORIX Post-Dose 1	M-M-R II Post-Dose 1	Medium Potency PRIORIX Post-Dose 2	M-M-R II Post-Dose 2
Immediate AE: 30 minutes	0.1% (1/1497)	0	0	0
Solicited local at injection site[b]: 0-3 days after each dose	28.6% (419/1464)	31.2% (462/1482)	21.1% (304/1440)	22.7% (330/1456)
Solicited systemic[c]: 0-14 days after dose 1	64.7% (948/1466)	62.4% (927/1486)	NA	NA
Fever (temperature ≥38.0 ºC): 0-42 days after each dose	42.0% (616/1466)	41.5% (616/1486)	32.5% (469/1443)	34.3% (499/1455)
Rash: 0-42 days after each dose	22.0% (322/1466)	22.4% (333/1486)	10.4% (150/1443)	9.7% (141/1455)
Varicella-like rash	3.6% (53/1466)	3.0% (45/1486)	0	0.1% (1/1455)
Measles/rubella-like rash	4.2% (61/1466)	4.6% (68/1486)	1.0% (14/1443)	1.0% (14/1455)
Other rash	15.7% (230/1466)	16.6% (247/1486)	9.6% (138/1443)	8.7% (127/1455)
Parotid/salivary gland swelling: 0-42 days after each dose	0.1% (2/1466)	0.2% (3/1486)	0.1% (2/1443)	0
Meningism[d]: 0-42 days after each dose	0.3% (4/1466)	0.2% (3/1486)	0.4% (6/1443)	0.3% (4/1455)
Unsolicited: 0-42 days	53.0% (794/1497)	50.9% (777/1526)	48.0% (703/1464)	46.5% (690/1483)
AEs leading to study w/d: Entire study period	NA	NA	0.1% (2/1497)	0.2% (3/1526)
SAEs: Entire study period	NA	NA	6.8% (102/1497)	6.0% (92/1526)
AEs of specific interest[e]: Entire study period	NA	NA	25.7% (384/1497)	24.2% (370/1526)
Deaths: Entire study period	NA	NA	0.06% (1/1497)	0.06% (1/1526)

Source: Adapted from STN 125748/0, MMR-161 Clinical Study Report Amendment 2, Section 8.2.1, Table 22, Tables 44-46, Table 8.2, and MMR (RIT) Analysis #16 Tables 7-12
Abbreviations: AE=adverse event; N=number of participants in cohort; n=number of participants who experienced the event; SAE=serious adverse event; TVC=Total Vaccinated Cohort was used as the analyses set for safety; w/d=withdrawal
Temperature 38.0 C =100.4 F
Note: For unsolicited events, the N is the number of participants in the TVC
Note: For solicited local events, the N is the number of participants from the TVC with documented local events
Note: For solicited systemic events, the N is the number of participants from the TVC with documented systemic events
a. Monitoring Period: time interval that the relevant type of AE was monitored for post-vaccination
b. Solicited local includes pain, redness, and swelling at injection site
c. Solicited systemic includes any systemic symptom including drowsiness, loss of appetite, or irritability
d. Signs or symptoms indicative of meningism (i.e., neck stiffness with or without light intolerance [photophobia] and headache; or convulsion/seizure) and includes febrile convulsions
e. AEs of specific interest includes new onset chronic disease (NOCD, e.g., autoimmune disorders, asthma, type I diabetes, vasculitis, celiac disease, conditions associated with sub-acute or chronic thrombocytopenia and allergies) and AEs prompting emergency room (ER) visit

Overall, for any solicited or unsolicited symptom, the rates were similar across groups. Post-dose 1, the rate was 85.1% in the minimum potency PRIORIX group, 86.3% in the medium potency PRIORIX group, and 84.8% in the M-M-R II group. Rates were also similar across groups post-dose 2, and lower than following the first dose, at 63.9%, 67.4%, and 67.0%, respectively. There were 4 AEs (2 in the min potency PRIORIX group and 1 each in the med potency PRIORIX and M-M-R II groups), 1 nonfatal SAE (M-M-R II group), and 3 fatal events (1 each in the min potency PRIORIX group, med potency PRIORIX group, and M-M-R II group) that led to premature discontinuation from the study. None of these events were considered by the investigator to be related to the study vaccination.

6.4.12.2 Overview of Adverse Events

Co-Primary objectives: Rates of Fever

The comparability of observed rates of fever between groups was determined if the upper limit of the 95% CI for the difference [PRIORIX minus M-M-R II] in fever rates was <5% when fever was defined as >39.0°C (Primary Objective #1) and was <10% when fever was defined as ≥38.0°C (Primary Objective 2). The co-primary objectives of Fever >39.0°C and Fever ≥38.0°C were ***met*** as shown in Table 46.

Table 46. Percentage Difference in Participants Reporting Fever, Days 5 Through 12 Post-Vaccination, TVC, Study MMR-162

Axillary Temperature	PRIORIX N=1,126 n (%)	M-M-R II N=555 n (%)	PRIORIX-M-M-R II Difference Percentage (95% CI)
All	250 (22.2%)	123 (22.2%)	0.04% (-4.28, 4.17)
≥38.0°C	205 (18.2%)	95 (17.1%)	1.09% (-2.89, 4.85)
>39.0°C	47 (4.2%)	17 (3.1%)	1.11% (-0.93, 2.89)

Source: Adapted from STN 125748/0, Study MMR-162 Amendment 2, Table 22
Abbreviations: CI=confidence interval; N=number of participants in TVC; n=number of participants fulfilling the item followed by (%); TVC=Total Vaccinated Cohort was used as the analyses set for safety
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.

Safety Overview

Safety data were presented for the PRIORIX group and the M-M-R II groups (pooled lots). Table 47 provides an overview of the rates of adverse events in the PRIORIX lot compared to the pooled M-M-R II lots during the study period.

Table 47. Proportion of Participants Reporting at Least One Adverse Event Following MMR Vaccination, TVC, Study MMR-162

AE Type: Monitoring Period[a]	PRIORIX % (n/N)	M-M-R II % (n/N)
Immediate AE: 30 minutes	0.1% (1/1164)	0
Solicited local at injection site[b]: 0-3 days	40.2% (451/1123)	38.5% (213/553)
Solicited systemic[c]: 0-14 days	71.3% (803/1126)	70.1% (389/555)
Measles-like illness[d]: 5-12 days	1.5% (18/1164)	0.9% (5/572)
Temperature ≥38.0ºC: 0-42 days	31.1% (350/11260)	32.3% (179/555)
Rash: 0-42 days	24.4% (275/1126)	27.4% (152/555)
Parotid gland swelling: 0-42 days	0	0
Meningism[e]: 0-42 days	0.2% (2/1126)	0
Unsolicited AE: 0-42 days	51.4% (598/1164)	48.4% (277/572)
AEs leading to study withdrawal: Entire study period	0	0
SAEs: Entire study period	2.1% (24/1164)	1.6% (9/572)

AE Type: Monitoring Period[a]	PRIORIX % (n/N)	M-M-R II % (n/N)
AEs of specific interest[f]: Entire study period	16.4% (191/1164)	11.0% (63/572)
Deaths: Entire study period	0	0

Source: Adapted from STN 125748/0, Study MMR-162, Clinical Study Report Amendment 2, Section 7.2.1, Table 17, Table 18, Tables 26-29, Table 33, and MMR (RIT) Analysis #16 Table 13
TVC: Total Vaccinated Cohort was used as the analyses set for safety. n: #participants who experienced the event; C: degrees Celsius. AE: adverse event; AEs leading to w/d: adverse events leading to study withdrawal; SAEs: serious adverse events.
Temperature 38.0 C =100.4 F
Note: For unsolicited events, the N is the number of participants in the TVC (see Table B); For solicited local events, the N is the number of participants from the TVC with documented local events; For solicited systemic events, the N is the number of participants from the TVC with documented systemic events.
a. Monitoring Period: time interval that the relevant type of AE was monitored for post-vaccination
b. Solicited local includes pain, redness, and swelling at injection site
c. Solicited systemic includes any systemic symptom including drowsiness, loss of appetite, or irritability
d. Measles-like illness is defined as the occurrence of the following signs and symptoms in the absence of another confirmed diagnosis: maculopapular rash and fever (≥38 C), and at least one symptom of cough, coryza, conjunctivitis, or diarrhea, with fever or rash occurring between Day 5 and Day 12 inclusive.
e. Signs or symptoms indicative of meningism (i e., neck stiffness with or without light intolerance [photophobia] and headache; or convulsion/seizure) and included febrile convulsions
f. AEs of specific interest included new onset chronic disease (NOCD, e.g., autoimmune disorders, asthma, type I diabetes, vasculitis, celiac disease, conditions associated with sub-acute or chronic thrombocytopenia and allergies) and AEs prompting emergency room (ER) visit

The rates for any reported AE including local and systemic solicited reactions, unsolicited AEs and SAEs were comparable between groups. Overall, 51.4% and 48.8% of participants in the PRIORIX and M-M-R II groups, respectively, reported at least one solicited or unsolicited symptom during the 43-day post-vaccination period. There were no AEs that lead to study withdrawal and no deaths throughout the entire study period for either group.

Subpopulation Analyses

Descriptive summary safety data were reported by country, gender, and race (geographic ancestry). In general, findings were similar to those reported in the safety analyses for the overall group. Number and percentages of those compliant in returning symptom information and incidence and nature of symptoms reported (local and systemic reactions) were similar when evaluated as sub-groups. No clinically meaningful differences between vaccine groups in incidence of solicited local or general symptoms were observed in females and males or in any race group.

Solicited Adverse Reactions

Table 48 includes the percentages of PRIORIX and M-M-R II participants who reported any solicited adverse reactions, which are stratified by grade.

Table 48. Proportion of Participants With Solicited Reactions Post-Vaccination, TVC, Study MMR-162

Solicited Adverse Reaction	PRIORIX N=1123-1126	M-M-R II N=553-555
Local (injection site)	--	--
Pain[a], % (n/N)	--	--
Any	27.8% (312/1123)	23.7% (131/553)
Grade 1	21.5% (242/1123)	18.6% (103/553)
Grade 2	5.7% (64/1123)	4.7% (26/553)
Grade 3	0.5% (6/1123)	0.4% (2/553)
Erythema, % (n/N)	--	--
Any	23.2% (260/1123)	24.8% (137/553)
Grade 1 (>0 to ≤5 mm)	18.1% (203/1123)	19.9% (110/553)
Grade 2 (>5 to ≤20 mm)	4.4% (49/1123)	3.6% (20/553)
Grade 3 (>20 mm)	0.7% (8/1123)	1.3% (7/553)

Safety data were presented for PRIORIX and M-M-R II groups. Table 55 provides an overview of the rates of adverse events in the PRIORIX compared to the M-M-R II groups during the study period.

