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Vaccine Safety in the United States: Overview and Considerations for COVID-19 Vaccines

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SUMMARY

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Vaccine Safety in the United States: Overview and Considerations for COVID-19 Vaccines

Widespread immunization efforts have been linked to increased life expectancy and reduced illness. U.S. vaccination programs, headed by the Centers for Disease Control and Prevention (CDC) within the Department of Health and Human Services (HHS), have helped eradicate smallpox and nearly eradicate polio globally, and eliminate several infectious diseases domestically. With the Coronavirus Disease 2019 (COVID-19) pandemic now causing major health and economic impacts across the world, efforts have been underway to make safe and effective vaccines available quickly to help curb spread of the virus. As of the date of this report, there are two COVID-19 vaccines authorized for emergency use by the U.S. Food and Drug Administration (FDA) and recommended by the CDC. Additional vaccines may receive authorization within months.

Background

Federal regulation of vaccine safety began with the Biologics Control Act of 1902, which was the first federal law to require premarket review of pharmaceutical products. Since the 1902 law was enacted, federal vaccine safety activities have expanded, with the aim of minimizing the possibility of adverse events following vaccination and detecting new adverse events as quickly as possible. Today, as covered in this report, federal efforts to ensure vaccine safety include the following activities:

- **Premarket requirements:** Clinical trials, or testing of investigational vaccines in human subjects, and U.S. FDA licensure or authorization.
- **Clinical recommendations:** Recommendations for the clinical use of vaccines by the Advisory Committee on Immunization Practices (ACIP), and CDC clinical guidance and resources.
- **Postmarket safety:** Manufacturing requirements and ongoing safety monitoring and studies of vaccines administered to patients.
- **Federal research on vaccine safety:** Ongoing research to inform a better scientific understanding of vaccine safety and comprehensive scientific reviews on the safety of vaccines in use.
- **Vaccine injury compensation:** The National Vaccine Injury Compensation Program (VICP) provides compensation to eligible individuals found to have been injured by a covered vaccine. In emergency circumstances, such as the COVID-19 pandemic, a separate Countermeasures Injury Compensation Program (CICP) may be used.
- **Vaccine distribution:** Programs and requirements to ensure safety controls in vaccine distribution programs, led by CDC.

COVID-19 Vaccine Safety

COVID-19 vaccines currently authorized for use under Emergency Use Authorization (EUA), specifically those of Pfizer-BioNTech and Moderna, have been determined to meet the safety and effectiveness standards for EUA issuance set forth in statute and by FDA in guidance. The safety and effectiveness data have been reviewed not only by FDA scientists, but also nonfederal scientists and experts of FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) and CDC's ACIP, both of which have recommended the vaccines for use among certain age groups and populations. ACIP has also issued recommendations for priority populations to receive the initial vaccine doses while supply is limited, adopted as official CDC recommendations. Federal agencies continue to assess the safety of vaccines available under EUAs, particularly to detect long-term and rare adverse health events, as well as safety in populations excluded from the initial clinical trials (e.g., children, pregnant individuals) through various postmarket activities. Efforts and requirements are also in place to maintain safety of vaccines distributed and administered to patients.

Congressional Considerations

Ever since the Biologics Control Act of 1902, Congress and the federal agencies (especially FDA and CDC) have strived to ensure the safety of vaccines in the United States—from initial development to patient administration. Congress may consider how to best leverage existing requirements and programs to ensure that risk of harm from COVID-19 vaccines is mitigated and minimized. Federal agencies, pharmaceutical and biotech companies, and others have worked to expedite the

availability of COVID-19 vaccines and to implement a nationwide immunization campaign while balancing a need for safety. Congress may consider how to best provide oversight and make legislative changes to ensure a safe and successful COVID-19 vaccination campaign. In addition, Congress may consider and evaluate the entire federal vaccine safety system and assess whether this system warrants any policy changes to help ensure ongoing safety of all recommended vaccines.

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Introduction

Widespread immunization efforts have been linked to increased life expectancy and reduced illness.[1] In 1900, for every 1,000 babies born in the United States, 100 would die before their first birthday, often due to infectious diseases.[2] One study estimated that from 1993 to 2013, routine childhood immunization in the United States helped prevent 322 million illnesses, 21 million hospitalizations, and 732,000 premature deaths.[3] U.S. immunization programs, headed by the Centers for Disease Control and Prevention (CDC) within the Department of Health and Human Services (HHS), have helped eradicate smallpox and nearly eradicate polio globally.[4] U.S. immunization programs have also helped eliminate measles and rubella domestically, and have led to substantial reductions in hospitalizations linked to pneumococcus, rotavirus, and varicella (i.e., chickenpox).[5]

With the Coronavirus Disease 2019 (COVID-19) pandemic causing major health and economic impacts across the world, efforts have been underway to make safe and effective vaccines available quickly to help curb spread of the virus. Currently, several COVID-19 vaccines, including those of Pfizer-BioNTech and Moderna, are available under U.S. Food and Drug Administration (FDA) Emergency Use Authorizations (EUAs).

Available evidence from thousands of scientific studies shows that currently recommended vaccines are largely safe. At a population level, widespread vaccination with recommended vaccines is safer than the spread of the infectious diseases they prevent.[6] Adverse health events for which available scientific evidence shows a causal relationship with currently recommended vaccines are rare—ranging from 1 case per million doses administered (e.g., encephalitis caused by the pertussis vaccine) to 333 cases per million doses (e.g., febrile seizures caused by the measles-mumps-rubella; MMR vaccine).[7]

Undervaccination linked to concerns about vaccine safety has been an issue in recent years. U.S. outbreaks of measles in 2019—the highest number of annual measles cases since 1992—were

[1] Walter A. Orenstein and Rafi Ahmed, "Simply Put: Vaccination Saves Lives," *Proceedings of the National Academy of Sciences*, vol. 114, no. 16 (April 10, 2017).

[2] Institute of Medicine (now National Academy of Medicine), *Adverse Effects of Vaccines: Evidence and Causality*, Washington, DC, August 25, 2011, https://www.ncbi.nlm.nih.gov/books/NBK190024/.

[3] Cynthia G. Whitney, Fangjun Zhou, James Singleton et al., "Benefits from Immunization during the Vaccines for Children Program Era—United States, 1994–2013," *Morbidity and Mortality Weekly Report*, vol. 63, no. 16 (April 25, 2014), pp. 352-355.

[4] Eric E. Mast, Stephen L. Cochi, Olen M. Kew et al., "Fifty Years of Global Immunization at CDC, 1966-2015," *Public Health Reports*, vol. 132, no. 1 (Jan-Feb 2017), pp. 18-26.

[5] Pneumococcus is the most common form of bacteria that causes severe pneumonia. Rotaviruses are a genus of viruses that cause a large portion of severe diarrhea cases. Varicella is the scientific name for "chickenpox" disease. See Amanda Cohn, Lance E. Rodewald, Walter A. Orenstein et al., "Immunization in the United States," in *Plotkin's Vaccines*, ed. Stanley A. Plotkin, Walter A. Orenstein, and Paul A. Offit, 7th ed. (Elsevier, 2017), p. 1436.

[6] Margaret A. Maglione, Courtney Gidengil, Lopamudra Das et al. "Safety of Vaccines Used for Routine Immunization in the United States," *Agency for Healthcare Research and Quality*, July 2014, https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/vaccine-safety_research.pdf, and Institute of Medicine (now National Academy of Medicine), *Adverse Effects of Vaccines: Evidence and Causality*, Washington, DC, August 25, 2012, https://www.ncbi.nlm.nih.gov/books/NBK190010/#sec_0009.

[7] Frank DeStefano, Paul A. Offit, and Allison Fisher, Ch. 82, "Vaccine Safety," in *Vaccines*, ed. Stanley A. Plotkin, Walter A. Orenstein, Paul A. Offit et. al. 67h ed. (Elsevier, 2017), pp. 1584-1600.

driven in part by geographic clusters with low vaccination rates for the MMR vaccine.[8] U.S. surveys show that concerns about vaccine safety are a top reason for vaccine delays or refusals.[9]

From a public health perspective, vaccines for infectious diseases often work by helping provide *herd immunity*, meaning that enough of the population has vaccine-induced immunity against the target disease to curb ongoing transmission and protect those who cannot receive vaccines (e.g., persons with compromised immune systems).[10] Widespread vaccination can help with achieving *elimination* or *eradication* of a given disease (see **text box**). To effectively prevent disease spread, many vaccines must be administered to a large segment of the population. Public health practice generally aims for near 100% vaccination rates among populations recommended to receive vaccines, though the level required for herd immunity is generally lower and can vary by vaccine and population (75%-95% of the population).[11] Nonetheless, widespread vaccination that does not meet target rates can aid in significantly curbing disease spread.[12]

Vaccines are often held to a higher safety standard than most other medical products for many reasons. For one, vaccines are often administered to healthy individuals to prevent disease; therefore, the expectation is that such individuals will remain healthy following vaccination. In addition, vaccines are often administered to vulnerable populations, including infants and pregnant people. Also, since vaccines are often mandated by state and sometimes federal law for certain groups (e.g., school children and military service members), the government has an interest in ensuring that vaccines are as safe as possible. Because vaccines are often administered to a large segment of the population, even a rare risk of adverse reactions to a vaccine could affect a sizeable number of people.[13]

Definitions: Elimination and Eradication

The World Health Organization (WHO) defines disease elimination and eradication as follows:

Elimination (or interruption) of transmission: Reduction to zero of the incidence of infection caused by a specific pathogen in a defined geographical area, with minimal risk of reintroduction, as a result of deliberate efforts; continued actions to prevent reestablishment of transmission may be required.

Eradication: Permanent reduction to zero of a specific pathogen, as a result of deliberate efforts, with no more risk of reintroduction.

Source: WHO, "Generic Framework for the Control, Elimination, and Eradication of Neglected Tropical Diseases," 2015, https://www.who.int/neglected_diseases/resources/NTD_Generic_Framework_2015.pdf.

FDA has issued EUAs for several COVID-19 vaccines, including those of Pfizer-BioNTech and Moderna, determining that they may be effective in preventing COVID-19, and that their known and potential benefits outweigh their known and potential risks.[14] This is consistent with the

[8] CDC, "Measles Cases and Outbreaks," last updated August 2020, https://www.cdc.gov/measles/cases-outbreaks.html.

[9] CRS Insight IN11125, *Measles Outbreaks, Vaccine Hesitancy, and Federal Policy Options*, and Amanda Cohn, Lance E. Rodewald, Walter A. Orenstein et al., "Immunization in the United States," in *Plotkin's Vaccines*, ed. Stanley A. Plotkin, Walter A. Orenstein, and Paul A. Offit, 7th ed. (Elsevier, 2017), p. 1432.

[10] Paul Fine, Ken Eames, and David L. Heymann, "''Herd Immunity'': A Rough Guide," *Vaccines*, vol. 52 (2011).

[11] Ibid., and Pedro Plans-Rubió, "Evaluation of the Establishment of Herd Immunity in the Population by Means of Serological Surveys and Vaccination Coverage," *Human Vaccines & Immunotherapeutics*. vol. 8, no. 2 (February 2012), pp. 184-88.

[12] Paul Fine, Ken Eames, and David L. Heymann, "''Herd Immunity'': A Rough Guide," *Vaccines*, vol. 52 (2011).

[13] Frank DeStefano, Paul A. Offit, and Allison Fisher, "Vaccine Safety," in *Vaccines*, ed. Stanley A. Plotkin, Walter A. Orenstein, Paul A. Offit et al. 67h ed. (Elsevier, 2017), pp. 1584-1600, and Matthew Z. Dudley, Daniel A. Salmon, Neal A. Halsey et al., "Monitoring Vaccine Safety," in *The Clinician's Vaccine Safety Resource Guide* (Springer, Cham, 2018).

[14] FDA, *Emergency Use Authorization (EUA) for an Unapproved Product- Pfizer, Inc. on behalf of Pfizer and BioNTech*, December 11, 2020, https://www.fda.gov/media/144416/download; and FDA, *Emergency Use*

statutory standard for EUA issuance (see the section "Emergency Use Authorization (EUA)"), as well as the safety and effectiveness standards set forth by FDA in guidance.[15] The safety and effectiveness data have been reviewed not only by FDA scientists, but also by nonfederal scientists and experts on the FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) and CDC's Advisory Committee on Immunization Practices (ACIP). The majority of experts on these advisory committees have recommended the vaccines for emergency use among certain age groups and populations—adults 16 years of age and older for Pfizer-BioNTech's vaccine and adults 18 years of age and older for Moderna's vaccine.[16] ACIP has also issued recommendations for priority populations to receive the initial vaccine doses while supply is limited—these recommendations have been adopted as official CDC recommendations.[17] Federal agencies and vaccine manufacturers continue to assess the safety of vaccines available under EUA, particularly to detect long-term and rare adverse health events, as well as their safety in populations excluded from the initial clinical trials (e.g., pregnant individuals) through various postmarket activities, as discussed in this report. Efforts and requirements are also in place to maintain safety of vaccines distributed and administered to patients.

Scope of This Report

This report provides an overview of the federal government's role in ensuring safety of vaccines for infectious diseases. Specifically, this report

- describes federal statutory and regulatory requirements and administrative functions governing vaccine licensure or authorization (including pre- and post-market safety), development of clinical recommendations, and vaccine injury compensation;
- summarizes ongoing federal activities related to vaccine post-market safety (e.g., ongoing safety monitoring and research), as well as safety assurances in federal vaccine distribution programs; and
- discusses safety considerations in the context of developing and making available vaccine(s) for COVID-19, discussed in "Safety Considerations for COVID-19 Vaccines."

This report does not provide a comprehensive scientific review on the safety of existing vaccines, nor does it specifically address vaccines for noninfectious diseases (e.g., cancer). Discussions of

Authorization (EUA) for an Unapproved Product- ModernaTx, Inc, December 18, 2020, https://www.fda.gov/media/144673/download.

[15] FDA, "Emergency Use Authorization for Vaccines to Prevent COVID-19," Guidance for Industry, October 2020, https://www.fda.gov/media/142749/download.

[16] FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC), "2020 Meeting Materials, Vaccines and Related Biological Products Advisory Committee," https://www.fda.gov/advisory-committees/vaccines-and-related-biological-products-advisory-committee/2020-meeting-materials-vaccines-and-related-biological-products-advisory-committee; Sara E. Oliver, Julia W. Gargano, Mona Marin et al., "The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Moderna COVID-19 Vaccine—United States, December 2020," *Morbidity and Mortality Weekly Report (MMWR)*, vol. 69, no. 5152 (January 1, 2021), pp. 1653-56; and Sara E. Oliver, Julia W. Gargano, Mona Marin et al., "The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine—United States, December 2020," *Mortality and Morbidity Weekly Report*, vol. 69, no. 50 (December 18, 2020), pp. 1922-24.

[17] See for example, Kathleen Dooling, Mona Marin, Megan Wallace et al., "The Advisory Committee on Immunization Practices' Updated Interim Recommendation for Allocation of COVID-19 Vaccine—United States, December 2020," *Morbidity and Mortality Weekly Report*, vol. 69, no. 5152 (January 1, 2021), pp. 1657-60.

payment and coverage for vaccines and related health care services, and logistical implementation of the vaccine distribution program, are outside the scope of this report.

What Is a Vaccine?

A vaccine is a biological preparation that contains small amounts of weak, dead, or modified disease-causing agents known as *antigens*, which can include viruses, bacteria, fractions of these agents, or the toxins they produce.[18] The new messenger RNA (mRNA) vaccines instead rely on genetic material that tells the body to make a protein (the antigen).[19] Once introduced to the body, the antigen elicits a response by the immune system creating antibodies and immune memory cells that prevent future infection from the same disease. The immune response from a vaccine is similar to the immune response from acquiring an infectious disease naturally; however, since the antigen in the vaccine is weakened or dead, the vaccine usually does not cause disease. In the case of vaccines made with weakened live attenuated viruses or bacteria, the vaccine may cause a form of the disease that is usually much milder than the actual disease. In addition, the immune response triggered by any vaccine may cause some symptoms in some patients.[20]

Along with the antigen, vaccines contain other ingredients such as preservatives, stabilizers, and adjuvants. Preservatives, like thimerosal, can help keep the vaccine free of contamination by other germs (e.g., bacteria, fungi). Thimerosal is currently used only in multidose vials of vaccines, such as certain formulations of the influenza (flu) vaccine. Stabilizers, like sugar or gelatin, allow the vaccine to be stored for a period of time and help keep the antigen stable. Adjuvants, such as aluminum salts, help trigger the immune response to the vaccine, particularly for vaccines made with fractions of disease-causing agents. Vaccines may also contain small amounts of residual material from the manufacturing process, such as egg proteins, formaldehyde, and antibiotics.[21]

Federal Vaccine Safety Regulation and Programs

Federal regulation of vaccine safety began with the Biologics Control Act of 1902, which was the first federal law to require premarket review of pharmaceutical products.[22] The Biologics Control Act was enacted in response to deaths (many of them children) from tetanus contamination of smallpox vaccine and diphtheria antitoxin (a prophylaxis used for diphtheria at the time). The act imposed requirements on the manufacturing and labeling of biological products ("biologics") and required inspection of manufacturing facilities before a federal license was issued for marketing the products. The Biologics Control Act was revised and recodified when the Public Health

[18] CDC, "Principles of Vaccination," in *Epidemiology and Prevention of Vaccine-Preventable Diseases*, ed. Jennifer Hamborsky, Andrew Kroger, and Charles Wolfe, 13th ed. (Washington, DC: Public Health Foundation, 2015).

[19] CDC, "Understanding mRNA COVID-19 Vaccines," December, 2020, https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/mrna.html.

[20] CDC, "Principles of Vaccination," in *Epidemiology and Prevention of Vaccine-Preventable Diseases*, ed. Jennifer Hamborsky, Andrew Kroger, and Charles Wolfe, 13th ed. (Washington, DC: Public Health Foundation, 2015).