Table 55. Proportion of Participants Reporting at Least One Adverse Event Following MMR Vaccination, TVC, Study MMR-159

AE Type: Monitoring Period[a]	PRIORIX % (n/N)	M-M-R II % (n/N)
Immediate AE: 30 minutes	0.4% (2/454)	1.1% (5/457)
Solicited local at vaccine site[b]: 0-3 days	19.4% (84/433)	19.3% (86/445)
Solicited systemic[c]:	NA	NA
Temperature ≥38.0 ºC: 0-42 days	3.0% (13/431)	5.2% (23/445)
Rash: 0-42 days	2.1% (9/431)	1.1% (5/445)
Parotid gland swelling: 0-42 days	0.2% (1/431)	0.2% (1/445)
Arthralgia/Joint pain	1.9% (8/431)	0.9% (4/445)
Meningism[d]: 0-42 days	0.2% (1/431)	0.2% (1/445)
Unsolicited AE: 0-42 days	20.9% (95/454)	17.9% (82/457)
AEs leading to study withdrawal: Entire study period	0	0
SAEs: Entire study period	0	0
AEs of specific interest[e]: Entire study period	3.5% (16/454)	2.2% (10/457)
Deaths: Entire study period	0	0

Source: Adapted from STN 125748/0, MMR-159, Clinical Study Report Amendment 1, Table 14, Table 15, Tables 24-30, and MMR (RIT) Analysis #16 Table 4
Abbreviations: AE=adverse event; N=number of participants in cohort; n=number of participants who experienced the solicited event; SAE=serious adverse event; TVC=Total Vaccinated Cohort was used as the analyses set for safety
Temperature 38.0 C=100.4 F
Note: For unsolicited events, the N is the number of participants in the TVC; For solicited local events, the N is the number of participants from the TVC with documented local events; For solicited systemic events, the N is the number of participants from the TVC with documented systemic events
a. Monitoring Period: time interval that the relevant type of AE was monitored for post-vaccination.
b. Solicited local includes pain, redness, and swelling at injection site.
c. Due to ages of the participants, the following solicited systemic reactions were not collected in this study: drowsiness, loss of appetite, or irritability/fussiness.
d. Signs or symptoms indicative of meningism (i.e., neck stiffness with or without light intolerance [photophobia] and headache; or convulsion/seizure) and included febrile convulsions.
e. AEs of specific interest included new onset chronic disease (NOCD, e.g., autoimmune disorders, asthma, type I diabetes, vasculitis, celiac disease, conditions associated with sub-acute or chronic thrombocytopenia and allergies) and AEs prompting emergency room (ER) visit

Within 43 days post-vaccination, the rates for any reported AE, including local and systemic, solicited reactions, unsolicited AEs, and SAEs were generally similar between the PRIORIX and M-M-R II groups. Overall, 35.7% and 33.9% of participants, respectively reported at least one solicited or unsolicited symptom during the 43-day post-vaccination period. There were no AEs in the PRIORIX group that let to study withdrawal and no deaths throughout the entire study period for either group.

Subpopulation Analyses

Descriptive summary safety data were reported by country, gender, and age. In general, findings were similar to those reported in the safety analyses for the overall group. No clinically meaningful differences between vaccine groups in incidence of solicited local or general symptoms were observed in females and males or in any age group.

Solicited Adverse Reactions

Table 56 includes the percentages of PRIORIX and M-M-R II participants who reported any solicited adverse reactions, which are stratified by grade.

Exhibit 21

What is a Serious Adverse Event?

Reporting Serious Problems to FDA

What is a Serious Adverse Event?

Product Problems

Reporte problemas serios a la FDA

¿Qué es una reacción adversa grave?

Problemas con los productos

Content current as of:
05/18/2023

An adverse event is any undesirable experience associated with the use of a medical product in a patient. The event is serious and should be reported to FDA when the patient outcome is:

Death

Report if you suspect that the death was an outcome of the adverse event, and include the date if known.

Life-threatening

Report if suspected that the patient was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the patient.

Hospitalization (initial or prolonged)

Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event.

Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

Disability or Permanent Damage

Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.

Congenital Anomaly/Birth Defect

Report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

Required Intervention to Prevent Permanent Impairment or Damage (Devices)

Report if you believe that medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.

Other Serious (Important Medical Events)

Report when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic brochospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

Resources For You

- Report a Serious Medical Product Problem Online
- Report Dietary Supplements and Tobacco Product Problems Online
- Form FDA 3500 - Voluntary Reporting

Exhibit 22

VITAL STATISTICS RATES IN THE UNITED STATES 1940–1960

By
Robert D. Grove, Ph. D.
and
Alice M. Hetzel

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
Washington, D.C. 1968
National Center for Health Statistics

For sale by the Superintendent of Documents, U.S. Government Printing Office
Washington, D.C. 20402 - Price $5.25

NATIONAL CENTER FOR HEALTH STATISTICS

Division of Vital Statistics

Public Health Service Publication No. 1677

Figure 19.—Death Rates for Measles: Death-registration States, 1900–32, and United States, 1933–60

(Rates per 100,000 population)

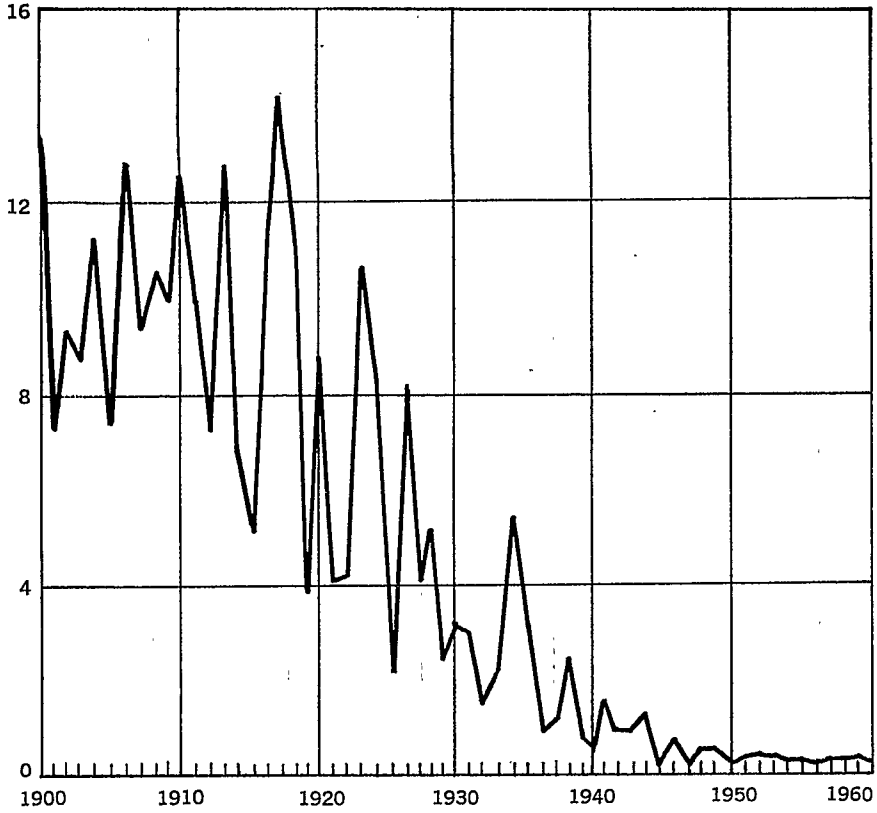

TABLE 65.—*Death rates for detailed causes: Death-registration States, 1900–1932, and United States, 1933–60*

Section A, 1900–1909

[Rates are deaths per 100,000 population. Numbers before causes of death are category numbers of First Revision of the International Lists]

Int. List No.	Cause of death	1900	1901	1902	1903	1904	1905	1906	1907	1908	1909
	All causes	1,719.1	1,641.5	1,548.1	1,562.8	1,640.0	1,588.9	1,571.8	1,592.5	1,468.2	1,424.7
	I.—General diseases	466.5	456.0	412.2	421.4	430.1	408.3	412.6	416.3	391.5	372.3
1	Typhoid fever (abdominal typhus)	31.3	27.6	26.4	24.6	23.9	22.4	30.9	28.2	23.4	20.2
2	Exanthematic typhus	*0.0*	—	*0.0*	—	*0.0*	*0.0*	—	*0.0*	—	*0.0*
3	Relapsing fever	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	—	*0.0*	—	*0.0*	—
4	Intermittent fever and malarial cachexia	6.2	5.0	4.0	3.0	2.9	2.5	2.3	1.8	1.3	1.4
5	Smallpox	0.3	3.6	6.5	1.5	0.8	0.6	0.2	0.1	0.2	0.1
6	Measles	13.3	7.4	9.3	8.8	11.3	7.4	12.9	9.6	10.6	10.0
7	Scarlet fever	9.6	13.6	11.9	12.3	11.6	6.8	7.3	9.3	12.4	11.1
8	Whooping cough	12.2	8.7	12.4	14.3	5.8	8.9	16.1	11.3	10.7	10.0
9	Diphtheria and croup	40.3	33.5	29.8	31.1	29.3	23.5	26.3	24.2	21.9	19.9
10	Influenza	26.7	36.5	10.4	19.2	21.8	20.5	10.2	25.0	21.1	13.3
11	Miliary fever	—	—	*0.0*	*0.0*	*0.0*	—	—	—	*0.0*	—
12	Asiatic cholera	—	—	—	—	—	—	—	—	—	—
13	Cholera nostras	2.8	1.8	1.4	1.2	1.2	1.4	1.4	1.0	1.1	0.8
14	Dysentery	12.0	11.1	10.1	7.3	8.1	8.3	8.0	6.1	6.1	5.4
15	Bubonic plague	—	*0.0*	—	—	—	—	—	0.2	*0.0*	*0.0*
16	Yellow fever	*0.0*	*0.0*	*0.0*	—	—	*0.0*	—	—	—	—
17	Leprosy	—	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*
18	Erysipelas	5.4	4.5	4.1	4.0	5.1	4.7	4.3	4.4	3.8	3.9
19	Other epidemic diseases	0.2	0.1	0.2	0.2	0.2	0.2	0.4	0.3	0.3	0.3
20	Purulent infection and septicemia	7.2	5.9	5.9	4.7	4.9	4.4	3.8	3.7	3.2	2.9
21	Glanders and farcy	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*
22	Malignant pustule	*0.1*	0.1	*0.1*	*0.1*	*0.1*	*0.1*	*0.1*	0.1	*0.0*	*0.0*
23	Rabies	*0.1*	0.1	*0.1*	*0.1*	*0.0*	0.1	0.2	0.2	0.2	0.1
24	Actinomycosis, trichinosis, etc.	*0.0*	*0.0*	*0.0*	*0.0*	*0.1*	*0.1*	*0.0*	*0.0*	0.1	0.1
25	Pellagra	*0.0*	—	—	*0.0*	—	—	—	—	—	*0.0*
	Tuberculosis (all forms)	194.4	189.9	174.2	177.2	188.1	179.9	175.8	174.2	162.1	156.3
26	Tuberculosis of the larynx	1.2	1.6	1.6	1.5	1.6	1.6	1.5	1.6	1.5	1.6
27	Tuberculosis of the lungs	173.3	167.9	152.8	154.2	164.2	155.5	151.8	150.4	138.6	133.3
28	Tuberculosis of the meninges	9.4	9.1	9.2	9.6	9.8	9.9	9.8	9.8	9.4	9.1
29	Abdominal tuberculosis	4.9	5.4	5.1	5.2	5.8	5.8	6.0	5.8	5.7	5.9
30	Pott's disease	1.5	1.4	1.4	1.5	1.6	1.6	1.5	1.4	1.6	1.4
31	Cold abscess, abscess by congestion	0.1	0.1	0.1	0.2	0.2	0.2	0.1	0.2	0.2	0.1
32	White swelling	0.6	0.6	0.6	0.6	0.7	0.8	0.8	0.6	0.8	0.7
33	Tuberculosis of other organs	1.0	1.2	1.1	1.4	1.6	1.5	1.6	1.6	1.7	1.7
34	General tuberculosis	2.3	2.7	2.4	3.0	2.7	3.0	2.6	2.8	2.8	2.3

TABLE 65.—*Death rates for detailed causes: Death-registration States, 1900–1932, and United States, 1933–60*—Continued
Section F, 1949–1960—Continued

Cause of death		1949	1950	1951	1952	1953	1954	1955	1956	1957	1958	1959	1960
I.—Infective and parasitic diseases—Continued													
Syphilis and its sequelae—Continued													
Other syphilis of central nervous system	026	0.6	0.5	0.5	0.4	0.3	0.3	0.3	0.2	0.2	0.2	0.2	0.1
All other syphilis	027–029	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0
Gonococcal infection	030–035	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Typhoid fever	040	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Paratyphoid fever and other Salmonella infections	041, 042	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Cholera	043	—	—	—	—	—	—	—	—	—	—	—	—
Brucellosis (undulant fever)	044	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Dysentery, all forms	045–048	1.0	0.6	0.7	0.6	0.6	0.4	0.3	0.3	0.3	0.2	0.2	0.2
Food poisoning (infection and intoxication)	049	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0
Scarlet fever	050	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Streptococcal sore throat	051	0.3	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Erysipelas	052	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Septicemia and pyemia	053	0.4	0.4	0.4	0.5	0.5	0.6	0.6	0.7	0.8	1.0	1.0	1.1
Diphtheria	055	0.4	0.3	0.2	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0
Whooping cough	056	0.5	0.7	0.6	0.3	0.2	0.2	0.3	0.2	0.1	0.1	0.2	0.1
Meningococcal infections	057	0.6	0.6	0.7	0.9	0.8	0.6	0.6	0.5	0.5	0.4	0.4	0.4
Plague	058	0.0	0.0	—	—	—	—	—	0.0	—	—	0.0	—
Leprosy	060	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Tetanus	061	0.3	0.2	0.3	0.2	0.2	0.2	0.2	0.1	0.2	0.2	0.2	0.1
Anthrax	062	—	0.0	0.0	0.0	—	—	—	—	0.0	0.0	—	—
Acute poliomyelitis	080	1.8	1.3	1.0	2.0	0.9	0.8	0.6	0.3	0.1	0.1	0.3	0.1
Late effects of acute poliomyelitis	081	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Acute infectious encephalitis	082	0.3	0.3	0.3	0.3	0.2	0.3	0.2	0.3	0.3	0.3	0.3	0.3
Late effects of acute infectious encephalitis	083	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0
Smallpox	084	0.0	0.0	0.0	—	0.0	—	—	—	—	—	—	—
Measles	085	0.6	0.3	0.4	0.4	0.3	0.3	0.2	0.3	0.2	0.3	0.2	0.2
Yellow fever	091	—	—	—	—	—	—	—	—	—	—	—	—
Infectious hepatitis	092	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Rabies	094	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Tick-borne typhus	104	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Typhus, other and unspecified, and other rickettsial diseases	100–103, 105–108	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	—
Malaria	110–117	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Schistosomiasis	123	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Hydatid disease	125	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Filariasis	127	0.0	0.0	—	0.0	—	—	—	—	—	—	—	—
Ancylostomiasis	129	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	—	0.0	0.0	—
Other diseases due to helminths	124, 126, 128, 130	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
All other infective and parasitic diseases	036–039, 054, 059, 063–074, 086–090, 093, 095, 096, 120–122, 131–138	0.7	0.7	0.8	0.8	0.8	0.7	0.7	0.8	0.7	0.7	0.8	0.8

Exhibit 23

VITAL STATISTICS OF THE UNITED STATES

1962

VOLUME II—MORTALITY

PART A

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE

ANTHONY J. CELEBREZZE, SECRETARY

PUBLIC HEALTH SERVICE

LUTHER L. TERRY, SURGEON GENERAL

WASHINGTON: 1964

For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C., 20402 - Price $3.75

Table 1-8. Death Rates for 60 Selected Causes: United States, 1953-62

(Data refer only to deaths occurring within the United States Alaska included beginning 1959, and Hawaii, 1960. Excludes fetal deaths. Rates per 100,000 population residing in area, enumerated as of April 1 for 1960 and estimated as of July 1 for all other years Numbers after causes of death are category numbers of the Seventh Revision of the International Lists, 1955. Deaths are classfied according to the Sixth Revision for 1953-57 and according to the Seventh Revision for 1958-62)

CAUSE OF DEATH	1962	1961	1960	1959	1958	1957	1956	1955	1954	1953
ALL CAUSES	945.4	929.6	954.7	938.6	950.7	958.5	935.1	930.4	919.0	959.0
Tuberculosis, all forms---001-019	5.1	5.4	6.1	6.5	7.1	7.8	8.4	9.1	10.2	12.4
Tuberculosis of respiratory system---001-008	4.7	5.0	5.6	6.0	6.6	7.3	7.8	8.3	9.3	11.3
Tuberculosis, other forms---010-019	0.4	0.4	0.4	0.5	0.5	0.6	0.6	0.8	0.8	1.1
Syphilis and its sequelae---020-029	1.5	1.6	1.6	1.7	2.0	2.2	2.3	2.3	3.0	3.3
Dysentery, all forms---045-048	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.4	0.6
Scarlet fever and streptococcal sore throat---050,051	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.2
Diphtheria---055	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1
Whooping cough---056	0.0	0.0	0.1	0.2	0.1	0.1	0.2	0.3	0.2	0.2
Meningococcal infections---057	0.3	0.3	0.4	0.4	0.4	0.5	0.5	0.6	0.6	0.8
Acute poliomyelitis---080	0.0	0.0	0.1	0.3	0.1	0.1	0.3	0.6	0.8	0.9
Measles---085	0.2	0.2	0.2	0.3	0.2	0.3	0.2	0.3	0.3	0.3
Other infective and parasitic diseases---030-044,049,052-054,058-074,081-084,086-139	3.1	3.1	3.2	3.1	3.2	2.8	2.7	2.6	2.7	2.7
Malignant neoplasms, including neoplasms of lymphatic and hematopoietic tissues---140-205	148.9	149.4	149.2	147.3	146.8	148.6	147.8	146.5	145.6	144.8
Malignant neoplasm of buccal cavity and pharynx---140-148	3.5	3.5	3.4	3.4	3.3	3.4	3.3	3.4	3.3	3.2
Malignant neoplasm of digestive organs and peritoneum, not specified as secondary---150-156A,157-159	49.5	50.1	50.8	50.7	50.9	51.7	52.4	52.3	53.0	53.4
Malignant neoplasm of respiratory system, not specified as secondary---160-164	24.0	23.1	22.2	21.2	20.4	19.9	19.2	18.2	17.1	16.7
Malignant neoplasm of breast---170	13.4	13.4	13.4	13.1	13.1	13.3	13.3	13.4	13.0	13.0
Malignant neoplasm of genital organs---171-179	21.3	21.4	21.6	21.6	22.1	22.6	22.6	22.8	22.9	22.9
Malignant neoplasm of urinary organs---180,181	7.2	7.1	7.1	7.1	7.0	7.1	7.0	7.0	6.9	6.9
Malignant neoplasm of other and unspecified sites---156B,165,190-199	16.6	16.4	16.5	16.2	16.1	16.7	16.3	16.4	16.5	16.3
Leukemia and aleukemia---204	7.0	7.0	7.1	7.0	6.9	6.9	6.8	6.6	6.5	6.3
Lymphosarcoma and other neoplasms of lymphatic and hematopoietic tissues---200-203,205	7.4	7.4	7.2	7.1	6.9	7.0	6.8	6.5	6.3	6.1
Benign neoplasms and neoplasms of unspecified nature---210-239	3.6	3.6	2.7	2.6	2.9	3.0	2.9	3.1	3.2	3.3
Asthma---241	3.6	2.7	3.0	2.6	2.9	3.9	3.6	3.6	3.8	4.3
Diabetes mellitus---260	16.8	16.4	16.7	15.8	15.9	16.0	15.6	15.5	15.6	16.3
Anemias---290-293	1.8	1.8	1.9	1.8	1.8	1.8	1.9	1.9	2.0	2.3
Meningitis, except meningococcal and tuberculous---340	1.2	1.2	1.3	1.3	1.3	1.2	1.2	1.1	1.1	1.3
Major cardiovascular-renal diseases---330-334,400-468,592-594	521.4	511.5	521.8	515.9	523.5	523.4	510.5	506.0	495.2	514.8
Diseases of cardiovascular system---330-334,400-466	515.2	505.1	515.1	508.9	515.5	514.6	501.4	496.3	484.6	503.0
Vascular lesions affecting central nervous system---330-334	106.3	108.4	109.0	108.4	110.1	110.2	108.3	106.0	104.1	107.3
Diseases of heart---400-402,410-443	370.3	362.4	369.0	363.2	367.6	369.4	361.0	356.5	348.3	361.4
Rheumatic fever and chronic rheumatic heart disease---400-402,410-416	9.6	9.8	10.3	10.4	10.8	11.8	12.0	12.0	12.1	13.3
Arteriosclerotic heart disease, including coronary disease---420	283.9	274.4	275.6	268.6	266.2	265.6	255.5	247.0	235.7	236.1
Nonrheumatic chronic endocarditis and other myocardial degeneration---421,422	29.4	29.8	31.8	31.8	33.8	36.8	37.7	39.9	41.0	46.3
Other diseases of heart---430-443	13.9	15.8	14.5	13.8	14.2	12.8	12.6	12.6	13.0	14.3
Hypertensive heart disease---440-443	35.3	34.6	37.0	36.6	42.7	42.5	43.3	45.0	46.6	51.3
Other hypertensive disease---444-447	6.7	6.7	7.1	7.4	8.0	8.5	8.5	8.8	7.1	7.8
General arteriosclerosis---450	19.8	19.3	20.0	19.6	19.9	19.5	19.1	19.8	18.9	20.4
Other diseases of circulatory system---451-469	12.2	11.3	11.0	10.3	9.9	9.0	8.4	7.3	6.4	6.0
Chronic and unspecified nephritis and other renal sclerosis---592-594	6.1	6.3	6.7	7.0	8.0	8.8	9.1	9.6	10.6	11.9
Influenza and pneumonia, except pneumonia of newborn---480-493	32.3	30.1	37.3	31.2	33.1	35.8	28.2	27.1	25.4	33.0
Influenza---480-483	1.8	1.2	4.4	1.6	2.6	4.4	1.4	1.7	1.7	6.0
Pneumonia, except pneumonia of newborn---490-493	30.4	29.0	32.9	29.6	30.6	31.4	26.8	25.4	23.8	27.0
Bronchitis---500-502	2.5	2.2	2.4	2.2	2.3	2.1	1.9	1.9	1.8	1.8
Other bronchopulmonic diseases---525-527	10.6	9.7	9.6	8.5	8.2	8.1	7.0	6.1	5.4	5.1
Ulcer of stomach and duodenum---540,541	6.6	6.3	6.3	6.0	6.2	6.1	6.0	5.9	5.8	5.8
Appendicitis---550-553	1.0	1.0	1.0	1.0	1.1	1.2	1.3	1.4	1.4	1.5
Hernia and intestinal obstruction---560,561,570	5.2	5.0	5.1	5.2	5.1	5.0	5.1	5.3	5.3	5.5
Gastritis, duodenitis, enteritis, and colitis, except diarrhea of newborn---543,571,572	4.4	4.3	4.4	4.4	4.5	4.7	4.5	4.7	4.9	5.4
Cirrhosis of liver---581	11.7	11.3	11.3	10.9	10.8	11.3	10.7	10.2	10.1	10.4
Cholelithiasis, cholecystitis, and cholangitis---534,585	2.6	2.6	2.6	2.5	2.7	2.9	3.1	3.6	3.5	3.5
Acute nephritis, and nephritis with edema including nephrosis---590,591	0.8	0.9	0.9	1.0	1.3	1.3	1.4	1.5	1.6	1.8
Infections of kidney---600	4.7	4.4	4.3	3.9	4.0	3.7	3.4	3.0	2.7	[illegible]
Hyperplasia of prostate---610	2.2	2.3	2.5	2.6	2.7	3.0	3.2	3.7	3.8	3.9
Deliveries and complications of pregnancy, childbirth, and the puerperium---640-689	0.8	0.9	0.9	0.9	0.9	1.0	1.0	1.2	1.3	1.5
Abortion---650-652	0.2	0.2	0.2	0.2	0.1	0.2	0.1	0.2	0.2	0.2
Other complications of pregnancy, childbirth, and the puerperium---640-649,660-689	0.6	0.7	0.7	0.7	0.8	0.9	0.9	1.0	1.1	1.3
Congenital malformations---750-759	11.4	12.0	12.2	12.5	12.4	12.8	12.6	12.[illegible]	12.5	12.6
Certain diseases of early infancy---760-776	34.6	35.9	37.4	38.5	39.8	39.1	38.6	39.0	38.4	40.1
Birth injuries, postnatal asphyxia, and atelectasis---760-762	15.2	15.6	16.6	17.1	18.2	17.8	17.7	17.8	17.8	17.9
Infections of newborn---763-768	2.1	2.6	2.7	2.9	3.2	3.0	2.8	2.6	2.7	2.6
Other diseases peculiar to early infancy, and immaturity unqualified---769-776	16.9	17.5	18.2	18.5	18.4	18.3	18.1	18.6	18.9	19.8
Symptoms, senility, and ill-defined conditions---780-795	10.6	10.4	11.4	10.8	11.4	11.2	11.3	12.1	12.5	13.7
All other diseases---Residual	28.1	28.2	29.0	28.8	28.4	26.9	25.9	25.7	25.7	27.1
Accidents---E800-E962	52.3	50.4	52.3	52.2	52.3	55.9	56.6	56.9	55.9	60.1
Motor vehicle accidents---E810-E835	22.0	20.9	21.3	21.5	21.3	22.7	23.7	23.4	22.1	24.0
Other accidents---E800-E802,E840-E962	30.3	29.6	31.0	30.7	30.9	33.2	33.0	33.5	33.8	36.1
Suicide---E963,E970-E979	10.9	10.4	10.6	10.6	10.7	9.8	10.0	10.2	10.1	10.1
Homicide---E964,E980-E985	4.9	4.7	4.7	4.6	4.5	4.5	4.6	4.5	4.8	4.8