[21] Department of Health and Human Services (HHS), "Vaccine Ingredients," *Vaccines.gov*, December 2017, https://www.vaccines.gov/basics/vaccine_ingredients; CDC, "What's in Vaccines?" August 2019, https://www.cdc.gov/vaccines/vac-gen/additives.htm; and the Food and Drug Administration (FDA), "Common Ingredients in U.S. Licensed Vaccines," https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/common-ingredients-us-licensed-vaccines.

[22] P.L. 57-244, enacted July 1, 1902. David M. Dudzinski, "Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies," *Food & Drug Law Journal*, 2005, vol. 60, no. 2., p. 147.

Service Act (PHSA) was enacted in 1944. Biologics are now subject to regulation by the U.S. Food and Drug Administration (FDA) under the PHSA and the Federal Food, Drug, and Cosmetic Act (FFDCA).[23]

Since the 1902 law was enacted, federal vaccine safety activities have expanded to minimize the possibility of adverse events following vaccination (such as by vaccine contamination) and to detect new adverse events as quickly as possible, as discussed throughout this report. Major reforms to federal vaccine safety programs were enacted as a part of the National Childhood Vaccine Injury Act of 1986 (NCVIA; P.L. 99-660, Title III), which mandated reporting of adverse events caused by vaccines to FDA and CDC, established the National Vaccine Program Office (NVPO) within HHS to coordinate federal vaccine efforts, granted FDA mandatory recall authority for biological products, and established the National Vaccine Injury Compensation Program (VICP). NCVIA was enacted after a spate of lawsuits against vaccine manufacturers alleging safety issues. The lawsuits caused several vaccine manufacturers to exit the market, leading to concerns about the vaccine supply and possible reintroduction of certain diseases.[24]

Federal Agencies Involved in Vaccine Safety

Within the Department of Health and Human Services (HHS):

- FDA regulates the safety, effectiveness, and quality of vaccines through premarket review and postmarket requirements (e.g., adverse event reporting).
- CDC supports cross-cutting immunization programs that include, as relevant to vaccine safety: safety monitoring, clinical guidance for vaccines, vaccine safety research, and efforts to ensure safety in public vaccine distribution.
- The National Institutes of Health (NIH) is the primary federal agency that supports medical and health research, including vaccine research.
- The Centers for Medicare & Medicaid Services (CMS) monitors vaccine safety among the Medicare population.
- The Agency for Healthcare Research and Quality (AHRQ) conducts vaccine safety reviews.
- The Health Resources and Services Administration (HRSA) administers the VICP.

The Department of Veterans Affairs (VA) conducts some vaccine research and monitors vaccine safety among veterans who receive care in the VA system.

The Department of Defense (DOD) conducts some vaccine research and has a database for monitoring adverse events from vaccination among military service members and their families.

As covered in this report, efforts to ensure vaccine safety include several federal activities:

- **Premarket requirements:** Clinical trials and FDA licensure or authorization.
- **Clinical recommendations:** Recommendations for the safe and appropriate clinical use of vaccines by the Advisory Committee on Immunization Practices (ACIP), and CDC clinical guidance and resources.
- **Postmarket safety:** Manufacturing requirements and ongoing safety monitoring of vaccines administered to patients.

[23] Until 1972, biologics, including vaccines, were regulated by the National Institutes of Health (NIH, or its precursors) under the Biologics Control Act of 1902. In 1972, regulatory responsibility over biologics was transferred from NIH to the U.S. Food and Drug Administration (FDA). See David M. Dudzinski, "Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies," *Food and Drug Law Journal*, 2005, vol. 60, no. 2, pp. 143-260. See also CRS Report R44620, *Biologics and Biosimilars: Background and Key Issues*.

[24] Geoffrey Evans, "Update on Vaccine Liability in the United States: Presentation at the National Vaccine Program Office on Strengthening the Supply of Routinely Recommended Vaccines in the United States, 12 February 2002," *Clinical Infectious Diseases*, vol. 42 (2006), pp. S130-7, and Nora Freeman Engstrom, "A Dose of Reality for Specialized Courts: Lessons from the VICP," *University of Pennsylvania Law Review*, vol. 163 (June 28, 2015), pp. 1655-1658.

- **Federal research on vaccine safety:** Ongoing research to inform a better scientific understanding of vaccine safety, and comprehensive scientific reviews on the safety of vaccines.
- **Vaccine injury compensation:** The VICP can provide compensation to eligible individuals found to have been injured by a covered vaccine. In emergency circumstances, such as the COVID-19 pandemic, a separate Countermeasures Injury Compensation Program (CICP) may be used.
- **Vaccine distribution:** Programs and requirements to ensure safety controls in vaccine distribution programs, led by CDC.

Vaccine Safety Basics

As defined by FDA regulations, safety is "the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time."[25] Vaccine safety is distinct from efficacy and effectiveness; however, it is useful to consider vaccine safety in the context of efficacy and effectiveness, which are defined as follows:

- Vaccine *efficacy* is defined as the reduction in disease incidence in a vaccinated group compared with an unvaccinated group under optimal conditions (i.e., healthy individuals and proper administration).
- Vaccine *effectiveness* is defined as the reduction in disease incidence in a vaccinated group compared with an unvaccinated group under real-world conditions.[26]

Like all pharmaceutical products, though vaccines approved or authorized for use by FDA are generally safe for the vast majority of patients, they are not 100% safe for all patients. Vaccine safety programs continually assess the benefits and risks of vaccination. Adverse events following vaccination can be classified in many ways:[27]

- Frequency—is the adverse event common or rare?
- Severity—is the adverse event mild, such as minor pain or swelling, or severe, such as leading to hospitalization, disability, or death?
- Causality—can a causal relationship be established with the vaccine with clinical, laboratory, or epidemiologic evidence? (see **text box** below)
- Preventability—is the adverse event intrinsic to the vaccine (e.g., provoked by the immune response caused by the vaccine), or related to faulty production or administration of the vaccine?

Some adverse events following vaccination may be linked directly to the antigen in the vaccine, such as paralytic poliomyelitis (i.e., paralysis), which is rarely caused by the live oral polio

[25] 21 C.F.R. §600.3(p).

[26] Vaccine efficacy and effectiveness definitions are based on Shelly McNeil, *Overview of Vaccine Efficacy and Vaccine Effectiveness*, Canadian Center for Vaccinology, Presentation to the World Health Organization, https://www.who.int/influenza_vaccines_plan/resources/Session4_VEfficacy_VEffectiveness.PDF, and Centers for Disease Control and Prevention (CDC), "How Flu Vaccine Effectiveness and Efficacy Is Measured," 2016, https://www.cdc.gov/flu/vaccines-work/effectivenessqa.htm.

[27] CDC, "Vaccine Safety," in *Epidemiology and Prevention of Vaccine-Preventable Diseases*, ed. Jennifer Hamborsky, Andrew Kroger, and Charles Wolfe, 13th ed. (Washington, DC: Public Health Foundation, 2015).

vaccine. Other adverse events are precipitated by the vaccine, such as febrile seizures that occur following a vaccine-induced fever. Some adverse events can be linked to improper vaccine administration; for example, a vaccine administered too high on the arm of an adult can cause deltoid bursitis (inflammation of the shoulder joint).[28] In the past, improper vaccine manufacturing has been tied to large-scale adverse health events. In 1955, one polio vaccine manufacturer failed to completely inactivate the poliovirus in the manufacturing process. As a result, 40,000 people developed mild polio from the vaccine, 200 became paralyzed, and 10 died.[29]

In some cases, establishing a causal connection between a vaccine and an adverse event is difficult. Vaccination may *co-occur* with an adverse health event. For example, early childhood—a time when several recommended pediatric vaccines are typically administered—coincides with the same period when signs and symptoms of developmental disorders, such as autism, may begin to appear.[30] Available evidence rejects a causal relationship between childhood vaccines and autism.[31] To determine causality between a vaccine and a given health event, scientists and public health experts evaluate many kinds of evidence, including the time period between vaccination and the event; the biologic plausibility that the health event was caused by vaccination; clinical or laboratory evidence that supports causation by the vaccine; and population-based epidemiological analyses that assess whether vaccinated individuals are more likely to develop a certain health outcome within a certain time period following vaccination compared to either individuals who did not receive the vaccine in that time period or expected rates of the adverse health event in the population (referred to as "background rates").[32] Several of the programs covered in this report generate data or other evidence that can allow for causality assessments to link certain adverse events with vaccination (see **text box**).

What Is a Causality Assessment?

Immune systems are arguably among the most complex biological systems—therefore, studying vaccines and their effect on the human body can be difficult. Individual studies may provide suggestive evidence of adverse health effects linked to vaccines. For example, an analysis of health data on a population of thousands of individuals could find that vaccination with a certain vaccine is statistically associated with higher rates of a certain adverse health event that occurred following vaccination. Yet, another similar analysis among a different population could find no such evidence. In addition, further evidence based on the research in the laboratory, such as with animals or human tissue samples, might find that a certain adverse event following vaccination is or is not likely based on an understanding of biological systems. Therefore, in order to determine if all the available evidence favors a *causal* relationship between a vaccine and a subsequent adverse health event, researchers will combine evidence across many types of studies as a part of a causality assessment. Good quality systematic causality assessments usually include the following attributes:

- Search methods to identify all possible studies of interest within all relevant areas of research.

[28] CDC, "Vaccine Safety," in *Epidemiology and Prevention of Vaccine-Preventable Diseases*, ed. Jennifer Hamborsky, Andrew Kroger, and Charles Wolfe, 13th ed. (Washington, DC: Public Health Foundation, 2015).

[29] Frank DeStefano, Paul A. Offit, and Allison Fisher, "Vaccine Safety," in *Plotkin's Vaccines*, ed. Stanley A. Plotkin, Walter A. Orenstein, and Paul A. Offit, 7th ed. (Elsevier, 2017), p. 1584.

[30] Frank DeStefano, Paul A. Offit, and Allison Fisher, "Vaccine Safety," in *Plotkin's Vaccines*, ed. Stanley A. Plotkin, Walter A. Orenstein, and Paul A. Offit, 7th ed. (Elsevier, 2017), p. 1593.

[31] Frank DeStefano, Heather Monk Bodenstab, and Paul A. Offit, "Principal Controversies in Vaccine Safety in the United States," *Clinical Infectious Diseases*, vol. 69 (August 15, 2019), pp. 726-31, and Institute of Medicine (now National Academy of Medicine), *Immunization Safety Review: Vaccines and Autism*, 2004, Washington, DC: The National Academies Press.

[32] CDC, "Vaccine Safety," in *Epidemiology and Prevention of Vaccine-Preventable Diseases*, ed. Jennifer Hamborsky, Andrew Kroger, and Charles Wolfe, 13th ed. (Washington, DC: Public Health Foundation, 2015).

- A selection process to determine which studies are actually relevant and used rigorous scientific methods that provide quality evidence based on defined criteria.
- A review process to compare evidence across studies, considering differences such as study populations, study design, and the quality of each study.
- Methods to weigh different types of evidence and combine evidence across studies in order to determine whether all the evidence, in total, supports or does not support a causal relationship between vaccination with a specific vaccine and a subsequent adverse event, or yields inconclusive results.

For a further discussion, see the "Federal Research on Vaccine Safety" section. Causality assessments may also be conducted on an ongoing basis using data and information from postmarket monitoring systems (see the "Postmarket Safety" section).

For examples of causality assessments on the safety of vaccines, see Institute of Medicine (now National Academy of Medicine, "Adverse Effects of Vaccines: Evidence and Causality," 2012, https://www.nap.edu/catalog/13164/adverse-effects-of-vaccines-evidence-and-causality; and Margaret A. Maglione, Courtney Gidengil, Lopamudra Das et al. "Safety of Vaccines Used for Routine Immunization in the United States," *Agency for Healthcare Research and Quality*, July 2014, https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/vaccine-safety_research.pdf. Also, for an overview of causality assessments for vaccines, see Frank DeStefano, Paul A. Offit, and Allison Fisher, "Ch. 82: Vaccine Safety," in *Plotkin's Vaccines*, ed. Stanley A. Plotkin, Walter A. Orenstein, and Paul A. Offit, 7th ed. (Elsevier, 2017), p. 1589.

Premarket Safety

Vaccines generally follow the same clinical development and approval process as drugs and other biologics (i.e., therapeutics derived from living organisms).[33] To be marketed in the United States, a new vaccine must first receive licensure (i.e., approval) from FDA. Licensure is based on a determination by FDA that the vaccine and the facility in which it is manufactured, processed, packed, or held meet standards to ensure that the product is safe, pure, and potent (effective).[34] Except under very limited circumstances, FDA requires data from clinical trials—formally designed, conducted, and analyzed studies of human subjects—to provide evidence of a vaccine's safety and effectiveness. These requirements apply to all vaccines marketed in the United States, regardless of whether the manufacturing facility is located domestically or in a foreign country.

Existing vaccines have often taken several years to develop.[35] One analysis of FDA vaccine licensures between January 2010 and June 2020 found that the median time from initiation of clinical testing to FDA approval was 8.1 years.[36]

Clinical Trials

Vaccines are typically tested in several stages of human clinical trials. Before beginning clinical testing, a vaccine's sponsor must file an investigational new drug (IND) application, which is a

[33] Biological products include vaccines, monoclonal antibodies, and cytokines, among other examples. For additional information about biologics, see CRS Report R44620, *Biologics and Biosimilars: Background and Key Issues*.

[34] PHSA §351(a)(2)(C) [42 U.S.C. §262(a)(2)(C)]. FDA approves drugs that are *safe and effective*; the equivalent terminology for biologics is *safe, pure, and potent*. FDA has interpreted *potency* to include effectiveness. See the FDA Guidance for Industry, *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*, https://www.fda.gov/media/82647/download.

[35] R. Gordon Douglas and Vijay B. Samant, "Chapter 4: The Vaccine Industry," in *Plotkin's Vaccines*, ed. Stanley A. Plotkin, Walter A. Orenstein, and Paul A. Offit, 7th ed. (Elsevier, 2017), p. 1593.

[36] Jeremy Puthumana, Alexander C. Egilman, Audrey D. Zhang et al., "Speed, Evidence, and Safety Characteristics of Vaccine Approvals by the U.S. Food and Drug Administration," *Journal of the American Medical Association- Internal Medicine*, November 10, 2020.

request for FDA authorization to administer an investigational biologic (or drug) to humans.[37] The IND must include information about the proposed clinical study design, completed animal test data, and the lead investigator's qualifications.[38] The investigator also must provide assurance that an Institutional Review Board (IRB) will provide initial and continuous review and approval of each of the studies in the clinical investigation to ensure that participants are aware of the drug's investigational status, and that any risk of harm will be necessary, explained, and minimized.[39] FDA has 30 days to review an IND, after which a manufacturer may begin clinical testing if FDA has not objected and imposed a clinical hold.

Clinical trials for an IND may be sponsored by the drug company seeking to commercially market the vaccine, a university or nonprofit organization, a government agency, or a combination or partnership of all the above. The funder(s) may differ for each stage of testing. In typical circumstances, the public sector (e.g., federal agencies, nonprofit organizations) generally finances more of the earlier stages of clinical trials, such as Phase 1 clinical trials. Later-stage testing, such as Phase 3 clinical trials, are typically funded more so by drug companies than government agencies.[40]

The sponsor of the trial is responsible for selecting qualified investigators, maintaining an effective IND, and ensuring proper monitoring of the investigations, including that they are conducted in accordance with the IND. In certain cases, the sponsor may establish an independent Data and Safety Monitoring Board (DSMB) of relevant experts with no relevant financial or other ties to the sponsor to oversee the investigations.[41] The DSMB often advises the sponsor on the ongoing safety of trial subjects and the continuing validity and scientific merit of the trial. One DSMB may be responsible for overseeing multiple clinical trials.

In general, vaccine clinical trials occur in three sequential phases:

- **Phase 1** trials are the first in-human studies of a vaccine candidate, and they assess safety and immunogenicity[42] in a small number of volunteers.
- **Phase 2** trials assess side effects and the dosing at which the investigational vaccine may have a protective effect and may enroll hundreds of volunteers.
- **Phase 3** trials assess effectiveness, continue to monitor safety and typically enroll thousands of volunteers.[43]

Most clinical trials for vaccines include a control group, such as a placebo or alternative vaccine, to compare outcomes for those who received the target vaccine compared with those who did not. Phase 3 clinical trial data are typically needed to fully assess the safety and effectiveness of an

[37] FFDCA §505(i) [21 U.S.C. §355(i)], PHSA §351(a)(3) [42 U.S.C. §262(a)(3)], 21 C.F.R. Part 312.

[38] 21 C.F.R. 312 Subpart B.

[39] 21 C.F.R. §312.23(a)(1)(iv) and 21 C.F.R. Part 56.

[40] Stuart O. Schweitzer and Z. John Lu, "The Pharmaceutical Industry," in *Pharmaceutical Economics and Policy: Perspectives, Promises, and Problems* (New York, NY: Oxford University Press, 2018), pp. 37-40, and Gillian K. Gresham, Stephan Erhardt, Jill L. Meinert et al., "Characteristics and Trends of Clinical Trials Funded by the National Institutes of Health Between 2005 and 2015," *Clinical Trials*, vol. 15, no. 1 (September 7, 2017), pp. 65-74.

[41] FDA, "Guidance for Clinical Trial Sponsors Establishment and Operation of Clinical Trial Data Monitoring Committees," March 2006, https://www.fda.gov/media/75398/download.

[42] *Immunogenicity* refers to the extent to which a substance is able to stimulate an immune response. An immune response to a pharmaceutical product may affect its safety and effectiveness. See Jonathan Law and Elizabeth Martin, ed., *Concise Medical Dictionary* (Oxford University Press).

[43] 21 C.F.R. §312.21. FDA, "Vaccine Product Approval Process," https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/vaccine-product-approval-process.

investigational vaccine. Typically, only the Phase 3 clinical trials are large enough to allow for robust scientific evidence on the safety and effectiveness of the investigational vaccine among different population segments (e.g., younger vs. older adults).[44] Under typical circumstances, a vaccine candidate moves through each phase of clinical testing upon successful completion of the prior phase.