11 times footnote

SECTION 1 · MORTALITY

Table 1-24. Deaths From 258 Selected Causes, by Color

(By place of residence. Data refer only to deaths occurring within the United States. Excludes fetal deaths. Numbers after causes of death are category numbers of the Seventh Revi- did not require reporting of the

CAUSE OF DEATH	UNITED STATES						
	Total			White		Nonwhite	
	Both sexes	Male	Female	Male	Female	Male	Female
ALL CAUSES	1,756,720	994,789	761,931	846,458	641,655	114,262	92,321
I. INFECTIVE AND PARASITIC DISEASES	19,774	12,838	6,936	9,355	4,910	3,082	1,809
TUBERCULOSIS, ALL FORMS 001-019	9,506	6,942	2,564	5,028	1,704	1,660	767
TUBERCULOSIS OF RESPIRATORY SYSTEM 001-008	8,792	6,531	2,261	4,792	1,552	1,504	635
TUBERCULOSIS OF MENINGES AND CENTRAL NERVOUS SYSTEM 010	225	119	106	71	53	43	47
TUBERCULOSIS OF INTESTINES, PERITONEUM, AND MESENTERIC GLANDS 011	51	32	19	16	7	16	12
TUBERCULOSIS OF BONES AND JOINTS 012,013	80	39	41	25	35	13	6
TUBERCULOSIS OF OTHER ORGANS AND SYSTEMS 014-018	143	83	60	62	37	16	17
DISSEMINATED TUBERCULOSIS 019	215	138	77	62	20	68	50
SYPHILIS AND ITS SEQUELAE 020-029	2,811	1,998	813	1,391	527	564	264
CONGENITAL SYPHILIS 020	50	32	18	14	11	16	7
EARLY SYPHILIS 021	1	1	-	-	-	1	-
ANEURYSM OF AORTA 022	1,440	1,019	421	811	315	181	93
OTHER CARDIOVASCULAR SYPHILIS 023	836	589	247	316	119	263	120
TABES DORSALIS 024	59	49	10	42	8	6	2
GENERAL PARALYSIS OF INSANE 025	145	107	38	79	25	28	13
OTHER SYPHILIS OF CENTRAL NERVOUS SYSTEM 026	222	167	55	110	32	55	23
ALL OTHER SYPHILIS 027-029	58	34	24	19	17	14	6
GONOCOCCAL INFECTION 030-035	23	20	3	9	-	11	3
TYPHOID FEVER 040	15	11	4	5	3	6	1
PARATYPHOID FEVER AND OTHER SALMONELLA INFECTIONS 041,042	62	36	26	25	18	11	8
CHOLERA 043	-	-	-	-	-	-	-
BRUCELLOSIS 044	12	9	3	7	3	2	-
DYSENTERY, ALL FORMS 045-048	323	183	140	114	79	68	61
FOOD POISONING, INFECTION AND INTOXICATION 049	39	18	21	13	13	4	8
SCARLET FEVER 050	10	4	6	3	5	1	1
STREPTOCOCCAL SORE THROAT 051	92	47	45	35	32	10	12
ERYSIPELAS 052	25	11	14	11	12	-	1
SEPTICEMIA AND PYEMIA 053	2,084	1,126	958	847	730	251	198
DIPHTHERIA 055	41	23	18	11	11	12	6
WHOOPING COUGH 056	83	45	38	21	13	24	25
MENINGOCOCCAL INFECTIONS 057	649	366	283	294	232	57	36
PLAGUE 058	-	-	-	-	-	-	-
LEPROSY 060	8	5	3	3	1	2	2
TETANUS 061	215	123	92	66	44	57	48
ANTHRAX 062	-	-	-	-	-	-	-
ACUTE POLIOMYELITIS 080	60	37	23	29	17	7	5
LATE EFFECTS OF ACUTE POLIOMYELITIS 081	123	57	66	51	60	4	6
ACUTE INFECTIOUS ENCEPHALITIS 082	582	283	299	235	238	38	48
LATE EFFECTS OF ACUTE INFECTIOUS ENCEPHALITIS 083	80	52	28	45	26	4	-
SMALLPOX 084	-	-	-	-	-	-	-
MEASLES 085	408	180	228	126	153	51	69
YELLOW FEVER 091	-	-	-	-	-	-	-
INFECTIOUS HEPATITIS 092	911	386	525	317	436	52	69
RABIES 094	1	1	-	1	-	-	-
TICK-BORNE TYPHUS 104	12	7	5	5	4	2	-
ALL OTHER RICKETTSIAL DISEASES 100-103,105-108	4	3	1	3	1	-	-
MALARIA 110-117	12	10	2	6	1	4	1
SCHISTOSOMIASIS 123	2	1	1	1	1	-	-
HYDATID DISEASE 125	7	4	3	3	3	1	-
FILARIASIS 127	1	1	-	1	-	-	-
ANCYLOSTOMIASIS 129	6	3	3	2	3	1	-
OTHER DISEASES DUE TO HELMINTHS 124,126,128,130	60	24	36	6	9	17	27
ALL OTHER INFECTIVE AND PARASITIC DISEASES RESIDUAL	1,507	822	685	641	531	161	143
II. NEOPLASMS	283,243	152,146	131,097	131,866	113,500	14,137	12,265
MALIGNANT NEOPLASMS, INCLUDING NEOPLASMS OF LYMPHATIC AND HEMATOPOIETIC TISSUES 140-205	278,562	150,009	128,553	130,050	111,449	13,884	11,856
MALIGNANT NEOPLASM OF BUCCAL CAVITY AND PHARYNX 140-148	6,481	4,920	1,561	4,253	1,350	455	145
OF LIP 140	219	199	20	189	17	5	1
OF TONGUE 141	1,552	1,181	371	1,015	329	91	25
OF OTHER AND UNSPEC. PARTS OF BUCCAL CAVITY 142-144	2,092	1,443	649	1,268	560	125	64
OF PHARYNX 145-148	2,618	2,097	521	1,781	444	234	55
MALIGNANT NEOPLASM OF DIGESTIVE ORGANS AND PERITONEUM, NOT SPECIFIED AS SECONDARY 150-156A,157-159	92,047	49,936	42,111	42,709	36,729	5,026	3,519
OF ESOPHAGUS 150	5,088	3,973	1,115	3,028	871	755	191
OF STOMACH 151	19,378	11,947	7,431	9,840	6,301	1,603	821
OF SMALL INTESTINE, INCLUDING DUODENUM 152	745	388	357	330	317	37	28
OF LARGE INTESTINE, EXCEPT RECTUM 153	29,837	13,561	16,276	12,019	14,501	884	1,030
CECUM, APPENDIX, AND ASCENDING COLON 153.0	4,264	1,812	2,452	1,609	2,205	97	141
TRANSVERSE COLON 153.1	1,608	745	863	661	763	45	44
DESCENDING COLON 153.2	1,256	533	723	467	652	42	41
SIGMOID COLON 153.3	6,188	3,000	3,188	2,677	2,863	161	156
MULTIPLE PARTS OF LARGE INTESTINE 153.7	74	37	37	32	36	1	-
LARGE INTESTINE, PART UNSPECIFIED 153.8	14,929	6,823	8,106	6,039	7,179	490	591
INTESTINAL TRACT, PART UNSPECIFIED 153.9	1,518	611	907	534	803	48	57
OF RECTUM 154	10,853	6,131	4,722	5,460	4,101	370	369
OF BILIARY PASSAGES AND OF LIVER, PRIMARY SITE 155	6,423	2,822	3,601	2,406	3,253	308	216
LIVER 155.0	2,145	1,384	761	1,119	656	215	82
OT. & MULT. SITES OF BILIARY PASSAGES 155.1,155.8	4,278	1,438	2,840	1,287	2,597	93	134
OF LIVER NOT STATED WHETHER PRIMARY OR SECONDARY 156A	2,958	1,533	1,425	1,283	1,205	190	153
OF PANCREAS 157	15,019	8,725	6,294	7,660	5,447	753	594
OF PERITONEUM AND OF UNSPEC. DIGESTIVE ORGANS 158,159	1,746	856	890	683	733	126	117