According to one analysis of vaccines licensed by FDA between January 2010 and June 2020, each vaccine was supported by a median of seven clinical trials, including two pivotal efficacy trials (e.g., late stage such as Phase 3 clinical trials). The median number of patients evaluated for each vaccine was 6,710, and the median follow-up for serious adverse events was six months.[45] Aspects specific to each vaccine and infectious disease inform vaccine development considerations, including the prevalence of the disease in the population, risk of infection, available scientific understanding of immune responses, and potential for serious adverse events linked to the vaccine and/or disease. These considerations inform clinical trial design, number of study participants, age and population groups recruited to the study, and development timelines.[46]

To determine efficacy, late-stage clinical trials use what are called "endpoints" to measure the clinical effect of the drug on patient outcomes (in this case, disease prevention) as compared to the control group. For vaccines, endpoints can include *clinical endpoints* that are a direct measure of vaccine efficacy on patient outcomes, such as laboratory-confirmed infections or disease cases with symptoms, or *surrogate endpoints* (also called immune response endpoints) that measure an indicator of a protective immune response, such as the presence of antibodies to the disease in the bloodstream.[47] Whether a surrogate endpoint can be used to measure the efficacy of a given vaccine depends on the available scientific understanding of protective immune responses to that pathogen. While scientific understanding of protective immune responses has improved for many pathogens over the years, there are some pathogens that have been studied for decades for which scientists do not fully understand the biology of protective immune responses induced by vaccination.[48] Of new vaccines licensed between January 2010 and June 2020 against pathogens for which no vaccine had been previously licensed, four out of five used clinical endpoints rather than surrogate endpoints.[49] Various factors determine whether a surrogate endpoint is appropriate for use in a vaccine development program, and these decisions are made on a case-by-case basis.[50] If a surrogate endpoint previously had been used to support licensure of a vaccine, it may be appropriate for use in future vaccine development programs for that same disease. A surrogate endpoint that has less evidentiary support may be more appropriate for the accelerated approval

[44] Frank DeStefano, Paul A. Offit, and Allison Fisher, "Vaccine Safety," in *Plotkin's Vaccines*, ed. Stanley A. Plotkin, Walter A. Orenstein, Paul A. Offit, and Kathryn Edwards, 7th ed. (Elsevier, 2017), pp. 1584.

[45] Jeremy Puthumana, Alexander C. Egilman, Audrey D. Zhang et al., "Speed, Evidence, and Safety Characteristics of Vaccine Approvals by the U.S. Food and Drug Administration," *Journal of the American Medical Association- Internal Medicine*, November 10, 2020.

[46] Marion F. Gruber and Valerie B. Marshall, "Chapter 79: Regulation and Testing of Vaccines," in *Plotkin's Vaccines*, ed. Stanley Plotkin Walter Orenstein Paul Offit, and Kathryn M. Edwards, 7th ed., vol. 1555-6 (Elsevier, 2017).

[47] Ibid.

[48] Stanley A. Plotkin and Peter Gilbert, "Chapter 3: Correlates of Protection ," in *Plotkin's Vaccines,* ed. Stanley A. Plotkin, Walter A. Orenstein, Paul A. Offit, and Kathryn Edwards, 7th ed. (Elsevier, 2017), p. 39 and Stanley A. Plotkin, "Updates on Immunologic Correlates of Vaccine-Induced Protection," *Vaccine*, vol. 38 (November 22, 2019).

[49] Jeremy Puthumana, Alexander C. Egilman, Audrey D. Zhang et al., "Speed, Evidence, and Safety Characteristics of Vaccine Approvals by the U.S. Food and Drug Administration," *Journal of the American Medical Association- Internal Medicine*, November 10, 2020.

[50] FDA, "Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure," https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure.

pathway rather than traditional licensure when it is "reasonably likely to predict a clinical benefit."[51] In other instances, relying on a surrogate endpoint for vaccine licensure may not be appropriate until more information is available about the immune response or disease.[52]

In some cases, an experimental vaccine that showed promise in Phase 1 and Phase 2 clinical trials was found to be ineffective in Phase 3 trials. For example, an experimental vaccine for herpes simplex virus type 2 (HSV-2) showed safety and preliminary evidence of an immune response to the virus in Phase 2 clinical trials (i.e., HSV-2 antibodies in the bloodstream). However, during the Phase 3 clinical trials, by a year after vaccination, there was no difference in rates of acquired HSV-2 infections between the recipient and control groups, despite vaccine recipients showing a preliminary immune response.[53]

In addition to providing insights into the effectiveness of investigational vaccines, long-term Phase 3 studies can uncover important safety data. For example, three years of safety data on the vaccine for dengue virus produced by Sanofi Pasteur (Dengvaxia) found an issue of *antibody-mediated enhancement* of infections, where the antibodies raised in response to vaccination could worsen the severity of dengue for those without a prior dengue infection. Data on the vaccine showed a higher rate of hospitalizations for dengue three years after vaccination in young children compared with children who were unvaccinated.[54]

For some vaccines, Phase 3 clinical trials are very large to detect rare adverse events. For instance, two second-generation rotavirus vaccines (RotaTeq and RotaRix) were subject to Phase 3 clinical trials involving over 60,000 infants in order to ascertain the risk of intussusception (intestinal obstruction) following vaccine administration (estimated to be about 1 in 10,000 in the first-generation vaccine).[55] Such large trials can involve higher costs and increased time to licensure.

Biologics License Application (BLA) and Licensure Requirements

After completing clinical trials, a sponsor may submit a Biologics License Application (BLA) to FDA's Center for Biologics Evaluation and Research (CBER). A BLA is a request for permission to market the vaccine and must contain certain information, including data from nonclinical laboratory and clinical studies demonstrating that the product meets requirements of safety, purity, and potency.[56] For each nonclinical laboratory study, the BLA must include either (1) a statement that the study was conducted in compliance with FDA regulations governing Good Laboratory Practice (GLP) for nonclinical laboratory studies[57] or (2) if the study was not conducted in compliance with GLP regulations, a brief statement explaining the reason for

[51] FDA, "Surrogate Endpoint Resources for Drug and Biologic Development," https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development.

[52] FDA, "Development and Licensure of Vaccines to Prevent COVID-19," Guidance for Industry, June 2020, p. 18, https://www.fda.gov/media/139638/download.

[53] FDA, *22 Case Studies Where Phase 2 and Phase 3 Trials had Divergent Results*, January 2017.

[54] S.R. Hadinegoro, J.L. Arredondo-Garcia, and M.R. Capeding et al., "Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease," *The New England Journal of Medicine*, vol. 373, no. 13 (September 24, 2015). Helen Branswell, "Caution on New Dengue Vaccine: In Some Countries, Harm Outweighs Benefit," *STAT*, September 1, 2016.

[55] Frank DeStefano, Paul A. Offit, and Allison Fisher, "Vaccine Safety," in *Plotkin's Vaccines*, ed. Stanley A. Plotkin, Walter A. Orenstein, and Paul A. Offit, 7th ed. (Elsevier, 2017), pp. 1584.

[56] FDA regulations at 21 C.F.R. §601.2(a) specify the required contents of a BLA.

[57] 21 C.F.R. Part 58 "Good Laboratory Practice for Nonclinical Laboratory Studies."

noncompliance. In addition, for each clinical investigation involving human subjects, the BLA must contain statements that each clinical investigation either was conducted in compliance with the requirements for institutional review set forth in FDA regulations,[58] or that it was not subject to such requirements and was conducted in compliance with requirements for informed consent.[59] The BLA also must contain "a full description of manufacturing methods; data establishing stability of the product through the dating period; sample(s) representative of the product for introduction or delivery for introduction into interstate commerce; summaries of results of tests performed on the lot(s) represented by the submitted sample(s); specimens of the labels, enclosures, and containers;" and the address of each location involved in the manufacture of the vaccine. If applicable, a BLA must contain any medication guide proposed to be used for the product. Finally, the BLA must include a financial certification or disclosure statement(s) or both for clinical investigators.

As noted above, a vaccine manufacturer must submit proposed vaccine labeling as part of a BLA. FDA reviews the proposed labeling to determine whether it is scientifically accurate and that it conforms to regulatory requirements. As for prescription drugs and other biologics, vaccine labeling must include warnings and precautions, contraindications, dosage and administration, storage and handling conditions, and adverse reactions, among other information.[60] Labeling for vaccines must specifically contain a statement describing how suspected adverse reactions can be reported.[61] In addition, the labels affixed to each container or package of a vaccine must include the name of the manufacturer, the lot number or other lot identification,[62] and the recommended individual dose (for multiple dose containers), among other information.[63] Vaccines require special processing and handling, such as refrigeration and proper storage, and information about storage temperature and other handling instructions must be on the label affixed to each package containing a vaccine.[64]

FDA regulations also provide for biological product manufacturing establishment standards. Such standards cover personnel, the physical establishment in which a product is manufactured, records maintenance, retention of samples, reporting of product deviations, and product temperature during shipment.[65] Most of these requirements apply broadly to biologics, but several provisions are vaccine-specific, including requirements for live vaccine work areas[66] and live vaccine processing,[67] as well as product-specific maintenance temperatures.[68] In addition, FDA regulations establish requirements for testing product potency, sterility, purity, and identity, as well as requirements for constituent materials used in licensed products, including preservatives, diluents, and adjuvants.[69] Vaccines, like other biological products, are subject to lot release

[58] 21 C.F.R. Part 56 "Institutional Review Boards."

[59] 21 C.F.R. Part 50 "Protection of Human Subjects."

[60] 21 C.F.R. §§201.56 and 201.57.

[61] 21 C.F.R. §201.57(a)(11)(iii).

[62] "Lot" refers to "that quantity of uniform material identified by the manufacturer as having been thoroughly mixed in a single vessel." 21 C.F.R. § 600.3(x).

[63] 21 C.F.R. §§610.60 and 610.61.

[64] 21 C.F.R. §610.61.

[65] 21 C.F.R. Part 600.

[66] 21 C.F.R. §600.10(c)(4).

[67] 21 C.F.R. §600.11(c)(4).

[68] 21 C.F.R. §600.15.

[69] 21 C.F.R. Part 610.

requirements, which provide that "[n]o lot of any licensed product shall be released by the manufacturer prior to the completion of tests for conformity with standards applicable to such product."[70] FDA may require that samples of any lot of any licensed product and the protocols and applicable test results be submitted to CBER. In such case, a manufacturer may not distribute a lot of a vaccine until it is released by FDA.[71]

Expedited Pathways and Access to Unapproved Vaccines

Because clinical testing and the FDA review process typically take several years, FDA and Congress have established mechanisms to expedite the premarket development and review processes for pharmaceutical products, including vaccines, coming onto the market, as well as to expand access to products that are still under investigation. Historically, certain FDA expedited pathways such as Emergency Use Authorization (EUA) have been used infrequently for vaccines. However, a public health emergency, such as a pandemic, may affect the risk assessment in making a vaccine available before full long-term safety data are available.

Expedited Development and Review

To address unmet medical needs in the treatment or prevention of serious or life-threatening diseases or conditions, FDA can expedite the development and review processes for drugs and biologics, including vaccines, through four programs:

- fast track product designation,
- breakthrough therapy designation,
- accelerated approval, and
- priority review.[72]

Vaccines may be designated to more than one program. Fast track product designation and breakthrough therapy are both intended to streamline the clinical development process, but the qualifying criteria and features of these programs differ.

To qualify for *fast track product designation*, a vaccine must be intended for a serious condition, and nonclinical or clinical data must demonstrate its potential to address an unmet medical need.[73] The sponsor of a fast track-designated product is eligible for frequent interactions with the FDA review team, priority review, and rolling review (in which FDA reviews portions of a BLA before a complete application is submitted).[74]

To qualify for *breakthrough designation*, a vaccine must be intended for a serious condition, and preliminary clinical evidence must indicate that it demonstrates potential substantial improvement on a clinically significant endpoint(s) over available therapies. Features of breakthrough therapy designation include rolling review; intensive FDA guidance on designing an efficient drug development program; involvement of "senior managers and experienced review and regulatory health project management staff in a proactive, collaborative, cross-disciplinary review" to

[70] 21 C.F.R. §610.1.

[71] 21 C.F.R. §610.2.

[72] FFDCA §506 [21 U.S.C. §356]. FDA, "Guidance for Industry Expedited Programs for Serious Conditions–Drugs and Biologics," May 2014, https://www.fda.gov/media/86377/download.

[73] FFDCA §506(b) [21 U.S.C. §356(b)].

[74] FFDCA §506(a) [21 U.S.C. §356(a)].

expedite the development and review of a breakthrough therapy; and eligibility for other expedited programs.

Interested sponsors must submit to FDA a request for fast track product designation or breakthrough therapy designation. The request may be submitted with either the IND or any time after,[75] as further specified in FDA guidance.[76]

The *accelerated approval* pathway allows a vaccine to be licensed based on its effect on a surrogate endpoint (e.g., a laboratory measurement such as development of neutralizing antibodies) that predicts effectiveness, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality. To qualify for accelerated approval, a vaccine must (1) be intended for a serious condition, (2) generally provide a meaningful advantage over available therapies, and (3) demonstrate an effect on an endpoint that is reasonably likely to predict clinical benefit. Postmarketing confirmatory studies generally must be completed to demonstrate actual effectiveness.[77]

A *priority review* designation signifies that FDA's goal is to take action on an application within 6 months of its filing, compared with 10 months for standard review. A BLA may qualify for priority review designation if, for example, it is for a vaccine intended for a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. A BLA also may qualify for priority review if submitted with a priority review voucher.[78]

Animal Rule

As mentioned above, FDA typically requires substantial evidence of effectiveness from adequate and well-controlled trials conducted in humans prior to licensing a vaccine. However, in certain cases, evaluating a vaccine's efficacy or effectiveness through human trials is not possible. For example, it would not be ethical to expose human subjects to lethal toxic substances in order to test an investigational vaccine.

Under the Animal Rule, if human efficacy studies are not ethical, and if field trials (i.e., trials conducted outside of the clinical setting) are not feasible, FDA may license a vaccine based on adequate and well-controlled animal efficacy studies if those studies establish that the vaccine is likely to produce clinical benefit in humans.[79] The Animal Rule is intended for drugs and biologics that would treat or prevent serious or life-threatening conditions caused by chemical, biological, radiological, or nuclear substances (e.g., nerve agents, emerging infectious pathogens, snake venom, and industrial chemicals). For FDA to rely on evidence from animal studies to provide evidence of effectiveness, four criteria must be met:

[75] FFDCA §506(a)(2) & (b)(2) [21 U.S.C. §356(a)(2) & (b)(2)].

[76] FDA, "Guidance for Industry Expedited Programs for Serious Conditions–Drugs and Biologics," May 2014, https://www.fda.gov/media/86377/download.

[77] FFDCA §506(c) [21 U.S.C. §356(c)].

[78] Three priority review voucher programs are currently authorized in the FFDCA: (1) the tropical disease priority review program, (2) the rare pediatric disease priority review program, and (3) the material threat MCM priority review voucher program. Under each of these programs, the sponsor of an NDA or BLA that meets the statutory requirements of the specific program is eligible to receive, upon approval, a transferable voucher, and the sponsor may either use that voucher for the priority review of another application or sell it to another sponsor to use.

[79] 21 C.F.R. §601.90 through §601.95 for biologics, including vaccines. See also FDA Guidance for Industry, "Product Development Under the Animal Rule," October 2015, https://www.fda.gov/media/88625/download.

> There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product;
>
> The effect is demonstrated in more than one animal species expected to react with response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans;
>
> The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity; and
>
> The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans.[80]

Drugs and vaccines evaluated for efficacy under the Animal Rule are evaluated for safety under the existing requirements for drugs and biologics. Postmarketing studies, such as field studies, must be conducted once feasible, and the sponsor of the vaccine must prepare certain patient-specific information explaining that the approval was based on efficacy studies conducted in animals alone. FDA also may impose postmarketing restrictions on distribution of the product if necessary to ensure safety (e.g., restricting distribution to certain facilities or practitioners with special training or experience).[81] To date, FDA has licensed one vaccine under the Animal Rule: BioThrax (Anthrax Vaccine Adsorbed [injection]). Specifically, in 2015, the Animal Rule was used to approve a new use—post-exposure prophylaxis of disease—of a previously licensed anthrax vaccine.[82]

Emergency Use Authorization (EUA)

In general, a vaccine may be provided to patients only if FDA has licensed its marketing under a BLA or authorized its use in a clinical trial under an IND. In certain circumstances, however, FDA may allow patients to access investigational vaccines outside this framework, including through emergency use authorization (EUA).

FDA may enable access to an unapproved vaccine by granting an EUA, if the HHS Secretary declares that circumstances exist to justify the emergency use of an unapproved product or an unapproved use of an approved medical product.[83] The HHS Secretary's declaration must be based on one of four determinations; for example, a determination that an actual or significant potential exists for a public health emergency that affects or has significant potential to affect national security or the health and security of U.S. citizens living abroad.[84] Following the HHS Secretary's declaration, FDA, in consultation with the Assistant Secretary for Preparedness and Response (ASPR), the National Institutes of Health (NIH), and CDC, may issue an EUA authorizing the emergency use of a vaccine, provided that the following criteria are met:

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[80] 21 C.F.R. §601.91. FDA Guidance for Industry, "Product Development Under the Animal Rule," October 2015, https://www.fda.gov/media/88625/download.

[81] 21 C.F.R. §601.91.

[82] FDA, "CBER Regulated Biologic Animal Rule Approvals," https://www.fda.gov/media/107839/download. FDA, "FDA approves vaccine for use after known or suspected anthrax exposure," November 23, 2015, http://wayback.archive-it.org/7993/20171114165441/https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm474027.htm.