Table 1-24. Deaths From 258 Selected Causes, by Color

(By place of residence. Data refer only to deaths occurring within the United States. Excludes fetal deaths. Numbers after causes of death are category numbers of the Seventh Revi- did not require reporting of the

CAUSE OF DEATH	WEST VIRGINIA					WISCONSIN				
	Total	White		Nonwhite		Total	White		Nonwhite	
		Male	Female	Male	Female		Male	Female	Male	Female
ALL CAUSES	18,684	10,371	7,153	717	443	38,380	21,494	16,218	376	292
I. INFECTIVE AND PARASITIC DISEASES	247	146	68	25	8	256	142	99	9	6
TUBERCULOSIS, ALL FORMS 001-019	145	89	38	14	4	103	65	29	7	2
TUBERCULOSIS OF RESPIRATORY SYSTEM 001-008	138	86	35	13	4	87	57	24	5	1
TUBERCULOSIS OF MENINGES AND CENTRAL NERVOUS SYSTEM 010	6	2	3	1	-	2	-	-	2	-
TUBERCULOSIS OF INTESTINES, PERITONEUM, AND MESENTERIC GLANDS 011	-	-	-	-	-	1	1	-	-	-
TUBERCULOSIS OF BONES AND JOINTS 012,013	-	-	-	-	-	3	1	2	-	-
TUBERCULOSIS OF OTHER ORGANS AND SYSTEMS 014-018	-	-	-	-	-	7	4	3	-	-
DISSEMINATED TUBERCULOSIS 019	1	1	-	-	-	3	2	-	-	1
SYPHILIS AND ITS SEQUELAE 020-029	39	22	9	7	1	33	23	9	-	1
CONGENITAL SYPHILIS 020	-	-	-	-	-	-	-	-	-	-
EARLY SYPHILIS 021	-	-	-	-	-	-	-	-	-	-
ANEURYSM OF AORTA 022	22	15	6	1	-	16	12	4	-	-
OTHER CARDIOVASCULAR SYPHILIS 023	9	5	2	2	-	8	4	3	-	1
TABES DORSALIS 024	-	-	-	-	-	3	3	-	-	-
GENERAL PARALYSIS OF INSANE 025	2	-	-	2	-	3	2	1	-	-
OTHER SYPHILIS OF CENTRAL NERVOUS SYSTEM 026	4	2	-	1	1	3	2	1	-	-
ALL OTHER SYPHILIS 027-029	2	-	1	1	-	-	-	-	-	-
GONOCOCCAL INFECTION 030-035	1	-	-	1	-	1	-	-	-	1
TYPHOID FEVER 040	-	-	-	-	-	1	-	1	-	-
PARATYPHOID FEVER AND OTHER SALMONELLA INFECTIONS 041,042	-	-	-	-	-	-	-	-	-	-
CHOLERA 043	-	-	-	-	-	-	-	-	-	-
BRUCELLOSIS 044	-	-	-	-	-	1	1	-	-	-
DYSENTERY, ALL FORMS 045-048	1	1	-	-	-	-	-	-	-	-
FOOD POISONING, INFECTION AND INTOXICATION 049	1	1	-	-	-	-	-	-	-	-
SCARLET FEVER 050	1	-	1	-	-	-	-	-	-	-
STREPTOCOCCAL SORE THROAT 051	1	-	1	-	-	2	1	1	-	-
ERYSIPELAS 052	-	-	-	-	-	3	1	2	-	-
SEPTICEMIA AND PYEMIA 053	16	11	3	1	1	37	14	23	-	-
DIPHTHERIA 055	-	-	-	-	-	-	-	-	-	-
WHOOPING COUGH 056	-	-	-	-	-	3	1	1	1	-
MENINGOCOCCAL INFECTIONS 057	4	3	-	1	-	10	5	5	-	-
PLAGUE 058	-	-	-	-	-	-	-	-	-	-
LEPROSY 060	-	-	-	-	-	-	-	-	-	-
TETANUS 061	2	1	1	-	-	3	2	1	-	-
ANTHRAX 062	-	-	-	-	-	-	-	-	-	-
ACUTE POLIOMYELITIS 080	1	1	-	-	-	1	1	-	-	-
LATE EFFECTS OF ACUTE POLIOMYELITIS 081	-	-	-	-	-	3	1	2	-	-
ACUTE INFECTIOUS ENCEPHALITIS 082	7	2	3	1	1	16	7	9	-	-
LATE EFFECTS OF ACUTE INFECTIOUS ENCEPHALITIS 082	-	-	-	-	-	1	-	1	-	-
SMALLPOX 084	-	-	-	-	-	-	-	-	-	-
MEASLES 085	3	2	1	-	-	2	2	-	-	-
YELLOW FEVER 091	-	-	-	-	-	-	-	-	-	-
INFECTIOUS HEPATITIS 092	10	3	6	-	1	10	4	6	-	-
RABIES 094	-	-	-	-	-	-	-	-	-	-
TICK-BORNE TYPHUS 104	-	-	-	-	-	-	-	-	-	-
ALL OTHER RICKETTSIAL DISEASES 100-103,105-108	-	-	-	-	-	-	-	-	-	-
MALARIA 110-117	-	-	-	-	-	-	-	-	-	-
SCHISTOSOMIASIS 123	-	-	-	-	-	-	-	-	-	-
HYDATID DISEASE 125	-	-	-	-	-	1	-	1	-	-
FILARIASIS 127	-	-	-	-	-	-	-	-	-	-
ANCYLOSTOMIASIS 129	-	-	-	-	-	-	-	-	-	-
OTHER DISEASES DUE TO HELMINTHS 124,126,128,130	1	1	-	-	-	-	-	-	-	-
ALL OTHER INFECTIVE AND PARASITIC DISEASES RESIDUAL	14	9	5	-	-	25	14	8	1	2
II. NEOPLASMS	2,799	1,430	1,205	109	55	6,407	3,388	2,937	44	38
MALIGNANT NEOPLASMS, INCLUDING NEOPLASMS OF LYMPHATIC AND HEMATOPOIETIC TISSUES 140-205	2,749	1,412	1,176	108	53	6,319	3,350	2,891	42	36
MALIGNANT NEOPLASM OF BUCCAL CAVITY AND PHARYNX 140-148	47	27	15	4	1	139	114	24	1	-
OF LIP 140	2	2	-	-	-	8	7	1	-	-
OF TONGUE 141	8	6	2	-	-	36	32	4	-	-
OF OTHER AND UNSPEC. PARTS OF BUCCAL CAVITY 142-144	18	8	8	1	1	35	20	15	-	-
OF PHARYNX 145-148	19	11	5	3	-	60	55	4	1	-
MALIGNANT NEOPLASM OF DIGESTIVE ORGANS AND PERITONEUM, NOT SPECIFIED AS SECONDARY 150-156A,157-159	865	413	404	32	16	2,289	1,271	998	14	6
OF ESOPHAGUS 150	32	14	14	4	-	119	95	17	6	1
OF STOMACH 151	179	95	73	9	2	529	322	205	2	-
OF SMALL INTESTINE, INCLUDING DUODENUM 152	2	2	-	-	-	15	6	9	-	-
OF LARGE INTESTINE, EXCEPT RECTUM 153	253	104	138	6	5	770	386	380	3	1
CECUM, APPENDIX, AND ASCENDING COLON 153.0	31	14	17	-	-	116	53	63	-	-
TRANSVERSE COLON 153.1	13	5	8	-	-	38	23	14	1	-
DESCENDING COLON 153.2	11	6	5	-	-	36	14	22	-	-
SIGMOID COLON 153.3	37	12	24	1	-	195	100	95	-	-
MULTIPLE PARTS OF LARGE INTESTINE 153.7	-	-	-	-	-	1	1	-	-	-
LARGE INTESTINE, PART UNSPECIFIED 153.8	142	60	72	5	5	341	175	163	2	1
INTESTINAL TRACT, PART UNSPECIFIED 153.9	19	7	12	-	-	43	20	23	-	-
OF RECTUM 154	90	45	41	2	2	274	173	100	1	-
OF BILIARY PASSAGES AND OF LIVER, PRIMARY SITE 155	59	23	34	1	1	168	68	96	1	3
LIVER 155.0	13	6	6	-	1	48	29	17	1	1
OT. & MULT. SITES OF BILIARY PASSAGES 155.1,155.8	46	17	28	1	-	120	39	79	-	2
OF LIVER NOT STATED WHETHER PRIMARY OR SECONDARY 156A	68	25	38	2	3	68	25	41	1	1
OF PANCREAS 157	160	91	58	8	3	313	180	133	-	-
OF PERITONEUM AND OF UNSPEC. DIGESTIVE ORGANS 158,159	22	14	8	-	-	33	16	17	-	-

Exhibit 24

Atherosclerosis 241 (2015) 682–686

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Association of measles and mumps with cardiovascular disease: The Japan Collaborative Cohort (JACC) study

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ARTICLE INFO

Article history:
Received 24 January 2015
Received in revised form
25 March 2015
Accepted 9 June 2015
Available online 18 June 2015

Keywords:
Measles
Mumps
Atherosclerosis
Stroke
Myocardial infarction
Mortality
Immune system

ABSTRACT

Objective: Although it has been suggested that exposure to infections during childhood could decrease risk of atherosclerotic cardiovascular disease (CVD), the evidence is scarce. We investigated the association of measles and mumps with CVD.
Methods: 43,689 men and 60,147 women aged 40–79 years at baseline (1988–1990) completed a lifestyle questionnaire, including their history of measles and mumps, and were followed until 2009. Histories of infections were categorized as having no infection (reference), measles only, mumps only, or both infections. Hazard ratios (HR) for mortality from CVD across histories of infections were calculated.
Results: Men with measles only had multivariable HR (95% confidence interval) of 0.92 (0.85–0.99) for total CVD, those with mumps only had 0.52 (0.28–0.94) for total stroke and 0.21 (0.05–0.86) for hemorrhagic stroke, and those with both infections had 0.80 (0.71–0.90) for total CVD, 0.71 (0.53–0.93) for myocardial infarction, and 0.83 (0.69–0.98) for total stroke. Women with both infections had 0.83 (0.74–0.92) for total CVD and 0.84 (0.71–0.99) for total stroke. We also compared subjects with measles only or mumps only (reference) and those with both infections. Men with both infections had 0.88 (0.78–0.99) for total CVD. Women with both infections had 0.85 (0.76–0.94) for total CVD, 0.79 (0.67–0.93) for total stroke, 0.78 (0.62–0.98) for ischemic stroke and 0.78 (0.62–0.98) for hemorrhagic stroke.
Conclusions: Measles and mumps, especially in case of both infections, were associated with lower risks of mortality from atherosclerotic CVD.