[83] FFDCA §564 [21 U.S.C. §360bbb-3]. For additional information, see CRS In Focus IF10745, *Emergency Use Authorization and FDA's Related Authorities*.

[84] FFDCA §564(b)(1) [21 U.S.C. §360bbb-3(b)(1)].

- the agent that is the subject of the EUA can cause a serious or life-threatening disease or condition;
- based on the totality of the available scientific evidence, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing such disease or condition, and that the known and potential benefits of the product outweigh its known and potential risks; and
- there is no adequate, approved, or available alternative to the product.[85]

The standard of evidence for an EUA is different than that for approval. EUA issuance, as noted above, is based on FDA's determination that the totality of the available scientific evidence suggests that a product *may be effective* in diagnosing, treating, or preventing a disease or condition, and that the known and potential benefits of the product outweigh its known and potential risks. This standard of evidence is different from the one required for full FDA approval or licensure, which is based on *substantial evidence* of effectiveness derived from adequate and well-controlled studies.[86]

FDA must impose certain conditions as part of an EUA to the extent practicable (e.g., distributing certain information to health care providers and patients) and may impose additional discretionary conditions where appropriate.[87] FDA may waive or limit current good manufacturing practices (e.g., storage and handling) and prescription dispensing requirements for products authorized under an EUA. In addition, FDA may establish conditions on advertisements and other promotional printed matter that relates to the emergency use of a product. An EUA remains in effect for the duration of the emergency declaration made by the HHS Secretary under FFDCA Section 564, unless revoked at an earlier date.

Until December 2020, FDA had never granted EUA for an unapproved (i.e., unlicensed) vaccine. The only instance of FDA issuing an EUA for a vaccine was in 2005 for the *unapproved use* of a previously licensed vaccine.[88] However, on December 11, 2020, FDA granted EUA to the vaccine manufactured by Pfizer-BioNTech, authorizing its use for the prevention of COVID-19 in individuals 16 years of age and older. A week later, on December 18, 2020, FDA granted EUA to the vaccine manufactured by Moderna, authorizing its use for the prevention of COVID-19 in individuals 18 years of age and older.

Advisory Committee Consultation

FDA consults with a federal advisory committee on various vaccine-related matters. Specifically, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) is made up of non-FDA medical and scientific experts who inform FDA's regulation of vaccines and related biological products. The committee "reviews and evaluates data concerning the safety, effectiveness, and appropriate use of vaccines and related biological products" and "considers the quality and relevance of FDA's research program which provides scientific support for the regulation of these products and makes appropriate recommendations" to the FDA

[85] FFDCA §564(c) [21 U.S.C. §360bbb-3(c)]. These criteria are explained in more detail in the FDA guidance Emergency Use Authorization of Medical Products and Related Authorities, January 2017, p. 7, https://www.fda.gov/media/97321/download.

[86] FFDCA §505(d) [21 U.S.C. §355(d)].

[87] FFDCA §564(e) [21 U.S.C. §360bbb-3(e)].

[88] Authorization of Emergency Use of Anthrax Vaccine Adsorbed for Prevention of Inhalation Anthrax by Individuals at Heightened Risk of Exposure Due to Attack With Anthrax, 70 *Federal Register* 5452, February 2, 2005.

Commissioner.[89] VRBPAC may, for example, meet to discuss approaches for demonstrating effectiveness of a particular vaccine in a specific population.[90] VRBPAC is subject to the requirements of the Federal Advisory Committee Act.[91]

Clinical Recommendations

Official HHS/CDC clinical recommendations for vaccination—such as the age and population groups recommended to receive each vaccine, as well as the number of doses and interval between doses—are informed by the Advisory Committee on Immunization Practices (ACIP), a federal advisory committee composed of medical and public health experts who make policy recommendations for the use of licensed vaccines and related agents for the control of vaccine-preventable diseases in the civilian population of the United States.[92] ACIP may also develop guidance for use of unlicensed vaccines "if circumstances warrant." Section 3091 of the 21st Century Cures Act (P.L. 114-255) added a requirement that ACIP make recommendations in a "timely manner, as appropriate" for vaccines that could be used in a public health emergency. ACIP was established by the U.S. Surgeon General in 1964, under authority provided by Public Health Service Act (PHSA) Section 222.[93] ACIP is subject to the requirements of the Federal Advisory Committee Act.[94]

After FDA licenses a new vaccine or licenses an existing vaccine for a new indication, ACIP typically makes one of two types of clinical recommendations:

- **Full recommendation** (also called "Category A")**:** The vaccine is recommended for all people in an age- or risk-based group, except for those with a *contraindication* (i.e., a condition that would make the vaccine harmful, such as a condition that compromises the immune system). For example, ACIP has issued a full recommendation for two doses of the measles-mumps-rubella (MMR) vaccine routinely for children, with the first dose administered at 12-15 months and the second dose administered before school entry at four to six years of age.[95]
- **Clinical Decisionmaking** (also called "Category B")**:** The vaccine is recommended for certain subpopulations, and its use is based on clinical decisionmaking.[96] For example, ACIP recommends the two Serogroup B

[89] Vaccines and Related Biological Products Advisory Committee, https://www.fda.gov/advisory-committees/blood-vaccines-and-other-biologics/vaccines-and-related-biological-products-advisory-committee.

[90] FDA, "2018 Meeting Materials, Vaccines and Related Biological Products Advisory Committee," https://www.fda.gov/advisory-committees/vaccines-and-related-biological-products-advisory-committee/2018-meeting-materials-vaccines-and-related-biological-products-advisory-committee.

[91] For additional information about the Federal Advisory Committee Act (FACA) and FACA committees, see CRS Report R44253, *Federal Advisory Committees: An Introduction and Overview*.

[92] Amanda Cohn, Lance E. Rodewald, Walter A. Orenstein et al., "Immunization in the United States," in *Plotkin's Vaccines*, ed. Stanley A. Plotkin, Walter A. Orenstein, and Paul A. Offit, 7th ed. (Elsevier, 2017), p. 1421.

[93] CDC, "ACIP Charter," June 5, 2018, https://www.cdc.gov/vaccines/acip/committee/charter.html.

[94] For additional information about the Federal Advisory Committee Act (FACA) and FACA committees, see CRS Report R44253, *Federal Advisory Committees: An Introduction and Overview*.

[95] Huong Q. McLean, Amy Parker Fibelkorn, Jonathan L. Temte et al., "Prevention of Measles, Rubella, Congenital Rubella Syndrome, and Mumps, 2013: Summary Recommendations of the Advisory Committee on Immunization Practices (ACIP)," *Morbidity and Mortality Weekly Report (MMWR)*, vol. 62, no. RR04 (June 14, 2013), pp. 1-34.

[96] Richard Hughes, Reed Maxim, and Alessandra Fix, "Vague Vaccine Recommendations May Be Leading to Lack of Provider Clarity, Confusion Over Coverage," *Health Affairs*, May 7, 2019; and Larry K. Pickering, Walter A. Orenstein, and Wellington Sun et al., "FDA Licensure of and ACIP Recommendations for Vaccines," *Vaccine*, vol. 35

Meningococcal vaccines for persons 10 years of age or older who have certain health conditions or are at increased risk of exposure to the disease, as specified.[97]

To make its vaccine recommendations, ACIP considers disease epidemiology and burden of disease,[98] vaccine efficacy and effectiveness, the quality of evidence reviewed, economic analyses, and implementation issues. Recommendations made by ACIP are reviewed by the CDC Director and, if adopted, published as official CDC recommendations.[99] ACIP recommendations inform which vaccines are provided through the CDC's Vaccines for Children program,[100] as well as which vaccines must be covered by private health care insurance plans subject to the preventive health services requirement (PHSA §2713) as added by the Patient Protection and Affordable Care Act (ACA; P.L. 111-148, as amended).[101]

ACIP recommendations are used to establish the CDC-recommended child and adult immunization schedules (for children, birth to 18 years of age; for adults, 19 years of age and older), which are used by health care providers, parents, and others to understand which vaccines should be administered at various ages. The immunization schedules distinguish between vaccines recommended to all people in a certain age group and vaccines recommended only for certain high-risk groups. As a part of the immunization schedules, CDC also publishes a specific table of vaccine recommendations by common contraindications, such as persons with HIV, immunocompromised individuals, and pregnant individuals. The table includes when recommended vaccines should *not* be administered to individuals with these contraindications.[102]

Once clinical recommendations are made, CDC develops and provides resources and training for health care providers on current vaccine recommendations, best practices for vaccine administration, and patient education.[103] CDC develops Vaccination Information Statements (VIS) on the risks and benefits of vaccinations; these statements are required to be given to vaccine recipients and their parents or legal guardians whenever vaccines recommended for routine use among children and pregnant women are administered.[104] VISs are developed by CDC in consultation with the Advisory Commission on Childhood Vaccines (ACCV; a committee of health care professionals, attorneys, and parents of vaccine-injured children), health care providers, and FDA, and are published in the *Federal Register* for public comment.[105]

(2017), p. 5027–5036.

[97] Monica E. Patton, David Stephens, and Kelly Moore, "Updated Recommendations for Use of MenB-FHbp Serogroup B Meningococcal Vaccine—Advisory Committee on Immunization Practices, 2016," *Morbidity and Mortality Weekly Report (MMWR)*, vol. 66, no. 19 (May 19, 2017), pp. 509-513.

[98] Burden of disease is a standardized measure for comparing the health impacts of different diseases based on cumulative disability, loss of full health, and premature mortality caused by each disease. See World Health Organization (WHO), "About the Global Burden of Diseases (GBD) Project," https://www.who.int/healthinfo/global_burden_disease/about/en/.

[99] CDC, "ACIP Charter," June 5, 2018, https://www.cdc.gov/vaccines/acip/committee/charter.html.

[100] Vaccines for Children is a Medicaid-financed program administered by CDC that provides vaccines at no cost to eligible children 18 years or younger, including those who are American Indian or Alaska Native, Medicaid-eligible, uninsured, or underinsured (as defined). See https://www.cdc.gov/features/vfcprogram/index.html.

[101] ACA, P.L. 111-148, as amended, which established PHSA §2713.

[102] CDC, "Immunization Schedules," https://www.cdc.gov/vaccines/schedules/index.html.

[103] CDC, "Vaccines- Healthcare Providers," 2018, https://www.cdc.gov/vaccines/hcp/index.html.

[104] Requirement established by the National Childhood Vaccine Injury Act, P.L. 99-660; PHSA §2126 [42 U.S.C. §300aa-26].

[105] P.L. 99-660; PHSA §2126 [42 U.S.C. §300aa-26].

Postmarket Safety

Although pre-licensure clinical trials and research are designed to identify common safety risks associated with a vaccine, such trials may not identify all long-term or rare adverse effects (similar to all pharmaceutical products). As such, vaccines may be subject to additional postmarket study requirements, called Phase 4 studies, or other safety monitoring to provide additional information about a vaccine's risks, benefits, and optimal use.[106] FDA may require a vaccine manufacturer to conduct a postapproval study or clinical trial to assess a known serious risk or signals of serious risk related to use of the vaccine, or to identify an unexpected serious risk when available data indicate the potential for a serious risk.[107] In addition, because vaccines require special manufacturing processes to avoid contamination, post-licensure safety programs are designed to ensure safety in vaccine manufacturing. Post-licensure safety requirements and programs are also intended to identify long-term or rare adverse health events that result from vaccination, and FDA may require vaccine manufacturers to revise vaccine product labeling if new information becomes available after licensure.[108]

Manufacturing Safety

FDA continues to inspect vaccine manufacturing facilities post-licensure.[109] The HHS Secretary may authorize any HHS officer, agent, or employee to "during all reasonable hours enter and inspect any establishment for the propagation or manufacture and preparation of any biological product [e.g., vaccine]."[110] If FDA determines that a batch, lot, or other quantity of a vaccine "presents an imminent or substantial hazard to the public health," the agency must issue an order immediately recalling the batch, lot, or other quantity of the vaccine.[111]

Manufacturers of vaccines listed in the Vaccine Injury Table (see the "National Vaccine Injury Compensation" section) or mandated to be state-administered must maintain records related to the safety and quality of each batch of vaccines produced, and must report any identified public health hazards to FDA.[112] Specifically, vaccine manufacturers are required to maintain records documenting the manufacturing, processing, testing, and reworking of each batch, lot, or other quantity of a vaccine, including whether any significant problems were identified during these processes, and to report if any safety test on such batch, lot, or other quantity indicates a potential imminent or substantial public health hazard.[113]

In addition, manufacturers of licensed vaccine are required to report adverse events to FDA. This includes the submission of 15-day alert reports and periodic safety reports. A 15-day alert report is required for each serious and unexpected adverse experience and must be submitted to FDA as

[106] 21 C.F.R. §312.85. See also FDA, "Vaccine Product Approval Process," https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/vaccine-product-approval-process.

[107] PHSA §351(a)(2)(D) [42 U.S.C. §262(a)(2)(D)] and FFDCA §505(o)(3) [21 U.S.C. §355(o)(3)].

[108] PHSA §351(a)(2)(D) [42 U.S.C. §262(a)(2)(D)] and FFDCA §505(o)(4) [21 U.S.C. §355(o)(4)].

[109] FDA, "Ensuring the Safety of Vaccines in the United States," last updated July 2011, https://www.fda.gov/media/83528/download.

[110] PHSA §351(c) [42 U.S.C. §262(c)].

[111] PHSA §351(d)(1) [42 U.S.C. §262(d)(1)].

[112] PHSA §2128 [42 U.S.C. §300aa–28]. This authority has been delegated from the HHS Secretary to the FDA Commissioner, per the FDA Staff Manual Guide 1410.10, item 31, effective date August 26, 2016, https://www.fda.gov/media/81983/download.

[113] PHSA §2128(a) [42 U.S.C. §300aa–28(a)].

soon as possible but no later than 15 days from initial receipt of the information by the manufacturer.[114] The manufacturer must "promptly investigate" such adverse event and submit follow-up reports within 15 days of receiving new information or as requested by FDA. Periodic safety reports are required for each adverse experience not reported in a 15-day alert report and must be submitted to FDA at quarterly intervals for three years from the date of issuance of the vaccine's license, and at annual intervals thereafter. Individual case safety reports for vaccines submitted to FDA must include specified information about the patient who is the subject of the report (e.g., name, age, gender) and the vaccine (e.g., manufacturer, lot number).[115] If a vaccine manufacturer fails to establish and maintain records or report adverse events, FDA can take enforcement action, including revocation of the BLA for that vaccine.[116]

As mentioned, for a vaccine made available under EUA, FDA must impose certain conditions on use of the authorized vaccine and may impose additional discretionary conditions where necessary or appropriate to protect the public health.[117] For example, FDA can require manufacturers and vaccination providers to monitor and report adverse events associated with the emergency use of the vaccine. FDA also can impose conditions concerning recordkeeping and reporting.

Surveillance

CDC and FDA are the primary federal agencies that conduct surveillance (i.e., data monitoring) activities on the safety of administered vaccines. Other federal agencies such as the Department of Defense (DOD) and the Centers for Medicare & Medicaid Services (CMS) also operate databases on vaccine safety events among their covered populations.[118] The NVPO within the HHS Office of Infectious Disease and HIV/AIDS Policy (OIDP) is tasked with coordinating vaccine safety monitoring across federal agencies.[119]

FDA and CDC monitor and conduct research on vaccine safety through various mechanisms. As discussed below, each of the programs or systems has strengths and limitations, but together they provide various ways of assessing vaccines to ensure their safety. Each of the systems allows for monitoring of adverse events linked to specific lots of manufactured vaccines. This lot-specific monitoring enables distinctions between adverse events linked to improper manufacturing, compared with adverse events

Key Terms: Passive and Active Surveillance

Public health surveillance, or ongoing data monitoring, can be passive or active. A *passive surveillance system* relies on reports, often from health care providers or patients. In an *active surveillance system*, data are collected proactively—either through active analysis of electronic health data (such as for the monitoring systems covered here), or where data are collected directly by contacting health care organizations or obtaining records.

Source: CDC, "Introduction to Public Health Surveillance," https://www.cdc.gov/publichealth101/surveillance.html.

[114] 21 C.F.R §600.80(c).

[115] 21 C.F.R §600.80(g).

[116] 21 C.F.R §600.80(l).

[117] FFDCA §564(e) [21 U.S.C. §360bbb-3(e)].

[118] Matthew Z. Dudley, Daniel A. Salmon, Neal A. Halsey et al., "Monitoring Vaccine Safety," in *The Clinician's Vaccine Safety Resource Guide* (Springer, Cham, 2018).

[119] National Vaccine Advisory Committee (NVAC), *White Paper on the United States Vaccine Safety System*,

linked to a particular type of vaccine.[120]

Vaccine Adverse Event Reporting System (VAERS)

VAERS, established in 1990 and operated jointly by FDA and CDC, is a monitoring system for adverse events related to vaccines. Using the VAERS system, anyone, including physicians, nurses, and the general public, can submit an online report of an adverse event following vaccination. Pursuant to PHSA Section 2125, health care providers and vaccine manufacturers are required to report the occurrence of any adverse event in the Vaccine Injury Table (see the "National Vaccine Injury Compensation" section), the occurrence of a contraindicating reaction specified on the vaccine label, and other serious and unexpected events as required through regulations.[121] Scientists at CDC and FDA monitor VAERS reports and use the information to conduct further investigations on the reported cases.[122] Consolidated data on reported adverse events in the VAERS system are publicly available online.[123]

VAERS is a passive reporting system. Its data represent reports of adverse health events related to vaccines, rather than validated cases. In addition, data in the system lack information on total vaccines administered in the covered populations. Therefore, VAERS data are often inadequate for epidemiological analyses of adverse health events at a population level.[124] VAERS is useful, however, for helping identify new and unusual clusters of cases of adverse health events linked to vaccination. VAERS also can provide some of the first postmarket safety data on newly introduced vaccines. In addition, VAERS can help identify extremely rare and unusual adverse health events that occur following vaccination. Researchers can use VAERS reports to generate hypotheses about vaccine safety and then use other sources of data (such as from the databases discussed below) and clinical evidence to assess their hypotheses.[125]

Vaccine Safety Datalink (VSD)

VSD, established in 1990 and operated by CDC, is an active surveillance system and a collaborative project for conducting studies on vaccine safety between CDC and eight integrated health care organizations (i.e., combined payer and provider organizations) around the country. VSD uses electronic patient and medical records from participating sites, which allows for large-scale and controlled analyses of medical events (e.g., hospitalizations, diagnoses) that occur after vaccination to identify associated risks.[126] VSD studies may supplement these records with other sources of information, such as patient surveys, medical charts, and pharmacy, laboratory, and

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September 2011, p. 21, https://www.hhs.gov/sites/default/files/nvpo/nvac/nvac_vswp.pdf.