1. Introduction

It has been suggested that infection can impact atherosclerotic cardiovascular disease (CVD) either deleteriously or positively [1]. The former proposes that inflammation caused by chronic infections with pathogens such as *Chlamydia pneumonia* and herpes simplex virus type I can accelerate atherosclerosis [1–6]. The latter suggests that infections suffered during childhood can protect from atherosclerosis [1]. The 'hygiene hypothesis' is a possible mechanism underlying this effect [1,7,8]. Improved hygiene decreases the opportunities for infections, which are necessary for normal development of the immune system. Weakened immune systems lead to decreased production, as well as inactivation, of regulatory T cells, which control the balance of T helper cell types, Th1 and Th2. As a result, inflammation at the arterial wall is not well controlled, leading to the development of atherosclerosis. Therefore, people with a history of infections may have a lower risk of CVD, especially atherosclerotic diseases such as stroke and myocardial infarction, compared to those without previous infections. However, to the best of our knowledge, only one previous study, which used a retrospective design and had a small number of participants, has suggested that viral or bacterial infections could protect against CVD [1].

To confirm the protective effect of infections against CVD, this study prospectively examined whether a history of measles and mumps, diseases typically seen in children, alters the risk of mortality from CVD before the era of measles, mumps, and rubella (MMR) vaccination [1,9].

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http://dx.doi.org/10.1016/j.atherosclerosis.2015.06.026
0021-9150/

2. Methods

2.1. Study population

The details of the Japan Collaborative Cohort (JACC) Study for Evaluation of Cancer Risks have been described previously [10]. Briefly, this study conducted a baseline survey from 1988 through 1990 in 45 areas in Japan. Participants completed self-administered questionnaires on their lifestyle and medical history with respect to previous CVD and cancer. The participants comprised 110,585 subjects (46,395 men and 64,190 women) aged 40–79 years. Participants were not vaccinated for measles and mumps, as the MMR vaccine was not introduced in Japan until 1989 [11]. This study excluded 6749 subjects (2706 men and 4043 women) due to missing information on their history of measles and mumps infections. Therefore, a total of 103,836 subjects (43,689 men and 60,147 women) were included in the study. The ethics committees of the Nagoya University School of Medicine and the Osaka University Graduate School of Medicine approved the present study.

2.2. Mortality surveillance

This study conducted systematic mortality surveillance by reviewing death certificates, which were transferred to their respective public health centers. After that, mortality data were gathered at the Ministry of Health and Welfare, where the underlying causes of death were coded for the National Vital Statistics according to the International Classification of Diseases. All deaths within the cohort were ascertained by death certificates from public health centers. Subjects who died after they had moved from their original community were treated as censored cases. The participants were followed up until the end of 2009. In addition to mortality from total CVD, follow-up endpoints included mortality from total stroke, ischemic stroke, hemorrhagic stroke, and myocardial infarction. Death from total CVD was defined as ICD-10 codes I00–I99, total stroke as I60–I69, ischemic stroke as I63 or I69.3, hemorrhagic stroke as I60–I62 or I69.0–I69.2, and myocardial infarction as I21–I23.

2.3. Main exposure: History of measles and mumps

Subjects were asked to provide information about their history of measles and mumps. Specifically, they were asked in the questionnaires, 'Have you ever had the following infectious diseases?: Measles, Mumps'. First, to examine the association of measles and mumps with CVD, participants were classified into the following four groups for comparison: those without a history of measles or mumps (reference group), those with a history of measles only, those with mumps only, and those with a history of both measles and mumps. In addition, to examine whether there is an additional decrease in risk by increased number of infections, we compared participants with a history of a single infection (measles only or mumps only) and those with a history of a double infection (both measles and mumps).

2.4. Potential confounding factors

Potential confounding factors were measured via self-reporting at baseline. They included age (years), body mass index (sex-specific quintiles), history of hypertension (yes or no), history of diabetes (yes or no), history of CVD (coronary heart disease and stroke), family history of CVD (yes or no), alcohol intake (never, ex-drinker, or current drinker with an ethanol intake of 1–22, 23–45, 46–48, or ≥69 g per day), smoking status (never, ex-smoker, or current smoker of 1–19 or ≥20 cigarettes per day), walking frequency (rarely, 30, 30–60, or ≥60 min per day), participation in sports (rarely, 1–2, 3–4, or ≥5 h per week), perceived mental stress (low, medium, or high), and education (elementary school, junior high school, high school, and college or higher).

2.5. Statistical analysis

The person-years of follow-up were calculated from the baseline in 1988–1990 to the first endpoint: death, moving from the community, or the end of follow-up. Multiplicative interactions with sex were tested using a cross-product term. Since there were statistically significant interactions between a history of infections and sex in relation to total stroke and hemorrhagic stroke, sex-specific analysis was conducted. Sex-specific mean values and the prevalence of selected factors were calculated and compared among the four groups using ANOVA and χ^2 tests, respectively. Sex-specific Kaplan–Meier's survival curves for men and women were constructed. Sex-specific hazard ratios (HRs) and their 95% confidence intervals (CIs) of mortality outcomes were calculated after adjustment for age and other potential confounding factors using Cox proportional hazard models. The proportional hazards assumption was tested and was not violated. SAS version 9.3 software (SAS Institute Inc., Cary, NC) was used for statistical analyses. All statistical tests were two-tailed, with values of $P < 0.05$ regarded as significant.

3. Results

Table 1 shows the baseline characteristics with respect to a history of measles or mumps. The higher the number of infections (no infection, measles only or mumps only, and both measles and mumps) in a participant's history was, the younger and less hypertensive both men and women were, the less often they took part in sports, and the higher education level they had. Compared with participants without a history of measles or mumps, those with a history of measles or mumps were more likely to have a family history of CVD and high perceived mental stress. In addition, as for men, the higher the number of infections was, the higher body mass index and the lower prevalence of a history of CVD they had. As for women, those with a history of infections were more likely to have a history of CVD than those without a history of infections.

During 1,690,123 person-years of follow-up of 103,836 subjects (43,689 men and 60,147 women), this study documented 7816 deaths from total CVD (4029 men and 3787 women), 3396 from total stroke (1729 men and 1667 women), 1955 from ischemic stroke (1062 men and 893 women), 1335 from hemorrhagic stroke (612 men and 723 women), and 1212 from myocardial infarction (694 men and 518 women).

Fig. 1 presents the survival curves for each category. The larger decline in survival rate was observed for both men and women without a history of infections than those with a history of infections. Table 2 shows sex-specific, age-adjusted, and multivariable HRs (95% CI) for cause-specific mortality according to infection history. In general, compared with participants without a history of infections, the hazard ratios of cause-specific mortality in those with a history of measles or mumps were likely to decrease. Men and women with measles or mumps displayed significantly lower risks (95% CI) than those without any infection after adjustment for potential confounding factors. It made no difference whether or not a history of CVD was included in potential confounding factors. Men with a history of measles only had hazard ratios of 0.92 (0.85–0.99) for total CVD, those with a history of mumps only had hazard ratios of 0.52 (0.28–0.94) for total stroke and 0.21 (0.05–0.86) for hemorrhagic stroke, and those with a history of both measles and mumps had hazard ratios of 0.80 (0.71–0.90) for

Table 1
Baseline characteristics according to history of Measles or Mumps infection.

History of measles or mumps infection	Men					Women				
	None	Measles only	Mumps only	Measles and mumps	P Value	None	Measles only	Mumps only	Measles and mumps	P Value
No. at risk	21,245	14,671	730	7043	–	24,950	21,202	1256	12,739	–
Age, years	58.7	57.7	54.0	53.0	<0.001	59.0	58.0	55.9	54.4	<0.001
Body mass index, kg/m^2	22.6	22.6	22.7	22.9	<0.001	22.9	23.0	22.9	22.9	0.419
History of hypertension, %	22.5	21.9	19.3	18.4	<0.001	24.2	23.9	23.1	20.6	<0.001
History of diabetes, %	7.4	6.5	7.9	6.0	<0.001	4.7	3.8	5.1	3.7	<0.001
History of cardiovascular disease, %	4.7	4.7	3.8	3.9	0.016	3.1	3.5	5.8	3.3	<0.001
Family history of cardiovascular disease, %	41.7	44.8	44.4	43.8	<0.001	41.6	45.0	44.2	45.6	<0.001
Ethanol intake, g/day	34.4	34.0	32.7	34.5	0.207	10.9	10.4	10.7	9.8	0.080
Current smoker, %	53.2	52.7	54.2	53.7	0.464	5.8	4.7	5.6	5.7	<0.001
Walking ≥1 h/day, %	47.7	50.5	45.6	49.6	<0.001	50.0	51.2	47.7	51.9	0.002
Sports ≥5 h/week, %	7.7	7.2	6.2	5.9	<0.001	5.3	4.7	4.0	3.6	<0.001
High perceived mental stress, %	20.0	21.5	34.5	30.2	<0.001	17.7	18.9	23.4	24.6	<0.001
College or higher education, %	15.8	16.8	21.6	22.2	<0.001	8.1	9.8	12.5	13.3	<0.001

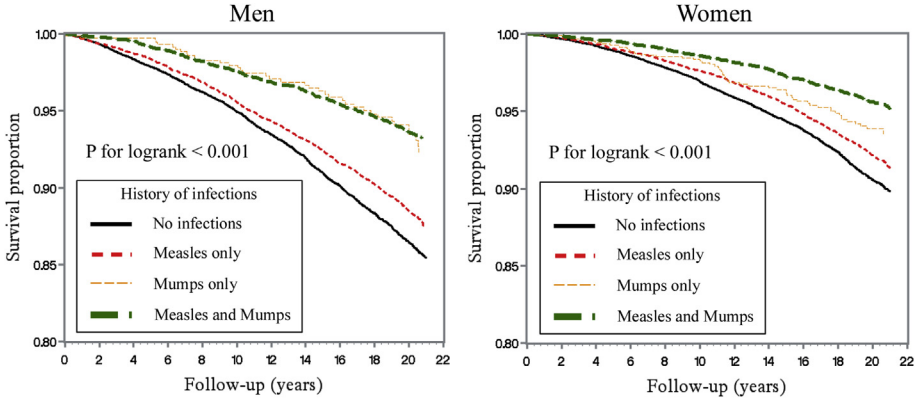

Fig. 1. Kaplan-Meire survival curves of mortality from total cardivascular disease according to the history of infections among men and women.

Table 2
Age-adjusted and multivariable hazard ratios (HR) and 95% Confidential Intervals (CI) for Cause-specific mortality according to history of measles or mumps.