[120] HHS, *Comprehensive Review of Federal Vaccine Safety Programs and Public Health Activities*, December 2008, https://www.hsdl.org/?abstract&did=6793; and Meghan A. Baker, Michael Nguyen, and David V. Cole, "Post-Licensure Rapid Immunization Safety Monitoring Program (PRISM) Data Characterization," *Vaccine*, vol. 31S (2013), pp. K98-K112.

[121] PHSA §2125 [42 U.S.C. §300aa-25]; 21 C.F.R. Part 600.

[122] CDC, "Understanding the Vaccine Adverse Event Reporting System (VAERS)," https://www.cdc.gov/vaccines/hcp/patient-ed/conversations/downloads/vacsafe-vaers-color-office.pdf.

[123] VAERS, "VAERS data," https://vaers.hhs.gov/data.html.

[124] CDC, "Vaccine Safety Datalink (VSD)," https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/; and Frank DeStefano, Paul A. Offit , and Allison Fisher, "Vaccine Safety," in *Plotkin's Vaccines*, ed. Stanley Plotkin, Walter Orenstein, Paul Offit, Kathryn M. Edwards, 7th ed. (Elsevier, 2018), pp. 1586.

[125] Frank DeStefano, Paul A. Offit, and Allison Fisher, "Vaccine Safety," in *Plotkin's Vaccines*, ed. Stanley A. Plotkin, Walter A. Orenstein, and Paul A. Offit, 7th ed. (Elsevier, 2017), pp. 1586-1587.

[126] CDC, "Vaccine Safety Datalink (VSD)," https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/.

radiology data, to validate vaccination data and outcomes. Health data on about 9 million people are included annually in VSD.[127]

VSD allows for near real-time detection of large-scale adverse health events linked to vaccination. Researchers have developed methods to use VSD data to study the health effects of vaccines, such as whether the measles-mumps-rubella (MMR) vaccine is associated with autism (studies have found no such association). Among its limitations, the population represented by VSD, while large, is not completely representative of the entire U.S. population in terms of geography, race, socioeconomic status, and other factors, particularly because the participating organizations are private health plans which generally over-represent people of higher socioeconomic status and non-minority groups.[128] In addition, VSD's population size may not be adequate for detecting extremely rare adverse events linked to vaccination.[129]

Sentinel Initiative

FDA established the Sentinel Initiative in 2008, fulfilling a statutory directive to collaborate with public, academic, and private entities to develop methods for obtaining access to disparate data sources and to validate means of linking and analyzing safety data from multiple sources.[130] As part of the Sentinel Initiative, FDA has established two programs that address vaccines: (1) the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) program, and (2) the Biologics Effectiveness and Safety (BEST) system.

PRISM is an active surveillance program that uses electronic health records from insurance providers and state immunization registries to monitor adverse events following vaccination. It was established in 2009 and deployed during the H1N1 influenza pandemic.[131] PRISM has been the largest linked database for monitoring vaccine safety in the United States, involving data on over 100 million people.[132] PRISM, similar to the CDC VSD program, can allow for population-level scientific analyses of adverse events following vaccination. Because of the larger population covered, PRISM can detect rarer adverse events than VSD and enable stratified analyses of vaccine-linked adverse events by subpopulation (e.g., by race/ethnicity).[133] As of 2012, VSD allowed for more rapid analyses than PRISM due to data-sharing agreements between the participating health organizations and CDC that allow for near real-time data collection.[134]

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[127] Frank DeStefano, Paul A. Offit, and Allison Fisher, "Vaccine Safety," in *Plotkin's Vaccines*, ed. Stanley A. Plotkin, Walter A. Orenstein, and Paul A. Offit, 7th ed. (Elsevier, 2017), pp. 1587.

[128] CDC, "Vaccine Safety Datalink (VSD)," https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/; and Frank DeStefano, Paul A. Offit, and Allison Fisher, "Vaccine Safety," in *Plotkin's Vaccines*, ed. Stanley Plotkin, Walter Orenstein, Paul Offit, Kathryn M. Edwards, 7th ed. (Elsevier, 2018), pp. 1584-1600.

[129] Michael Nguyen, Robert Ball, Karen Midthun et al., "The Food and Drug Administration's Post-Licensure Rapid Immunization Safety Monitoring Program: Strengthening the Vaccine Safety Enterprise,"*Pharmacoepidemiology and Drug Safety*, vol. 21, no. S1 (2012), pp. 291-97.

[130] The Sentinel system was implemented as an "Active Post-Market Risk Identification and Analysis program" under FFDCA §505(k)(3), as amended by §905 of the FDA Amendments Act, P.L. 110-85.

[131] PRISM is the vaccine component of FDA's Sentinel Initiative.

[132] FDA, "Advances in the Science, Surveillance, and Safety of Vaccines," 2013, https://www.hhs.gov/vaccines/national-vaccine-plan/annual-report-2013/goal-2/advances-in-science-surveillance-safety-of-vaccines/index.html; and Matthew Z. Dudley, Daniel A. Salmon, Neal A. Halsey et al., "Monitoring Vaccine Safety," in *The Clinician's Vaccine Safety Resource Guide* (Springer, Cham, 2018).

[133] Michael Nguyen, Robert Ball, Karen Midthun et al., "The Food and Drug Administration's Post-Licensure Rapid Immunization Safety Monitoring Program: Strengthening the Vaccine Safety Enterprise," *Pharmacoepidemiology and Drug Safety*, vol. 21, no. S1 (2012), pp. 291-97.

[134] Matthew Z. Dudley, Daniel A. Salmon, Neal A. Halsey et al., "Monitoring Vaccine Safety," in *The Clinician's*

PRISM has been used to inform FDA-required postmarket labeling changes.[135] For example, after some studies found an association between risk of intussusception (i.e., intestinal blockage) and administration of two rotavirus vaccines (RotaTeq and Rotarix), FDA launched a study in PRISM to assess whether infants faced a similar risk.[136] The PRISM study identified an increased, but rare, risk of intussusception with RotaTeq among infants, which led to FDA-required labeling changes for the licensed vaccine.[137]

In 2017, CBER initiated the BEST system as part of Sentinel to assure the safety and effectiveness of vaccines and other biologics. It is broader than PRISM in that it also covers blood and blood products, tissue products, and other advanced therapeutic biologics.[138] The goal of BEST is to "leverage high-quality data, analytics and innovation to enhance surveillance, real-world evidence generation, and clinical practice that benefits patients." Like other Sentinel components, BEST uses electronic health record, administrative, and claims-based data for active surveillance and research.[139]

Other Safety Monitoring Systems

As mentioned above, federal agencies other than FDA and CDC conduct vaccine safety monitoring. CMS has a database for vaccine safety among the Medicare population; the database represents vaccines administered to persons aged 65 and older. DOD has a database for monitoring adverse events from vaccination among military service members and their families, and the Department of Veterans Affairs (VA) has a database for veterans who receive care in the VA system. In addition, the Indian Health Service (IHS) operates a database for vaccine safety monitoring among the IHS-covered population.[140]

Safety Monitoring Using Multiple Surveillance Systems: A Case Study

Researchers have used information from multiple vaccine safety monitoring systems to draw associations between vaccines and subsequent adverse health events. For example, during the 2010-2011 influenza season, VAERS received an increased number of reports of febrile seizures following vaccination with Fluzone.™ FDA then initiated a PRISM study to investigate febrile seizures after vaccination with Fluzone™ and other trivalent

Vaccine Safety Resource Guide (Springer, Cham, 2018).

[135] FDA CBER, "Post-licensure Rapid Immunization Safety Monitoring (PRISM) Public Workshop," December 7, 2016, Bethesda, MD, https://www.fda.gov/media/103876/download.

[136] FDA, "RotaTeq (Rotavirus Vaccine) Questions and Answers," https://www.fda.gov/vaccines-blood-biologics/vaccines/rotateq-rotavirus-vaccine-questions-and-answers.

[137] According to FDA, "The Mini-Sentinel PRISM study is the largest study of intussusception after rotavirus vaccines to date and identified an increased risk of intussusception in the 21 day time period after the first dose of RotaTeq, with most cases occurring in the first 7 days after vaccination. No increased risk was found after the second or third doses. These findings translate into 1 to 1.5 additional cases of intussusception per 100,000 first doses of RotaTeq." See "FDA Safety Communication: FDA Approves Required Revised Labeling for RotaTeq Based Final Study Results of a Mini-Sentinel Postlicensure Observational Study of Rotavirus Vaccines and Intussusception," July 22, 2013, https://www.sentinelinitiative.org/communications/fda-safety-communications/fda-safety-communication-fda-approves-required-revised.

[138] Sentinel, "Vaccines, Blood, & Biologics Assessments," https://www.sentinelinitiative.org/assessments/vaccines-blood-biologics.

[139] FDA, "CBER Biologics Effectiveness and Safety (BEST) System," https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-biologics-effectiveness-and-safety-best-system.

[140] Matthew Z. Dudley, Daniel A. Salmon, Neal A. Halsey et al., "Monitoring Vaccine Safety," in *The Clinician's Vaccine Safety Resource Guide* (Springer, Cham, 2018).

inactivated influenza vaccines (TIVs). The study found no statistically significant association between TIVs and increased risk of febrile seizures.

Source: FDA, "Update: FDA Postlicensure Rapid Immunization Safety Monitoring (PRISM) study demonstrates no statistically significant association between Trivalent Inactivated Influenza Vaccine and Febrile Seizures in Children during the 2010-2011 influenza season," May 16, 2014, https://www.sentinelinitiative.org/communications/fda-safety-communications/update-fda-postlicensure-rapid-immunization-safety.

Clinical Assessment

The Clinical Immunization Safety Assessment (CISA), a CDC program established in 2001, is a network of clinical scientists who conduct clinical studies (i.e., studies with patients) on vaccine safety. Scientists in the network can conduct studies on complex individual patient cases of possible adverse health events that followed vaccination.[141] Using CISA, scientists can assess the biological mechanisms that cause adverse health events after vaccination.[142] In addition, CISA manages a repository of biospecimen samples from patients who experience unusual adverse events following vaccination.[143] These samples can be systemically analyzed to inform a mechanistic understanding of such adverse events.

Federal Research on Vaccine Safety

Postmarket surveillance systems and clinical assessments provide important data and evidence on potential adverse events following vaccination. To further understand and determine whether vaccines cause or could plausibly cause certain adverse health events, scientists conduct various types of research that inform a scientific understanding of vaccine safety (separate from the clinical trials under an IND). Such activities are supported primarily by HHS agencies, mainly CDC and the National Institutes of Health (NIH). In addition, FDA supports regulatory research related to methods for evaluating vaccine safety. Major areas of research related to vaccines can include the following:[144]

- **Biological research:** Research often with animals, cell cultures, or biological specimens (e.g., human tissue samples) to explore the mechanisms by which vaccines act in biological systems, informing an understanding of how adverse events may occur. (Also referred to as basic biomedical research).
- **Epidemiological research:** A form of statistical research involving health data collected among defined human populations (such as postmarket surveillance data) to explore whether statistical associations exist between vaccination and subsequent adverse events, and any related risk factors for those events among those populations.

[141] CDC, "Clinical Immunization Safety Assessment (CISA) Project," https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/cisa/index.html.

[142] Frank DeStefano, Paul A. Offit, and Allison Fisher, "Vaccine Safety," in *Plotkin's Vaccines*, ed. Stanley Plotkin, Walter Orenstein, Paul Offit, Kathryn M. Edwards, 7th ed. (Elsevier, 2018), pp. 1588.

[143] NVAC, *White Paper on the United States Vaccine Safety System*, September 2011, p. 16, https://www.hhs.gov/sites/default/files/nvpo/nvac/nvac_vswp.pdf.

[144] NVAC, *White Paper on the United States Vaccine Safety System*, September 2011, p. 16, https://www.hhs.gov/sites/default/files/nvpo/nvac/nvac_vswp.pdf.

- **Clinical research:** Research with patients to understand the clinical features of adverse health events among patients that are hypothesized to be connected to vaccination.

Research can also explore the underlying methodologies used to assess vaccine safety through any of these forms of research.

CDC Research

CDC conducts and supports many types of research on vaccine safety, including epidemiological and clinical studies. Many of CDC's research publications rely on data and findings from its safety monitoring systems, as listed above, including VAERS, VSD, and CISA. CDC research often focuses on the use of specific vaccines in specific populations, as well as hypothesized side effects and adverse events potentially attributable to vaccination.[145] For example, a recent CDC study published in 2020 explored probability-based methods of determining which vaccine or combination of vaccines were linked to an adverse event following vaccination (in this case, a seizure) when multiple vaccines were administered at once.[146]

NIH Research

In addition to CDC research, biological research related to immunology or infectious disease supported by NIH informs an understanding of vaccine safety. NIH tends to support more biological research than CDC, in that NIH research focuses on the fundamental biological mechanisms underlying vaccine safety, as well as research methodologies for examining it. For the past several years, NIH, in collaboration with CDC and NVPO, has issued annual funding opportunity announcements for "Research on Vaccine Safety." Research projects can include scientific investigations into physiological and immunological responses to vaccines; explorations of how genetic variations affect responses to vaccines; investigations into risk factors for adverse responses to vaccination; exploration and validation of statistical methods for analyzing data on vaccine safety; and the application of genomic and molecular technologies to assess vaccine safety.[147]

The National Institute of Allergy and Infectious Diseases (NIAID, which is one of 27 NIH Institutes and Centers) also supports the Human Immunology Project Consortium (HIPC), a program established in 2010 that collects in-depth biological data over time on the immune systems of a diverse cohort of patients. The program consolidates data on the cohort into centralized databases for use by researchers.[148] Researchers are using HIPC to study certain aspects of vaccine safety, such as whether a relationship exists between short-term adverse events caused by vaccination and long-term health effects.[149] When combined with postmarket

[145] CDC, "Vaccine Safety Publications," https://www.cdc.gov/vaccinesafety/research/publications/index.html.

[146] Shirley V. Wang, Kristina Stefanini, Edwin Lewis et al., "Determining Which of Several Simultaneously Administered Vaccines Increase Risk of an Adverse Event," *Drug Safety*, vol. 43 (July 1, 2020), pp. 1057-65.

[147] NIH, "Research to Advance Vaccine Safety (R01)," July 24, 2018, https://grants.nih.gov/grants/guide/pa-files/PA-18-873.html.

[148] NIH, "Human Immunology Project Consortium," https://www.immuneprofiling.org/hipc/page/showPage?pg=about.

[149] National Academy of Medicine, *The Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies*, Washington, DC, January 16, 2013, http://nationalacademies.org/HMD/Reports/2013/The-Childhood-Immunization-Schedule-and-Safety.aspx.

surveillance data and studies, NIH-supported research can contribute to robust evaluations on the safety of vaccines.

FDA Research

FDA conducts regulatory science research to facilitate its evaluation of vaccine safety and effectiveness, and to support the development of new vaccines. For example, CBER scientists have published studies on the agency's effort to develop and evaluate assays and animal models for studying the safety and efficacy of vaccines against specific pathogens, as well as to characterize biomarkers of vaccine safety and efficacy.[150] In addition, FDA has studied certain adjuvants and preservatives added to vaccines, including thimerosal and the impact of aluminum in vaccines on infants.[151] FDA research efforts have also focused on vaccine availability, specifically on influenza vaccine production and ensuring a sufficient supply of a safe vaccine.[152]

Other Federal Research

Other federal agencies conduct or support research related to vaccine safety. For example, the NVPO has issued Funding Opportunity Announcements (FOA) for grants to support vaccine safety research.[153] The Agency for Healthcare Research and Quality (AHRQ) has conducted vaccine safety reviews. The Department of Defense (DOD) and the Department of Veterans Affairs (VA) also support some vaccine safety research.[154]

Periodically, federal agencies (particularly HHS) conduct or commission comprehensive scientific reviews on the safety of recommended vaccines. As described in the text box (see "What Is a Causality Assessment?"), these reviews often evaluate and combine evidence from a large number of studies and a range of research types to make assessments about the safety of vaccines that are as conclusive as possible. For example, in 2011, under HHS contract, the National Academy of Medicine (NAM)[155] conducted a comprehensive review of the scientific evidence regarding the safety of eight pediatric vaccines. The resulting NAM report, *Adverse Effects of Vaccines: Evidence and Causality*, was used to inform an update of the Vaccine Injury Table for the National Vaccine Injury Compensation Program (see the "National Vaccine Injury Compensation" section).[156] This review was subsequently updated in 2014 with additional research by AHRQ, supported by the NVPO; AHRQ is currently in the process of updating this review.[157]

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[150] FDA, Vaccines Research, current as of August 14, 2020, https://www.fda.gov/vaccines-blood-biologics/biologics-research-projects/vaccines-research.

[151] L. K. Ball, R. Ball, R. D. Pratt, "An assessment of thimerosal use in childhood vaccines," *Pediatrics*, 2001, vol. 107 no. 5, pp. 1147-1154. The study was required by the FDA Modernization Act (FDAMA, P.L. 105-115). FDA, "Study Reports Aluminum in Vaccines Poses Extremely Low Risk to Infants," https://wayback.archive-it.org/7993/20170405003134/https:/www.fda.gov/BiologicsBloodVaccines/ScienceResearch/ucm284520.htm.

[152] FDA, "Facilitating Influenza Virus Vaccine Production by Optimizing Vaccine Strains," https://www.fda.gov/vaccines-blood-biologics/biologics-research-projects/facilitating-influenza-virus-vaccine-production-optimizing-vaccine-strains.

[153] See, for example, BetaSam.gov, "Research, Monitoring and Outcomes Definitions for Vaccine Safety," https://beta.sam.gov/fal/c8125303527f478981f6b7395c528788/view.

[154] Vaccines.gov, "Vaccine Safety," https://www.vaccines.gov/basics/safety.

[155] NAM was named the Institute of Medicine when the Immunization Safety Review Committee was formed.

[156] Institute of Medicine, *Adverse Effects of Vaccines: Evidence and Causality*, August 25, 2011.

[157] Margaret A. Maglione, Courtney Gidengil, Lopamudra Das et al. "Safety of Vaccines Used for Routine

Challenges of Vaccine Safety Reviews

As discussed earlier, causality assessments that combine evidence across many studies allow for researchers to assess if all the available evidence favors a causal relationship between a vaccine and a subsequent adverse health event. In general, establishing true causal linkages between a vaccine and certain subsequent adverse health events can be challenging; however, researchers draw conclusions using multiple forms of evidence. The clinical trials required for vaccine licensure are well-controlled scientific experiments that allow researchers to draw conclusions about the safety of products. Postmarket safety studies, on the other hand, can face a variety of methodological challenges. For one, the population of vaccinated individuals is often much larger than and demographically different from the population of unvaccinated individuals, making it difficult to draw comparisons in health outcomes between the two groups. Researchers therefore often rely on time intervals between vaccination and an adverse health event—assessing whether a certain adverse health event is more likely to occur within a defined time interval after vaccination compared with other time periods. While this approach can work for short-term health effects caused by vaccines, it can be less effective for hypothesized long-term effects of vaccines or adverse health events that are otherwise common in the population. Statistical *association* between vaccination and an adverse health event is often necessary but not sufficient to establish *causality*. As discussed earlier, to make a causality assessment about whether a particular vaccine causes an adverse health event, experts use evidence and results from many scientific studies, including epidemiological evidence, clinical evidence, and biological laboratory evidence, usually with methods to weigh, compare, and combine evidence across studies.[158] Such causality assessments may be conducted as a part of a comprehensive scientific review by federal or academic scientists, or by independent scientific advisory bodies, such as the NAM.

National Vaccine Injury Compensation

The National Vaccine Injury Compensation Program (VICP) provides compensation to individuals who file a petition and are found to have been injured by a covered vaccine. Under current law, the HHS Secretary is required to promulgate VICP regulations for vaccines recommended for "routine administration" to children and pregnant women.[159] Compensation can be provided for vaccines listed as a "taxable vaccine" in 26 U.S.C. §4132(a)(1).[160] Anyone injured by the covered vaccines—including nonpregnant adults—can file a claim.[161] VICP publishes a "Vaccine Injury Table" that lists vaccines covered by the program and the injuries associated with those vaccines for which claims may be filed, developed in part based on the causality assessments conducted by Institute of Medicine (IOM, now called the National Academy of

Immunization in the United States," *Agency for Healthcare Research and Quality*, July 2014, https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/vaccine-safety_research.pdf, and AHRQ, "Safety of Vaccines Used for Routine Immunization in the United States: Research Protocol," April 2020, https://effectivehealthcare.ahrq.gov/products/safety-vaccines/protocol.

[158] Frank DeStefano, Paul A. Offit, and Allison Fisher, "Vaccine Safety," in *Plotkin's Vaccines*, ed. Stanley A. Plotkin, Walter A. Orenstein, and Paul A. Offit, 7th ed. (Elsevier, 2017), pp. 1589.

[159] PHSA §2114 [42 U.S.C. §300aa-14], and26 U.S.C. §4132(a)(1).

[160] 26 U.S.C. §9510(c).

[161] U.S. Government Accountability Office, *Vaccine Injury Compensation: Most Claims Took Multiple Years and Many Were Settled through Negotiation*, GAO-15-142, November 21, 2014, https://www.gao.gov/products/GAO-15-142.

Medicine) and AHRQ. Claimants may submit claims for injuries that are not listed on the table, but they must present evidence that the vaccine caused the injury.[162]

VICP is funded by the Vaccine Compensation Trust Fund, which is funded by an excise tax on vaccines paid by manufacturers. Taxable vaccines included in the program are listed in 26 U.S.C. §4132(a)(1), and compensation cannot be paid from the trust fund unless the vaccine is listed as a "taxable vaccine" under that section.[163] Therefore, adding a new type of vaccine to the program would generally need action by Congress.

VICP was established in response to vaccine shortages that occurred after hundreds of injury lawsuits were filed against vaccine manufacturers in the 1980s, leading to halts in vaccine production and creating instability in the vaccine market. VICP is a no-fault system to compensate individuals who were injured as a result of vaccination. It serves to protect manufacturers from injury lawsuits. As of January 1, 2021, over 22,919 petitions have been filed with VICP, and 7,754 were determined to be compensable, with total compensation paid of about $4.5 billion since the program was established in 1988.[164]

VICP is based in the Health Resources and Services Administration (HRSA) and was established by the National Childhood Vaccine Injury Act of 1986 (P.L. 99-660).[165] In addition to HHS/HRSA, VICP involves the Department of Justice (DOJ) and the U.S. Court of Federal Claims.[166] The Advisory Committee on Childhood Vaccines (ACCV) also provides oversight of VICP by making recommendations to the HHS Secretary, including those related to the Vaccine Injury Table. ACCV is a nine-member federal advisory committee made up of health and legal representatives, as well as parents or legal representatives of children who have been injured by vaccines.[167]

During an emergency situation such as the COVID-19 pandemic, vaccines may be covered under a different injury compensation program—the Countermeasures Injury Compensation Program (CICP), as discussed in the "Injury Compensation and Patient Safety Information" section.[168]

Safety in Vaccine Distribution

Managing vaccine supply and distribution requires temperature control, safety controls, and regular monitoring of expiry dates due to the limited shelf life of products.[169] Given that public

[162] HRSA, "National Vaccine Injury Compensation Program—Covered Vaccines," June 2019, https://www.hrsa.gov/vaccine-compensation/covered-vaccines/index.html.

[163] 26 U.S.C. §9510(c).

[164] HRSA, "Data & Statistics," https://www.hrsa.gov/sites/default/files/hrsa/vaccine-compensation/data/data-statistics-report.pdf.

[165] HRSA, "National Vaccine Injury Compensation," https://www.hrsa.gov/vaccine-compensation/index.html.

[166] HRSA, "About the National Vaccine Injury Compensation Program," June 2019, https://www.hrsa.gov/vaccine-compensation/about/index.html.

[167] HHS, "Charter- Advisory Commission on Childhood Vaccines," https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/vaccines/accvcharter.pdf. For the parents or legal representatives of children who have suffered a vaccine-related injury or death, HRSA specifies that to be considered for appointment, "there must have been a finding (i.e., a decision) by the U.S. Court of Federal Claims or a civil court that a VICP-covered vaccine caused, or was presumed to have caused, the represented child's injury or death." From HRSA, "Advisory Commission on Vaccines: Frequently Asked Questions," 2018, https://www.hrsa.gov/sites/default/files/hrsa/vaccine-compensation/job-opportunities/ACCV-FAQs.pdf.

[168] CRS Legal Sidebar LSB10443, *The PREP Act and COVID-19: Limiting Liability for Medical Countermeasures*.

[169] Judith R. Kaufmann, Roger Miller, and James Cheyne, "Vaccine Supply Chains Need To Be Better Funded And

dollars (federal and state) pay for over 50% of vaccines (by volume) in the United States, federal agencies play a role in the supply and distribution of vaccines.[170] CDC, in particular, conducts activities to help improve management of the vaccine supply chain. Vaccine storage practices especially have implications for a vaccine's potency (i.e., effectiveness).[171]

Vaccines are distributed through a decentralized network of health care providers, health centers, pharmacies, and health departments. State requirements vary regarding the types of providers that can be licensed or authorized to administer various vaccines. In the CDC's Vaccines for Children (VFC) program, health care providers can apply to receive and provide VFC-covered vaccines through state or local coordinators, who ensure that the provider meets program requirements (e.g., ability to properly store and handle vaccines).[172] Any provider that is licensed or otherwise authorized to administer pediatric vaccines can apply to participate in a state's VFC program and receive and administer a supply of vaccine.[173]

Vaccine programs are expected to make vaccines widely available, while ensuring that they are safely stored, properly administered, and used or discarded before their expiry date. However, this requirement is a challenge for many vaccine programs. A 2012 HHS Inspector General report found that many VFC providers did not meet vaccine management requirements, either by exposing vaccines to improper temperatures, storing expired and nonexpired vaccines together, or failing to maintain documentation. CDC agreed with the report recommendations and committed to improving management among providers.[174] Following the report, CDC changed VFC program requirements and issued recommendations to providers and immunization program managers.[175]

CDC's immunization programs include several efforts among state and local partners to improve the vaccine supply chain and vaccine distribution:

- The **Vaccine Management Business Improvement Project** (VMBIP) is an effort among CDC and state and local partners to improve the management of the vaccine supply chain, particularly for vaccines distributed through VFC. Since the project began in 2003, it has changed funding mechanisms, forecasting for supply needs, provider distribution, and inventory tracking among vaccine providers.[176]

Strengthened, Or Lives Will Be At Risk," *Health Affairs*, vol. 30, no. 6 (2011), pp. 1113-1121.

[170] Matthew J. Robbins and Sheldon H. Jacobson, "Analytics for Vaccine Economics and Pricing: Insights and Observations," *Expert Review of Vaccines*, vol. 14, no. 4 (December 1, 2014), pp. 606-616.

[171] CDC, "Vaccine Storage and Handling Toolkit," January 2019, https://www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf.

[172] CDC, "Why Join and How to Become a VFC Provider," https://www.cdc.gov/vaccines/programs/vfc/providers/questions/qa-join.html.

[173] Social Security Act §1928(c); 42 U.S.C. §1396s(c).

[174] HHS Office of Inspector General, *Vaccines for Children Program: Vulnerabilities in Vaccine Management*, June 2012, https://oig.hhs.gov/oei/reports/oei-04-10-00430.pdf.

[175] Association of Immunization Managers, *AIM Statement on Vaccine Storage and Management*, February 7, 2017, https://cdn.ymaws.com/www.immunizationmanagers.org/resource/resmgr/policy/AIM_Statement_on_Vaccine_Sto.pdf.

[176] CDC, "Vaccine Management Business Improvement Project," https://www.cdc.gov/vaccines/programs/vtrcks/vmbip.html.

- The **Vaccine Tracking System** (VTrckS) is an information technology platform for managing the publicly funded vaccine supply chain available to CDC, state and local health departments, and providers.[177]

Safety Considerations for COVID-19 Vaccines

The COVID-19 vaccine development, approval, and distribution planning situation is evolving. Readers should note the date of this publication and be aware that this report may not reflect events or actions that occurred after that date.

As of the date of this report, two COVID-19 vaccines are authorized by FDA for emergency use. FDA has determined that these vaccines may be effective in preventing COVID-19, and that their known and potential benefits outweigh their known and potential risks,[178] consistent with the statutory standard for EUA issuance (see the section "FDA Marketing Authorization") and the safety and effectiveness standards set forth by FDA in guidance.[179] Ongoing programs, such as those concerning vaccine manufacturing, distribution, and clinical education, aim to ensure that vaccines are safely produced, distributed, stored, and administered. In addition, several postmarket programs continue to study and monitor vaccines in use to identify any new or rare safety risks. Any newly identified safety issues may lead to changes in vaccine labeling and clinical recommendations for use. In the event that risk of vaccination with a certain vaccine outweighs its benefits for any population, FDA may modify or revoke its EUA.

U.S. vaccine development efforts have been supported and coordinated by Operation Warp Speed (OWS), the nation's major COVID-19 vaccine, therapeutic, and diagnostic (medical countermeasures) initiative. This report refers to this initiative as OWS, although the Biden Administration reportedly plans to retire this name and to restructure this initiative.[180] OWS has chosen to support 14 potential COVID-19 vaccine candidates from a pool of 93, with the stated goal of reducing the number of candidates to 7 as additional results from clinical trials and research become available.[181] As of October 29, 2020, OWS had announced contracts in support of six vaccines out of the eight in OWS' portfolio.[182] OWS and CDC are implementing a federally coordinated nationwide COVID-19 vaccine distribution campaign.[183]

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[177] CDC, "Vaccine Tracking System," https://www.cdc.gov/vaccines/programs/vtrcks/index.html.

[178] FDA, *Emergency Use Authorization (EUA) for an Unapproved Product- Pfizer, Inc. on behalf of Pfizer and BioNTech*, December 11, 2020, https://www.fda.gov/media/144416/download; and FDA, *Emergency Use Authorization (EUA) for an Unapproved Product- ModernaTx, Inc*, December 18, 2020, https://www.fda.gov/media/144673/download.

[179] FDA, "Emergency Use Authorization for Vaccines to Prevent COVID-19," Guidance for Industry, October 2020, https://www.fda.gov/media/142749/download.

[180] White House Press Secretary Jen Psaki @jrpsaki, "OWS is the Trump team's name for their program. We are phasing in a new structure, which will have a different name than OWS ... " January 15, 2021, 11:44 a.m., https://twitter.com/jrpsaki/status/1350121790148902912.

[181] Department of Health and Human Services (HHS), "Fact Sheet: Explaining Operation Warp Speed," press release, updated August 7, 2020, https://www.hhs.gov/about/news/2020/06/16/fact-sheet-explaining-operation-warp-speed.html.

[182] Moncef Slaoui and Matthew Hepburn, "Developing Safe and Effective Covid Vaccines—Operation Warp Speed's Strategy and Approach," *New England Journal of Medicine*, October 29, 2020.

[183] Operation Warp Speed, "From the Factory to the Frontlines The Operation Warp Speed Strategy for Distributing a COVID-19 Vaccine," https://www.hhs.gov/sites/default/files/strategy-for-distributing-covid-19-vaccine.pdf?source=email, and CDC, *COVID-19 Vaccination Program: Interim Playbook for Jurisdiction Operations*, September 16, 2020, https://www.cdc.gov/vaccines/imz-managers/downloads/COVID-19-Vaccination-Program-Interim_Playbook.pdf.

Making safe and effective COVID-19 vaccines available within a year represents an unprecedented scientific and public health effort. The safety considerations and applicability of the requirements, processes, and programs described in this report differ when applied to COVID-19 vaccines in several key ways, particularly with respect to (1) vaccine development, (2) FDA marketing authorization, (3) clinical recommendations and prioritization, (4) surveillance and safety monitoring, (5) injury compensation and patient safety information, and (6) vaccine distribution. Each of these is described in more detail below.

Vaccine Development and Current Status

Typically, the vaccine development and testing process is linear, with an investigational vaccine progressing through each phase of clinical testing upon completion of the prior phase. As mentioned above, the first stage is basic research, and if laboratory and animal test data indicate that a vaccine candidate appears safe and effective against a pathogen, then a first-in-human Phase 1 trial generally follows. If the Phase 1 trial indicates that the vaccine is safe in humans, then Phase 2 testing commences, further examining safety and at what dosage the vaccine has an effect. Finally, if those studies are successful, then a large, placebo-controlled Phase 3 trial follows. This sequential process helps minimize potential health risks to study participants and financial risks to the company sponsoring the investigations. The OWS COVID-19 vaccine development process is not following this phased approach. Instead, it is conducting some of these steps simultaneously to generate safety and effectiveness data in a shorter period.[184]

FDA has published analyses of the Pfizer-BioNTech and Moderna Phase 3 clinical trial data, which show that these currently available vaccines, respectively, had a "favorable safety profile" and met the statutory criteria for EUA issuance. The vaccines' safety profile was generally similar across age groups, genders, and racial and ethnic groups. FDA analyses note a risk of mild side effects associated with the vaccines (e.g., fever, fatigue). The trials did not identify serious adverse health risks associated with the vaccines, but note the need for ongoing study and data collection to identify uncommon or long-term safety events.[185] Independent experts have characterized the data as strong; for example, medical experts characterized the Phase 3 trial results for the Pfizer-BioNTech vaccine as "impressive enough to hold up in any conceivable analysis."[186] Some key aspects of the Phase 3 clinical trials thus far include the following:

Independent review. All of the COVID-19 vaccines supported by OWS that are in Phase 3 clinical trials have a Data and Safety Monitoring Board (DSMB) that independently reviews safety and effectiveness data on the investigational vaccine to determine if the trial should continue, be modified, be terminated, or be considered for FDA marketing authorization (see the "FDA Marketing Authorization" section).[187] Members of the DSMB have no financial or other ties to the trial sponsor. Four Phase 3 clinical trials of candidate vaccines supported by OWS—

[184] FDA, "FDA Insight: Vaccines for COVID-19, Part 2," July 28, 2020, https://www.fda.gov/news-events/fda-insight/fda-insight-vaccines-covid-19-part-2.

[185] FDA, Emergency Use Authorization (EUA) for an Unapproved Product Review Memorandum- Pfizer, Inc. on behalf of Pfizer and BioNTech Review Memorandum, December 11, 2020, https://www.fda.gov/media/144416/download; and FDA, Emergency Use Authorization (EUA) for an Unapproved Product Review Memorandum-ModernaTx, Inc, December 18, 2020, https://www.fda.gov/media/144673/download.

[186] Eric J. Rubin and Dan L. Longo, "SARS-CoV-2 Vaccination—An Ounce (Actually, Much Less) of Prevention," *New England Journal of Medicine*, vol. 383 (December 31, 2020).