History of measles or mumps	Men				Women			
	None	Measles only	Mumps only	Measles and mumps	None	Measles only	Mumps only	Measles and mumps
No. at risk	21,245	14,671	730	7043	24,950	21,202	1256	12,739
Person-years	326,940	236,327	11,802	116,443	411,090	358,358	19,963	209,207
Total stroke, n	946	613	11	159	803	640	31	193
Age-adjusted HR (95% CI)	1.00	0.97 (0.87–1.07)	0.52 (0.29–0.94)	0.83 (0.70–0.98)	1.00	1.07 (0.96–1.18)	1.24 (0.86–1.77)	0.85 (0.73–0.99)
Multivariable HR (95% CI)[a]	1.00	0.95 (0.85–1.06)	0.52 (0.29–0.94)	0.83 (0.70–0.99)	1.00	1.06 (0.95–1.19)	1.27 (0.88–1.82)	0.85 (0.72–0.99)
+ history of CVD[b]	1.00	0.95 (0.85–1.06)	0.52 (0.28–0.94)	0.83 (0.69–0.98)	1.00	1.06 (0.94–1.19)	1.22 (0.87–1.75)	0.84 (0.71–0.99)
Ischemic stroke, n	588	375	8	91	456	334	12	91
Age-adjusted HR (95% CI)	1.00	0.98 (0.86–1.11)	0.67 (0.33–1.35)	0.85 (0.68–1.06)	1.00	1.03 (0.89–1.18)	0.93 (0.52–1.64)	0.80 (0.64–1.00)
Multivariable HR (95% CI)[a]	1.00	0.98 (0.85–1.13)	0.70 (0.35–1.42)	0.88 (0.70–1.11)	1.00	1.05 (0.90–1.22)	0.98 (0.55–1.75)	0.81 (0.64–1.03)
+ history of CVD[b]	1.00	0.98 (0.85–1.13)	0.70 (0.35–1.41)	0.87 (0.69–1.10)	1.00	1.04 (0.89–1.22)	0.93 (0.52–1.65)	0.81 (0.64–1.02)
Hemorrhagic stroke, n	324	221	2	65	325	284	18	96
Age-adjusted HR (95% CI)	1.00	0.98 (0.82–1.16)	0.23 (0.06–0.93)	0.81 (0.62–1.06)	1.00	1.12 (0.95–1.31)	1.59 (0.99–2.55)	0.90 (0.71–1.13)
Multivariable HR (95% CI)[a]	1.00	0.91 (0.75–1.09)	0.21 (0.05–0.85)	0.76 (0.58–1.01)	1.00	1.08 (0.91–1.29)	1.58 (0.97–2.56)	0.86 (0.68–1.10)
+ history of CVD[b]	1.00	0.91 (0.75–1.09)	0.21 (0.05–0.86)	0.76 (0.57–1.00)	1.00	1.08 (0.90–1.29)	1.54 (0.95–2.49)	0.86 (0.67–1.09)
Myocardial infarction, n	378	248	5	63	275	171	8	64
Age-adjusted HR (95% CI)	1.00	0.96 (0.81–1.12)	0.54 (0.22–1.31)	0.74 (0.56–0.96)	1.00	0.85 (0.70–1.03)	0.97 (0.48–1.96)	0.85 (0.64–1.12)
Multivariable HR (95% CI)[a]	1.00	0.92 (0.77–1.09)	0.52 (0.22–1.27)	0.71 (0.54–0.94)	1.00	0.87 (0.71–1.08)	1.01 (0.50–2.06)	0.85 (0.63–1.13)
+ history of CVD[b]	1.00	0.92 (0.77–1.09)	0.52 (0.22–1.27)	0.71 (0.53–0.93)	1.00	0.87 (0.71–1.07)	0.99 (0.48–2.00)	0.84 (0.63–1.13)
Total cardiovascular disease, n	2243	1383	38	365	1913	1378	57	439
Age-adjusted HR (95% CI)	1.00	0.92 (0.86–0.99)	0.76 (0.55–1.04)	0.80 (0.71–0.89)	1.00	0.97 (0.91–1.05)	0.98 (0.75–1.27)	0.83 (0.75–0.92)
Multivariable HR (95% CI)[a]	1.00	0.92 (0.86–0.99)	0.75 (0.55–1.04)	0.81 (0.72–0.91)	1.00	0.98 (0.91–1.06)	1.01 (0.78–1.32)	0.83 (0.75–0.93)
+ history of CVD[b]	1.00	0.92 (0.85–0.99)	0.75 (0.54–1.04)	0.80 (0.71–0.90)	1.00	0.97 (0.90–1.05)	0.97 (0.75–1.27)	0.83 (0.74–0.92)

[a] Adjusted for age, body mass index, history of hypertension, history of diabetes, family history of CVD, alcohol intake, energy intake, smoking status, walking, sports, perceived mental stress and education.
[b] Further adjustment for history of CVD. CVD indicates cardiovascular disease.

total CVD, 0.83 (0.69–0.98) for total stroke, and 0.71 (0.53–0.93) for myocardial infarction. Women with a history of both measles and mumps had hazard ratios of 0.83 (0.74–0.92) for total CVD and 0.84 (0.71–0.99) for total stroke.

To examine whether there is an additional decrease in risk by increased number of infections, participants with a history of a single infection (measles only or mumps only) and those with a history of a double infection (both measles and mumps) were compared (Table 3). Both men and women with a history of a double infection were likely to have lower risks of mortality from most diseases than those with a history of a single infection. Men with a history of a double infection showed significantly higher risks of age-adjusted mortality from total CVD than those with a history of a single infection. After adjustment for potential confounding factors, the associations were still statistically significant. The respective multivariable hazard ratios (95% CI) were 0.88 (0.78–0.99) for total CVD. As for women, we observed, compared with women with a history of a single infection, those with a history of a double infection had decreased risks of age-adjusted mortality from total CVD, total stroke, ischemic stroke, and hemorrhagic stroke, respectively. Further adjustment for potential confounding factors did not alter the relations between the number of a history of infections and mortality risks. The multivariable hazard ratios (95% CI) were as follows: 0.85 (0.76–0.94) for total CVD; 0.79 (0.67–0.93) for total stroke; 0.78 (0.62–0.98) for ischemic stroke; 0.78 (0.62–0.98) for hemorrhagic stroke.

4. Discussion

This prospective cohort study of middle-aged Japanese men and women found the following two things. First, both subjects with a history of measles and those with a history of mumps had a lower risk of mortality from CVD than those without a history of infections. Second, a higher number of infections was associated with a lower risk of mortality from CVD. To the best of our knowledge, this is the first population-based cohort study to prospectively investigate the positive impact of infections on CVD in both men and women.

A history of infections decreased the risk of mortality from atherosclerotic CVD. A mechanism that may explain this is the induction of regulatory T cells following acquisition of infection, and suppression of inflammation in the arterial wall, which prevents the progression of atherosclerosis [1,7,8]. Measles and mumps infections demonstrated this protective effect in the current study. Although reports indicate that measles infection has an immunosuppressive effect [12] and induces regulatory T cells via its nucleoprotein [8], there are no similar effects reported for mumps. In addition, a previous study has suggested that other infectious diseases, such as varicella and scarlet fever, can decrease the risk of CVD; however, the study was retrospective and included only a small number of subjects [1]. Therefore, other infections could also have a protective effect against CVD, similar to the effect shown in this study for measles and mumps. However, chronic infections, such as *C. pneumonia* and herpes simplex virus type I, as well as common viral respiratory infections, are unlikely to be purveyors of a protective effect [2–6,13].

We observed that a higher number of infections was associated with a lower risk of mortality from CVD. This result can also be explained by the 'hygiene hypothesis'. The more opportunities for infections during childhood produce and activate more regulatory T cells, which leads to the suppression of atherosclerosis.

In the current study, men with a history of infections were less likely to have a history of CVD at baseline than those without a history of infections, which could support our major findings. On the other hand, women with a history of infections were more likely to have a history of CVD than those without a history of infections. This seems incompatible with our major findings. One possible explanation for this is that since before the baseline survey more women without a history of infections already died from CVD than those with a history of infections, those without a history of infections were less likely to have a history of CVD at baseline. Another possible explanation is information bias (misclassification) on the assessment of a history of CVD or infections. We found no significant interactions between a history of infections and a history of CVD in relation to any outcomes (data not shown), and obtained almost similar results of the adjusted models before and after including a history of CVD in confounding factors. In addition, even if some women with a history of CVD (women with a high risk of mortality from CVD) were misclassified into not a group without a history of infections (a group with a higher risk of mortality from CVD) but groups with a history of infections (groups with a lower risk of mortality from CVD), then the association between a history of infections and the risk of mortality from CVD would approach null. Therefore, we assume that the possible information biases on

Table 3
Age-adjusted and multivariable[a] Hazard Ratios (HR) and 95% Confidential Intervals (CI) for cause-specific mortality according to history of single vs. double infection.

History of measles or mumps	Men		Women	
	Single (measles only or mumps only)	Double (measles and mumps)	Single (measles only or mumps only)	Double (measles and mumps)
No. at risk	15,401	7043	22,458	12 739
Person-years	248,129	116,443	378,321	209 207
Total stroke, n	624	159	671	193
Age-adjusted HR (95% CI)	1.00	0.87 (0.73–1.04)	1.00	0.79 (0.68–0.93)
Multivariable HR (95% CI)	1.00	0.89 (0.74–1.06)	1.00	0.79 (0.67–0.93)
Ischemic stroke, n	383	91	346	91
Age-adjusted HR (95% CI)	1.00	0.88 (0.70–1.18)	1.00	0.78 (0.62–0.99)
Multivariable HR (95% CI)	1.00	0.90 (0.71–1.13)	1.00	0.78 (0.62–0.98)
Hemorrhagic stroke, n	223	65	302	96
Age-adjusted HR (95% CI)	1.00	0.85 (0.65–1.13)	1.00	0.79 (0.63–0.99)
Multivariable HR (95% CI)	1.00	0.86 (0.65–1.14)	1.00	0.78 (0.62–0.98)
Myocardial infarction, n	253	63	179	64
Age-adjusted HR (95% CI)	1.00	0.78 (0.59–1.03)	1.00	0.99 (0.75–1.32)
Multivariable HR (95% CI)	1.00	0.78 (0.59–1.03)	1.00	0.96 (0.72–1.28)
Total cardiovascular disease, n	1421	365	1435	439
Age-adjusted HR (95% CI)	1.00	0.87 (0.78–0.98)	1.00	0.85 (0.77–0.95)
Multivariable HR (95% CI)	1.00	0.88 (0.78–0.99)	1.00	0.85 (0.76–0.94)

[a] Adjusted for age, body mass index, history of hypertension, history of diabetes, history of cardiovascular disease, family history of cardiovascular diseases, alcohol intake, energy intake, smoking status, walking, sports, perceived mental stress and education.

the assessment of a history of CVD or infections did not have enough influence to change the results.

Together with previous research [8,14], this study demonstrates the importance of the immune system's impact on CVD. Stimulation of immune function, as in vaccination, may be a novel treatment for CVD in the future, though whether conventional vaccinations have enough power to induce regulatory T cells is unclear.

Strengths of this study include its prospective design, long follow-up duration, and the inclusion of a large number of participants. In addition, setting not only total CVD but also cause-specific mortality as endpoints were useful for understanding the impact of infections on CVD.

Some limitations need to be addressed. Firstly, the assessment of measles and mumps infections was based on self-reporting. However, measles and mumps were significant problems in the era before MMR vaccination in Japan, meaning that these diseases were likely to be accurately recalled. Although we cannot negate such information biases as mentioned above, this study assumes that those biases did not significantly influence the results. Secondly, the study did not obtain information on the age that participants suffered from measles or mumps infections. However, the majority had measles or mumps during their childhood, in the era before MMR vaccination [1,9]. Thirdly, this study only examined exposure to measles and mumps infections, although other infections may have unknown influences on the risk of mortality from CVD. Despite this possibility, the fact remains that the more infections people acquire during childhood, the lower their risk of mortality from CVD, possibly due to the induction of regulatory T cells. Finally, this study used mortality data as endpoints, which may have led to misclassifications in the diagnosis of CVD. However, previous validation studies confirm the validity of using death certificate diagnoses for these outcomes due to the widespread use of computed tomography, magnetic resonance imaging, electrocardiography, and cardiac enzyme examinations [15,16].

In conclusion, measles and mumps infections were associated with decreased risks of mortality from CVD. In addition, people with a history of more infections were likely to have lower risks of mortality from CVD. Further studies are needed to assess whether other infections seen typically during childhood have similar associations with mortality from CVD.

Conflict of interest

All authors have no conflict of interest or financial disclosures to declare.

Funding sources

This study was supported by the Ministry of Education, Science, Sports and Culture of Japan (Monbusho) to the Japanese Ministry of Education, Culture, Sports, Science, and Technology (Monbukagaku-sho) in 2001, the grant numbers 61010076, 62010074, 63010074, 1010068, 2151065, 3151064, 4151063, 5151069, 6279102, 11181101, 17015022, 18014011, 20014026, and 20390156.

Acknowledgments

We thank all staff members involved in this study for their valuable help in conducting the baseline survey and follow-up.

References

[1] E. Pesonen, E. Andsberg, H. Ohlin, M. Puolakkainen, H. Rautelin, S. Sarna, et al., Dual role of infections as risk factors for coronary heart disease, Atherosclerosis 192 (2007) 370–375.
[2] M. Roivainen, G. Alfthan, P. Jousilahti, M. Kimpimäki, T. Hovi, J. Tuomilehto, Enterovirus infections as a possible risk factor for myocardial infarction, Circulation 98 (1998) 2534–2537.
[3] D.S. Siscovick, S.M. Schwartz, L. Corey, J.T. Grayston, R. Ashley, S.P. Wang, et al., Chlamydia pneumoniae, herpes simplex virus type 1, and cytomegalovirus and incident myocardial infarction and coronary heart disease death in older adults: the cardiovascular health Study, Circulation 102 (2000) 2335–2340.
[4] M. Roivainen, M. Viik-Kajander, T. Palosuo, P. Toivanen, M. Leinonen, et al., Infections, inflammation, and the risk of coronary heart disease, Circulation 101 (2000) 252–257.
[5] M. Mayr, S. Kiechl, J. Willeit, G. Wick, Q. Xu, Infections, immunity, and atherosclerosis: associations of antibodies to Chlamydia pneumoniae, Helicobacter pylori, and cytomegalovirus with immune reactions to heat-shock protein 60 and carotid or femoral atherosclerosis, Circulation 102 (2000) 833–839.
[6] J. Zhu, F.J. Nieto, B.D. Horne, J.L. Anderson, J.B. Muhlestein, S.E. Epstein, Prospective study of pathogen burden and risk of myocardial infarction or death, Circulation 103 (2001) 45–51.
[7] G.A. Rook, 99th Dahlem conference on infection, inflammation and chronic inflammatory disorders: Darwinian medicine and the 'hygiene' or 'old friends' hypothesis, Clin. Exp. Immunol. 160 (2010) 70–79.
[8] H. Ait-Oufella, B. Horvat, Y. Kerdiles, O. Herbin, P. Gourdy, J. Khallou-Laschet, et al., Measles virus nucleoprotein induces a regulatory immune response and reduces atherosclerosis in mice, Circulation 116 (2007) 1707–1713.
[9] R.M. Anderson, R.M. May, Age-related changes in the rate of disease transmission: implications for the design of vaccination programmes, J. Hyg. (Lond) 94 (1985) 365–436.
[10] A. Tamakoshi, K. Ozasa, Y. Fujino, K. Suzuki, K. Sakata, M. Mori, et al., Cohort profile of the Japan collaborative cohort study at final follow-up, J. Epidemiol. 23 (2013) 227–232.
[11] S. Isomura, Measles and measles vaccine in Japan, Nagoya J. Med. Sci. 55 (1993) 23–32.
[12] J.F. Bach, The effect of infections on susceptibility to autoimmune and allergic diseases, N. Engl. J. Med. 347 (2002) 911–920.
[13] B.B. Nafstad Per, A. Skrondal, W. Nystad, Early respiratory infections, asthma, and allergy: 10-year follow-up of the Oslo birth cohort, Pediatrics 116 (2005) 255–262.
[14] N. Sasaki, T. Yamashita, M. Takeda, M. Shinohara, K. Nakajima, H. Tawa, et al., Oral anti-CD3 antibody treatment induces regulatory T cells and inhibits the development of atherosclerosis in mice, Circulation 120 (2009) 1996–2005.
[15] Y. Kita, A. Okayama, H. Ueshima, M. Wada, A. Nozaki, S.R. Choudhury, et al., Stroke incidence and case fatality in Shiga, Japan 1989-1993, Int. J. Epidemiol. 28 (1999) 1059–1065.
[16] S. Baba, H. Ozawa, Y. Sakai, A. Terao, M. Konishi, K. Tatara, Heart disease deaths in a Japanese urban area evaluated by clinical and police records, Circulation 89 (1994) 109–115.

Exhibit 25

West Virginia Immunization Requirements for New School Enterers

State law and rules[1] require that all children entering school in West Virginia for the first time in grades K-12 must show proof of immunization against diphtheria, pertussis, tetanus, polio, measles, mumps, rubella, varicella, and hepatitis B unless properly medically exempted[2]. The table below outlines immunization requirements as most commonly met.[3] The West Virginia Bureau for Public Health recommends that vaccine doses administered 4 days or fewer before the minimum interval or age should be considered valid.

Vaccine	Requirements	Provisional Enrollment	Additional Information
DTaP/DTP Td/Tdap	Before admission, four doses required. One dose must be after the 4th birthday.	After one dose, student may be allowed up 8 months to complete the series if necessitated by the minimum intervals of the vaccine schedule.	• Three doses only for children completing primary series at age 7 years and older. • Children exempted from the pertussis component of DTaP vaccine should receive DT vaccine instead, or if past 7th birthday, Td / Tdap vaccine, as applicable.
Polio (IPV)	Before admission, three doses required. One dose must be after the 4th birthday.	After one dose, student may be allowed up 7 months to complete the series if necessitated by the minimum intervals of the vaccine schedule.	• If polio immunization series included both OPV and IPV, then a total 3 of 4 doses are required depending upon the age of the child.
Measles, Mumps & Rubella (MMR)	Before admission, two doses required. First dose must be after the 1st birthday.	After one dose, student may be allowed up to 30 days to complete the series.	• Doses should be a minimum of 28 days apart.
Varicella	Before admission, two doses required. First dose must be after the 1st birthday.	After one dose, children **less than 13 years of age** may be allowed up to 90 days to obtain 2nd dose; children aged **13 years and older** may be allowed up to 30 days to obtain the 2nd dose.	• Children less than 13 years of age are recommended to have an interval of 12 weeks between the 1st and 2nd doses, **however**, an interval of at least 4 weeks is acceptable. • Children aged 13 years and older may receive the 2nd dose 28 days after the first dose. • Immunity may also be demonstrated through the legal guardian's written or verbal attestation of varicella (chickenpox) disease.
Hepatitis B	Before admission, three doses required. Last dose must be after the age of 6 months.	After one dose, student may be allowed up to 4 months to complete the series if necessitated by the minimum intervals of the vaccine schedule.	• Final dose is not valid if administered before 24 weeks / 6 months of age.

[1] See WV Code §16-3-4 and 64CSR95 for further information.
[2] Medical exemptions must be requested by a physician who has treated or examined the child and be reviewed and submitted to the Immunization Officer of the Bureau for Public Health. Requests for exemptions must be based on current standards of immunization practice and include the following information: the vaccine(s) being exempted, the specific medical reason for the exemption, whether the exemption is temporary or permanent, and, if temporary, when the exemption should be reevaluated. West Virginia State Law does not allow for non-medical exemptions to immunization requirements.
[3] Occasionally, based on product used or the age at which a child is being immunized, deviations from these requirements may be acceptable. Any deviation must be consistent with applicable, age appropriate immunization schedules found at http://www.cdc.gov and searching under "Immunization Schedules".

WEST VIRGINIA Department of Health & Human Resources

Rev 04/22

West Virginia Immunization Requirements for 7th & 12th Graders

Beginning in 2012-2013, state law and rules[1] require that all children entering school in West Virginia in grades 7 and 12 must show proof of immunization against diphtheria, pertussis, tetanus, and meningococcal disease unless properly medically exempted[2]. The table below outlines immunization requirements as most commonly met.[3]
The West Virginia Bureau for Public Health recommends that vaccine doses administered 4 days or fewer before the minimum interval or age should be considered valid.

7th Grade School Entry Requirement

Vaccine	Requirement	Provisional Enrollment	Additional Information
Tdap (tetanus, diphtheria, acellular pertussis)	Proof of one dose of Tdap vaccine	No provisional enrollment permitted	
MCV4 (meningococcal / meningitis)	Proof of 1st dose of MCV4 vaccine	No provisional enrollment permitted	

12th Grade School Entry Requirement

Vaccine	Requirement	Provisional Enrollment	Additional Information
Tdap (tetanus, diphtheria, acellular pertussis)	Proof **of one dose only** of Tdap vaccine	No provisional enrollment permitted	This is not a requirement for a 2nd dose of Tdap.
MCV4 (meningococcal /meningitis)	Proof of 2st dose of MCV4 vaccine if indicated. **(See additional information)**	No provisional enrollment permitted	**Second dose of MCV4 is indicated if first dose was received before the 16th birthday**

1 See WV Code §16-3-4 and 64CSR95 for further information.
2 Medical exemptions must be requested by a physician who has treated or examined the child and be reviewed and approved by the local health officer in the county in which the child attends school. Requests for exemptions must be based on current standards of immunization practice and include the following information: the vaccine(s) being exempted, the specific medical reason for the exemption, whether the exemption is temporary or permanent, and, if temporary, when the exemption should be reevaluated. West Virginia State Law does not allow for non-medical exemptions to immunization requirements.
3 Occasionally, based on product used or the age at which a child is being immunized, deviations from these requirements may be acceptable. Any deviation must be consistent with applicable, age appropriate immunization schedules found at http://www.cdc.gov and searching under "Immunization Schedules".

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