[187] U.S. Congress, Senate Committee on Health, Education, Labor, and Pensions, *Senate Health, Education, Labor and Pensions Committee Holds Hearing on the Role of Vaccines in Preventing Outbreaks*, 116th Cong., 2nd sess., September 9, 2020.

those of Moderna, AstraZeneca, Johnson & Johnson, and Novavax—are overseen by a common DSMB developed in consultation with NIH as a part of its COVID-19 Prevention Network.[188] The Pfizer-BioNTech vaccine has a separate DSMB.[189]

Trial populations. The data submitted in support of EUA issuance are derived primarily from clinical trials that enrolled healthy, nonpregnant adults over the age of 18 (or age 16 for the Pfizer-BioNTech trial), as is typical in most vaccine development efforts. While pregnant individuals were excluded from the clinical trials, some became pregnant during testing and are being monitored. Clinical trials also have been initiated investigating both the Pfizer-BioNTech and Moderna vaccines in populations as young as 12 years of age.[190]

Safety follow-up. Per FDA's October 2020 guidance, data from Phase 3 clinical trials submitted to the agency for EUA are to include a median safety follow-up duration of at least two months after completion of the full vaccination regimen.[191] This is shorter than the median follow-up duration of six months typically used in vaccine efficacy trials. FDA officials noted in a separate commentary that the two-month follow-up is justified given the need for a vaccine to address the pandemic and based on "extensive historical experience with adverse events after vaccination." According to FDA representatives,

> Adverse events considered plausibly linked to vaccination generally start within six weeks after vaccine receipt. Two months of follow-up will provide time for potential immune-mediated adverse events that began within this six-week period to be observed and evaluated.[192]

In the commentary, FDA acknowledges the unknowns around the new technologies used for COVID-19 vaccines and that most prior vaccine approvals have included years of follow-up data on some trial participants.[193] In this circumstance, robust postmarket safety studies and data collection may therefore be especially important in detecting any new long-term safety issues linked to the vaccines. Experts have been concerned about the potential for *vaccine-enhanced disease* (VED), in which vaccination could worsen the health effects of COVID-19 infections, as seen with the dengue and other vaccines.[194] For the vaccines currently available under EUA, clinical trials incorporated ongoing analysis to detect potential for VED and found no evidence thus far indicating VED risk. Analyses do note the need for ongoing follow-up to monitor this

[188] National Institutes of Health, "Fourth Large-Scale COVID-19 Vaccine Trial Begins in the United States," press release, September 23, 2020, https://www.nih.gov/news-events/news-releases/fourth-large-scale-covid-19-vaccine-trial-begins-united-states.

[189] Matthew Harper, "A Layperson's Guide to How—and When—a Covid-19 Vaccine Could be Authorized," *STAT*, September 28, 2020, https://www.statnews.com/2020/09/28/a-laypersons-guide-to-how-and-when-a-covid-19-vaccine-could-be-authorized/.

[190] NCT04649151, A Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 Vaccine in Adolescents 12 to <18 Years Old to Prevent COVID-19 (TeenCove), https://clinicaltrials.gov/ct2/show/NCT04649151. NCT04368728, Pfizer Study to Describe the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals, https://clinicaltrials.gov/ct2/show/NCT04368728.

[191] FDA, "Emergency Use Authorization for Vaccines to Prevent COVID-19," Guidance for Industry, October 2020, https://www.fda.gov/media/142749/download.

[192] Philip R. Krause and Marion F. Gruber, "Emergency Use Authorization of Covid Vaccines—Safety and Efficacy Follow-Up Considerations," *New England Journal of Medicine*, vol. 383, no. 19 (November 5, 2020).

[193] Ibid.

[194] Paul-Henri Lambert, Donna M Ambrosino, and Svein R Andersen, "Consensus Summary Report for CEPI/BC March 12-13, 2020 Meeting: Assessment of Risk of Disease Enhancement with COVID-19 Vaccines," *Vaccine*, vol. 31 (June 26, 2020), pp. 4783-4791.

risk long-term.[195] Both Pfizer-BioNTech and Moderna intend to follow participants for an additional two years after administration of the second vaccine dose.[196] This is consistent with FDA guidance, which recommends follow-up of study participants for COVID-19 outcomes to continue as long as feasible, at least one to two years, to assess duration of protection and potential for VED.[197]

Vaccine Efficacy

For the vaccines currently available, Phase 3 clinical trial data have found the vaccines to be efficacious at preventing confirmed symptomatic COVID-19 cases—94.5% efficacy for Moderna's vaccine and 95.0% efficacy for Pfizer-BioNTech's vaccine.[198] Efficacy for both vaccines was similar across age, gender, and racial/ethnic groups.[199]

Some questions remain around effectiveness of the vaccines, including the effectiveness of the vaccines in preventing asymptomatic infections (and therefore transmission of the virus) and whether one dose is sufficient for protection against infection or if two doses are necessary. Currently, the answers to these questions are mostly unknown scientifically. Preliminary analysis on Moderna's vaccine suggests that it may be effective against asymptomatic infections and that protection may begin after the first dose.[200] No such data are available for Pfizer-BioNTech's vaccine at this time.[201] Continued clinical trials and other postmarket studies using data collected in real world settings continue to assess these questions on vaccine efficacy and effectiveness.[202]

In light of early distribution challenges (which are outside the scope of this report), some have proposed modifying vaccine dosing, either by altering the dose of the vaccine or the length of time between the first and second dose in order to speed up the vaccination timeline and increase

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[195] FDA, *Emergency Use Authorization (EUA) for an Unapproved Product Review Memorandum- Pfizer, Inc. on behalf of Pfizer and BioNTech*, December 11, 2020, https://www.fda.gov/media/144416/download; and FDA, *Emergency Use Authorization (EUA) for an Unapproved Product Review Memorandudm- ModernaTx, Inc,* December 18, 2020, https://www.fda.gov/media/144673/download.

[196] Pfizer, "Pfizer and BioNTech Announce Vaccine Candidate Against COVID-19 Achieved Success in First Interim Analysis from Phase 3 Study," November 9, 2020, https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-vaccine-candidate-against. Moderna, "Moderna Announces Publication of Results from the Pivotal Phase 3 Trial of the Moderna COVID-19 Vaccine in The New England Journal of Medicine," December 31, 2020, https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-publication-results-pivotal-phase-3-trial.

[197] FDA, "Development and Licensure of Vaccines to Prevent COVID-19," Guidance for Industry, June 2020, p. 12, https://www.fda.gov/media/139638/download.

[198] The clinical endpoint specifically was "incidence of COVID-19 among participants without evidence of SARS-CoV-2 infection before or during the 2-dose vaccination regimen" for the Pfizer/BioNTech vaccine, and "incidence of COVID-19 among participants without evidence of SARS-CoV-2 infection before the first dose of vaccine in the period after 14 days post-dose" for Moderna's vaccine.

[199] FDA, *Emergency Use Authorization (EUA) for an Unapproved Product Review Memorandum- Pfizer, Inc. on behalf of Pfizer and BioNTech*, December 11, 2020, https://www.fda.gov/media/144416/download; and FDA, *Emergency Use Authorization (EUA) for an Unapproved Product Review Memorandum- ModernaTx, Inc,* December 18, 2020, https://www.fda.gov/media/144673/download.

[200] Moderna, "mRNA-1273 Sponsor Briefing Document Addendum," p. 6, https://www.fda.gov/media/144453/download.

[201] Matthew Herper, "Pfizer and BioNTech speed up timeline for offering Covid-19 vaccine to placebo volunteers," *STAT News*, January 1, 2021, https://www.statnews.com/2021/01/01/pfizer-and-biontech-speed-up-timeline-for-offering-covid-19-to-placebo-volunteers/.

[202] CDC, "Ensuring COVID-19 Vaccines Work," https://www.cdc.gov/coronavirus/2019-ncov/vaccines/effectiveness.html.

the number of individuals vaccinated. FDA issued a statement that any such changes to the EUA-authorized doses and schedules would need to be supported by evidence.[203]

FDA Marketing Authorization

Until December 2020, FDA had never before issued an EUA for a previously unlicensed vaccine. As mentioned, the level of evidence required by statute for EUA issuance is different from licensure, although both require the submission of safety and effectiveness data to FDA. This is because the EUA pathway is intended to provide a rapid review mechanism for medical products such as vaccines during emergency circumstances. For licensure under a BLA, a vaccine must be proven safe and have *substantial evidence of effectiveness*. For EUA issuance, substantial evidence of effectiveness is not required by statute. Rather, the totality of the available scientific evidence must indicate that the vaccine *may be effective* in preventing COVID-19, and that the known and potential benefits of the vaccine outweigh its known and potential risks. The statutory provisions governing EUA do not specify the type of data that must be submitted to FDA in support of an EUA and as noted in guidance, "FDA intends to assess the potential effectiveness of a possible EUA product on a case-by-case basis using a risk-benefit analysis."[204] As such, the "may be effective" standard leaves some discretion to agency scientists.

In light of reported concerns from the public surrounding the safety and effectiveness of COVID-19 vaccines developed and authorized on an expedited timeline, FDA officials have sought to clarify that any vaccine candidate "will be reviewed according to the established legal and regulatory standards for medical products."[205] In addition, FDA officials have indicated that the amount of safety and effectiveness data needed to support EUA issuance is similar to the data that is appropriate for a BLA.[206] FDA has noted that sponsors of the EUA-authorized vaccines are expected to continue to collect data to support eventual submission of a BLA to obtain full licensure.[207]

To help companies develop a vaccine to prevent COVID-19, and to increase transparency regarding the FDA's expectations for safety and effectiveness data, the agency has issued two guidance documents. The first guidance, issued in June 2020, aims to clarify FDA's expectations regarding the data and information necessary to support licensure under a BLA.[208] The guidance notes, among other things, that with respect to effectiveness, FDA expects a COVID-19 vaccine to prevent disease or decrease disease severity in at least 50% of people who are vaccinated. On October 6, 2020, FDA issued a second guidance, which focuses on the agency's expectations for

[203] FDA, "FDA Statement on Following the Authorized Dosing Schedules for COVID-19 Vaccines," January 4, 2021, https://www.fda.gov/news-events/press-announcements/fda-statement-following-authorized-dosing-schedules-covid-19-vaccines.

[204] FDA, "Emergency Use Authorization of Medical Products and Related Authorities," Guidance for Industry and Other Stakeholders, January 2017, p.8, https://www.fda.gov/media/97321/download.

[205] Anand Shah, Peter Marks, and Jim Hahn, "Unwavering Regulatory Safeguards for COVID-19 Vaccines," *JAMA*, August 2020, vol. 324, no. 10, pp. 931-932.

[206] Duke Margolis Center for Health Policy, "Safe and Effective COVID-19 Vaccination: The Path from Here," September 10, 2020, meeting. Michael Mezher, "Marks, Hahn Confirm COVID Vaccine EUA Guidance Coming," September 11, 2020, https://www.raps.org/news-and-articles/news-articles/2020/9/marks-hahn-confirm-covid-vaccine-eua-guidance-comi.

[207] FDA, "Development and Licensure of Vaccines to Prevent COVID-19," Guidance for Industry, June 2020, p.4, https://www.fda.gov/media/139638/download.

[208] FDA, "Development and Licensure of Vaccines to Prevent COVID-19," Guidance for Industry, June 2020, https://www.fda.gov/media/139638/download.

the data and information needed to support an EUA for a COVID-19 vaccine.[209] The recommendations outlined in the October 2020 guidance have been characterized as more stringent than what typically may be required for an EUA.[210] For example, the guidance indicates that data from Phase 3 trials submitted to the agency should include a median follow-up duration of at least two months after completion of the full vaccination regimen to help provide adequate information to assess a vaccine's benefit-risk profile. FDA also expects clinical testing of an EUA-authorized vaccine to continue to support eventual licensure under a BLA. As such, the guidance recommends that sponsors submit, as part of the EUA request, strategies that will be implemented to (1) address loss of follow-up information for participants who choose to withdraw from the study to receive the vaccine under an EUA, and (2) ensure that ongoing clinical trials of the vaccine are able to assess long-term safety and effectiveness (e.g., evaluating for VED, decreased effectiveness over time) in sufficient numbers to support vaccine licensure.

At public meetings in December 2020, FDA's VRBPAC considered whether the available evidence for the Pfizer-BioNTech and Moderna vaccines met FDA's criteria for issuing an EUA. At both meetings, the majority of the committee's membership voted that the scientific evidence for both vaccines favored the vaccines' use—in individuals 16 years of age and older for the Pfizer-BioNTech vaccine and in individuals 18 years of age and older for Moderna's vaccine.[211]

Clinical Recommendations and Prioritization

ACIP has thus far issued two types of recommendations for the COVID-19 vaccines currently authorized for emergency use: (1) recommendations regarding the *clinical use* of each vaccine, in particular the age groups to receive each, and (2) recommendations regarding the *allocation* or priority groups to receive the limited vaccine supply. These recommendations have been adopted as official CDC recommendations. To date, ACIP's clinical recommendations have followed the age groups authorized by FDA under each vaccine EUA.[212] ACIP's allocation recommendations have evolved as projected vaccine supply has changed—to date, ACIP has issued the following allocation recommendations:[213]

- Phase 1a: health care personnel and long-term care facility residents,

[209] FDA, "Emergency Use Authorization for Vaccines to Prevent COVID-19," Guidance for Industry, October 2020, https://www.fda.gov/media/142749/download.

[210] Michael Erman and Manas Mishra, "U.S. FDA safety guidelines likely to push COVID-19 vaccine authorization past election," October 6, 2020, *Reuters*.

[211] FDA, "FDA Statement on Vaccines and Related Biological Products Advisory Committee Meeting," press release, December 17, 2020, https://www.fda.gov/news-events/press-announcements/fda-statement-vaccines-and-related-biological-products-advisory-committee-meeting-0; and FDA, "FDA Statement on Vaccines and Related Biological Products Advisory Committee Meeting," press release, December 11, 2020, https://www.fda.gov/news-events/press-announcements/fda-statement-vaccines-and-related-biological-products-advisory-committee-meeting.

[212] Sara E. Oliver, Julia W. Gargano, Mona Marin et al., "The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine—United States, December 2020," *Morbidity and Mortality Weekly Report (MMWR)*, vol. 69, no. 50 (December 18, 2020), pp. 1922-24, and Sara E. Oliver, Julia W. Gargano, Mona Marin et al., "The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Moderna COVID-19 Vaccine—United States, December 2020," *Mortality and Morbidity Weekly Report*, vol. 69, no. 5152 (January 1, 2021).

[213] Kathleen Dooling, Mona Marin, Megan Wallace et al., "The Advisory Committee on Immunization Practices' Updated Interim Recommendation for Allocation of COVID-19 Vaccine—United States, December 2020," *Morbidity and Mortality Weekly Report (MMWR)*, vol. 69, no. 5152 (December 22, 2020), https://www.cdc.gov/mmwr/volumes/69/wr/mm695152e2.htm?s_cid=mm695152e2_w.

- Phase 1b: persons aged 75 and over and nonhealth care frontline essential workers, and
- Phase 1c: persons aged 65-74, persons aged 16-64 with high-risk medical conditions, and essential workers not included in Phase 1b.

According to the CDC *COVID-19 Vaccination Program Provider Agreement* signed by all providers participating in the COVID-19 vaccination program, providers must administer COVID-19 vaccines in accordance with prioritization groups determined by appropriate public health authorities (e.g., federal, state, local).[214] In general, states and other jurisdictions are setting vaccine priority groups. Many states follow ACIP-recommended phases, but some states have departed from ACIP's recommendations.[215]

In early January 2021, following a slow initial vaccine rollout, then-HHS Secretary Alex Azar recommended that states expand vaccination priority groups to everyone aged 65 and older, as well as those aged 16 and older with high-risk medical conditions to avoid unused vaccine supply.[216] The Biden Administration's strategy also reiterates the recommendation to expand priority groups to those 65 and older and to frontline essential workers.[217] Some media reports indicate confusion among certain states following the new recommendations and apparent contradictions with the ACIP recommendations.[218] ACIP recommendations still remain the official CDC recommendations for priority groups.

Prior to the issuance of ACIP's recommendations, the National Academies of Science, Engineering, and Medicine (NASEM), at the direction of NIH and CDC, set up an ad hoc committee to develop a framework for equitably allocating COVID-19 vaccines domestically and globally.[219] NASEM published its draft framework on September 1, 2020, and published its final report with recommendations on October 2, 2020. The framework is shown below in **Figure 1**.[220] ACIP considered these recommendations in its deliberations; however, its Phase 1 recommendations have already differed from those proposed by NASEM, as described above. The NASEM framework assisted states with planning assumptions for the vaccine program.[221]

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[214] CDC, "CDC COVID-19 Vaccination Program Provider Requirements and Support," December 13, 2020, https://www.cdc.gov/vaccines/covid-19/vaccination-provider-support.html.

[215] Kaiser Family Foundation (KFF), "How are States Prioritizing Who Will Get the COVID-19 Vaccine First?" December 14, 2020, https://www.kff.org/policy-watch/how-are-states-prioritizing-who-will-get-the-covid-19-vaccine-first/.

[216] Stephanie Ebbs, Ben Gittleson, and Luis Martinez, "Azar, Trump Administration Will no Longer Hold Back 2nd Shots, Recommend 65 and Older get COVID Vaccine," *ABC News*, January 12, 2021, and Sheryl Gay Stolberg and Abby Goodnough, "States Told to Vaccinate Everyone 65 and Over as Deaths Surge," *New York Times*, January 12, 2021.

[217] White House, *National Strategy for the COVID-19 Response and Pandemic Preparedness*, January 21, 2021, p. 40, https://www.whitehouse.gov/wp-content/uploads/2021/01/National-Strategy-for-the-COVID-19-Response-and-Pandemic-Preparedness.pdf.

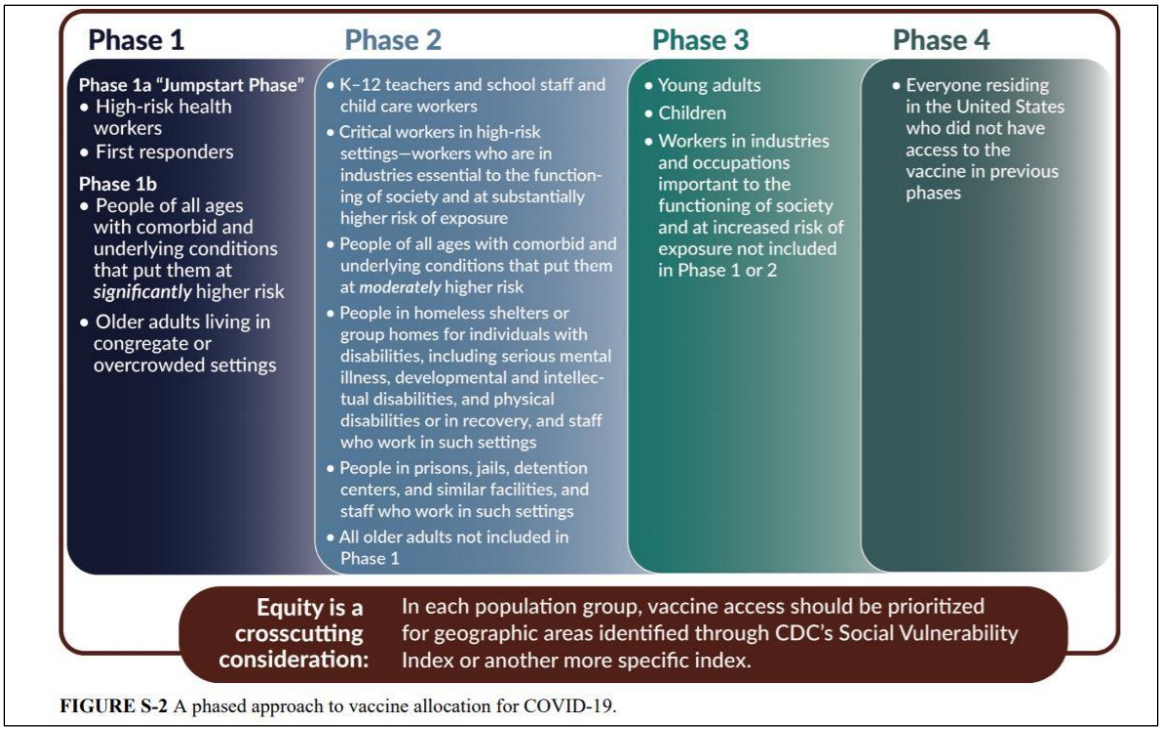
[218] Helen Branswell, "Confusion Spreads Over System to Determine Priority Access to Covid-19 Vaccines," *STAT*, July 22, 2020.

[219] National Academy of Sciences, Engineering, and Medicine (NASEM), "A Framework for Equitable Allocation of Vaccine for the Novel Coronavirus," https://www.nationalacademies.org/our-work/a-framework-for-equitable-allocation-of-vaccine-for-the-novel-coronavirus.

[220] National Academy of Sciences, Engineering, and Medicine, *Discussion Draft of the Preliminary Framework for Equitable Allocation of COVID-19 Vaccine*, September 1, 2020.

[221] CDC, "COVID-19 Vaccination Program Operational Guidance," November 5, 2020, https://www.cdc.gov/vaccines/covid-19/covid19-vaccination-guidance.html.

Figure 1. NASEM-Recommended Phased Approach to COVID-19 Vaccine Allocation



Source: National Academy of Sciences, Engineering, and Medicine, *Framework for Equitable Allocation of COVID-19 Vaccine*, October 2, 2020.

Safety in Vaccine Distribution

CDC has established requirements for vaccine management, including requirements related to storage and transportation. As announced on August 14, McKesson Corporation is to act as a central distributor for the COVID-19 vaccine campaign—the same distributor that managed the federally coordinated H1N1 influenza pandemic vaccine campaign.[222] States, localities, territories, and tribes (hereinafter, jurisdictions) are to have much of the responsibility for tracking vaccines provided and for local transportation of vaccines within the jurisdiction.

CDC, in collaboration with jurisdictions, is conducting trainings for newly registered providers regarding safe storage, handling, and administration of the vaccines. Providers who seek to participate in the COVID-19 vaccination program must be credentialed/licensed in the jurisdiction where vaccination takes place and sign and agree to the conditions in the *CDC COVID-19 Vaccination Program Provider Agreement*. The agreements includes requirements that the vaccines are stored and handled in accordance with the EUA and other CDC and manufacturer requirements.[223] Jurisdictions' immunization programs and health care providers administering COVID-19 vaccines are to be responsible for many aspects of vaccine tracking,

[222] HHS, "Trump Administration Collaborates with McKesson for COVID-19 Vaccine Distribution," press release, August 14, 2020, https://www.hhs.gov/about/news/2020/08/14/trump-administration-collaborates-mckesson-covid-19-vaccine-distribution.html, and CRS Report R40554, *The 2009 Influenza Pandemic: An Overview*.

[223] CDC, "CDC COVID-19 Vaccination Program Provider Requirements and Support," December 13, 2020, https://www.cdc.gov/vaccines/covid-19/vaccination-provider-support.html.

storage, and handling to ensure that vaccine safety and effectiveness are maintained.[224] This guidance is likely to evolve as new vaccines potentially become available and as more is learned about how to best store and administer the vaccines.

COVID-19 vaccines in development have different temperature control requirements: some must be refrigerated (2 to 8 degrees Celsius), some must be stored frozen (-15 to -25 degrees Celsius) and some must be kept ultra-cold (-60 to -80 degrees Celsius), such as Pfizer/BioNTech's vaccine. CDC's planning guidance to jurisdictions takes these different temperature requirements into account and seeks to minimize potential breaks in the cold chain during vaccine distribution. According to CDC, "certain COVID-19 vaccine products, such as those with ultra-cold temperature requirements, will be shipped directly from the manufacturer to the vaccination provider site," while others will be distributed by CDC's distributor directly to the provider sites or secondary depots for distribution (e.g., chain drug store's central distribution). CDC guidance includes detailed information about how vaccines should be stored onsite until usage.[225]

Postmarket Safety: Surveillance and Safety Monitoring

Postmarket safety activities on vaccines in use include (1) continued clinical trials of vaccines available under EUA, (2) additional postmarket studies on the vaccines, and (3) ongoing vaccine safety monitoring, or surveillance.

Given the condensed nature of the COVID-19 development programs, FDA has recommended that follow-up of study participants for COVID-19 outcomes continue as long as feasible, ideally at least one to two years, to assess duration of protection and potential for certain adverse outcomes.[226] In guidance, FDA further recommends that at the time of a BLA submission for a COVID-19 vaccine, a Pharmacovigilance Plan (PVP) be submitted to address known and potential risks of the vaccine. FDA may recommend that a PVP include expedited or more frequent adverse event reporting, or the establishment of a pregnancy exposure registry to collect information on associated pregnancy and infant outcomes. Pfizer and Moderna have submitted PVPs to FDA for their EUA-authorized vaccines, which discuss plans for longer term safety follow up.[227] FDA may require additional clinical studies to be conducted after eventual licensure to allow for continued evaluation of vaccine outcomes.[228]

As mentioned, manufacturers of BLA-licensed vaccines typically must report adverse events to FDA as soon as possible, but no later than 15 days of becoming aware of them. For EUA-

[224] CDC, *COVID-19 Vaccination Program: Interim Playbook for Jurisdiction Operations*, October 29, 2020, https://www.cdc.gov/vaccines/imz-managers/downloads/COVID-19-Vaccination-Program-Interim_Playbook.pdf, pp 21-22.

[225] CDC, *COVID-19 Vaccination Program: Interim Playbook for Jurisdiction Operations*, October 29, 2020, https://www.cdc.gov/vaccines/imz-managers/downloads/COVID-19-Vaccination-Program-Interim_Playbook.pdf, and CDC, "Vaccine Storage and Handling Toolkit," https://www.cdc.gov/vaccines/hcp/admin/storage/toolkit/index.html.

[226] FDA, "Development and Licensure of Vaccines to Prevent COVID-19," Guidance for Industry, June 2020, p.12, https://www.fda.gov/media/139638/download.

[227] FDA, "FDA Takes Key Action in Fight Against COVID-19 By Issuing Emergency Use Authorization for First COVID-19 Vaccine," December 11, 2020, https://www.fda.gov/news-events/press-announcements/fda-takes-key-action-fight-against-covid-19-issuing-emergency-use-authorization-first-covid-19. FDA, "FDA Takes Additional Action in Fight Against COVID-19 By Issuing Emergency Use Authorization for Second COVID-19 Vaccine," December 18, 2020, https://www.fda.gov/news-events/press-announcements/fda-takes-additional-action-fight-against-covid-19-issuing-emergency-use-authorization-second-covid.

[228] FDA, "Development and Licensure of Vaccines to Prevent COVID-19," Guidance for Industry, June 2020, p. 17, https://www.fda.gov/media/139638/download.

authorized vaccines, FDA must impose conditions of use concerning the monitoring and reporting of adverse events. The EUAs for the Pfizer-BioNTech and Moderna vaccines include requirements for vaccination providers and vaccine manufacturers to report adverse events to VAERS and maintain certain records with respect to the authorized vaccines.[229] Specifically, as noted in the EUA letters, vaccination providers and manufacturers must report (1) vaccine administration errors whether or not associated with an adverse event, (2) serious adverse events (whether or not attributed to vaccination), (3) cases of Multisystem Inflammatory Syndrome, and (4) cases of COVID-19 that result in hospitalization or death. Vaccine manufacturers must report adverse events to VAERS as soon as possible but no later than 15 calendar days from initial receipt of the information; no deadline is specified for vaccination providers. Per the *CDC COVID-19 Vaccination Program Provider Agreement*, providers are required to report adverse events following vaccination through VAERS and are advised to report such events even if the providers are not sure that vaccination caused the adverse event.[230]

Several federal safety monitoring databases are being created, enhanced, and leveraged to collect several types of postmarket safety data on COVID-19 vaccines in use. The multiple systems are designed to allow for rapid detection and robust assessments using both passive and active surveillance methods to collect safety data among different populations. The databases include those of CMS, VA, DOD, FDA, CDC, as presented in a December 2020 ACIP meeting shown in **Figure 2**. CDC officials expect that some of these systems, like VAERS and v-safe (a new smartphone-based health checker for vaccine recipients), will be used more in the early stages of the vaccine program, while others will be used more at later stages, such as VSD and FDA BEST & PRISM.[231] (For details about these systems, see the section "Postmarket Safety.")

[229] FDA, EUA letter to Pfizer Inc., issued December 11, 2020, and updated December 23, 2020, https://www.fda.gov/media/144412/download; and FDA, EUA letter to ModernaTX, Inc., December 18, 2020, https://www.fda.gov/media/144636/download.

[230] CDC, *COVID-19 Vaccination Program: Interim Playbook for Jurisdiction Operations*, October 29, 2020, p. 47, https://www.cdc.gov/vaccines/imz-managers/downloads/COVID-19-Vaccination-Program-Interim_Playbook.pdf.

[231] Tom Shimabukuro, "COVID-19 Vaccine Post-Authorization Safety Monitoring Update," Presented at December 1 Advisory Committee on Immunization Practices (ACIP) meeting, https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2020-12/COVID-04-Shimabukuro.pdf.

Figure 2. Federal Vaccine Safety Monitoring Systems, by System and Population

Monitoring systems and populations

	Monitoring systems	Population	Healthcare workers	LTCF residents
early	**VAERS** (CDC & FDA) VA ADERS DoD VAECS CDC NHSN	General U.S. population, VA and DoD patient populations, NHSN acute care and long-term care facilities	Yes	Yes
early	**V-safe** (CDC)	All COVID-19 vaccine recipients eligible	Yes	Limited
later	**VSD** (CDC)	Insured patients in VSD sites	Yes	Limited
later	**FDA-CMS**	Medicare recipients (90+% of 65 y/o in the U.S., including 650K LTCF residents)	Limited	Yes
later	**BEST & PRISM** (FDA)	Insured patients in BEST & PRISM sites	Yes	Limited
later	**VA EHR & data warehouse**	Enrolled VA patients	Limited	Yes
later	**DoD DMSS**	Active duty military (limited info on beneficiaries [i.e., family members, retirees])	Yes	Limited
later	**Genesis HealthCare** (Brown U. & NIH-NIA)	Long-term care facility residents (~35,000 long stay residents)	No	Yes

Source: Tom Shimabukuro, "COVID-19 Vaccine Post-Authorization Safety Monitoring Update," presented at December 1 Advisory Committee on Immunization Practices (ACIP) meeting, https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2020-12/COVID-04-Shimabukuro.pdf.

Severe Allergic Reactions

To date, concerns have focused on the issue of anaphylaxis or severe allergic reactions after receipt of mRNA-based vaccines. Based on VAERS data, CDC reported an estimate of 11.1 anaphylaxis cases per million doses of the Pfizer-BioNTech vaccine administered in late December 2020, mostly among patients with a history of allergies.[232] A similar report on Moderna's vaccine estimated 2.5 anaphylaxis cases per million doses administered in late December and early January, also mostly among patients with a history of allergies. These estimates may change as more data are collected.[233] CDC has emphasized that, as of January 6, 2021, the "known and potential benefits of the current COVID-19 vaccines outweigh the known and potential risks of getting COVID-19."[234]

CDC has identified certain contraindications to the mRNA vaccines, including a history of allergic reactions after receipt of mRNA vaccines or any of such vaccines' components. For individuals with such contraindications, mRNA-based COVID-19 vaccines are not recommended. CDC currently considers history of an allergic reaction to any other vaccine as a precaution, but not a contraindication, to receiving the vaccines. CDC has also issued clinical

[232] CDC COVID-19 Response Team and FDA, "Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine—United States, December 14–23, 2020," *Morbidity and Mortality Weekly Report (MMWR)*, January 15, 2021.

[233] CDC COVID-19 Response Team and FDA, "Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Moderna COVID-19 Vaccine—United States, December 21, 2020- January 10, 2021," *Morbidity and Mortality Weekly Report (MMWR)*, January 22, 2021.

[234] CDC, *Transcript: CDC Update on COVID-19*, press briefing, January 6, 2021, https://www.cdc.gov/media/releases/2021/t0106-cdc-update-covid-19.html.

guidance for managing potential anaphylaxis after vaccine receipt.[235] These recommendations may evolve as more is learned about the potential for this adverse health event through further postmarket safety studies.

Injury Compensation and Patient Safety Information

Vaccine injury compensation for COVID-19 vaccines differs from usual injury compensation under VICP. HRSA has indicated that COVID-19 vaccines are covered under the Countermeasures Injury Compensation Program (CICP), not VICP.[236] Use of CICP for COVID-19 vaccine injury compensation was established by the Public Readiness and Emergency Preparedness Act (PREP Act) declaration effective February 4, 2020, which established certain immunity from legal liability related to the "manufacture, testing, development, distribution, administration, and use" of covered countermeasures as part of the public health response to COVID-19.[237] Vaccines are listed as among the covered countermeasures in the declaration.[238] Persons who suffer serious injury or death from a covered countermeasure may seek compensation through the Covered Countermeasure Process Fund as a part of the CICP. The HHS Secretary may transfer funds available in the Public Health and Social Services Emergency Fund (PHSSEF), as provided in several coronavirus supplemental appropriations acts, to this fund.[239] Congress could take legislative action to add COVID-19 vaccines to be covered under VICP.

Because COVID-19 vaccines will likely not be added to the vaccines covered under VICP (at least initially), CDC is not required to develop Vaccine Information Statements (VIS) for COVID-19 vaccines. For vaccines available under EUA, the manufacturers have developed fact sheets for recipients and caregivers.[240] Providers participating in the COVID-19 vaccine program are required to either give such factsheets to recipients (or their parents or legal guardians) prior to vaccination or direct recipients to the website where the fact sheet is available.[241] CDC and vaccine manufacturers have also developed other educational material regarding the vaccines.[242]

Congressional Considerations

Since enactment of the Biologics Control Act of 1902, Congress and the executive branch (especially through FDA and CDC) have strived to ensure the safety of vaccines in the United States—from initial development to patient administration. With the COVID-19 pandemic causing considerable health and economic consequences, there is significant interest in safe and effective vaccines to help curb transmission of the disease. Congress may consider how to best leverage existing requirements and programs to ensure that risk of harm from COVID-19 vaccines is mitigated and minimized. Several efforts are underway through OWS, FDA, CDC,

[235] CDC, "Interim Clinical Considerations for Use of mRNA COVID-19 Vaccines Currently Authorized in the United States," https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html.

[236] HRSA, "Frequently Asked Questions About the VICP," https://www.hrsa.gov/vaccine-compensation/FAQ.

[237] CRS Legal Sidebar LSB10443, *The PREP Act and COVID-19: Limiting Liability for Medical Countermeasures*.

[238] HHS, "Declaration Under the Public Readiness and Emergency Preparedness Act for Medical Countermeasures Against COVID-19," 85 *Federal Register* 15198, March 17, 2020.

[239] CRS Legal Sidebar LSB10443, *The PREP Act and COVID-19: Limiting Liability for Medical Countermeasures*.

[240] FDA, "Emergency Use Authorization," accessed January 8, 2021, https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

[241] CDC, *COVID-19 Vaccination Program: Interim Playbook for Jurisdiction Operations*, October 29, 2020, p. 46, https://www.cdc.gov/vaccines/imz-managers/downloads/COVID-19-Vaccination-Program-Interim_Playbook.pdf.

[242] Ibid., p. 23.

and other agencies to monitor and ensure the safety of COVID-19 vaccines—both those available under EUA and those under development. Congress may consider how to best provide oversight and make legislative changes to ensure a safe and successful COVID-19 vaccination campaign. In addition, Congress may consider and evaluate the entire federal vaccine safety system and assess whether this system warrants any policy changes to help ensure the safety of all recommended vaccines.

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