



Vaccine Safety

Overview, History, and How the Safety Process Works

Vaccines are one of the greatest success stories in public health. Through use of vaccines, we have eradicated smallpox and nearly eliminated wild polio virus. The number of people who experience the devastating effects of preventable infectious diseases like measles, diphtheria, and whooping cough is at an all-time low. To ensure the continued success of vaccines in the United States, it's crucial to make sure that vaccines are safe.

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Before vaccines are approved by the Food and Drug Administration (FDA), scientists test them extensively to ensure they are effective and safe. Vaccines are the best defense we have against infectious diseases, but no vaccine is actually 100% safe or effective for everyone because each person's body reacts to vaccines differently. [1, 2, 3]

As infectious diseases become less common, we hear less about the serious consequences of preventable illnesses like diphtheria and tetanus and more about the risks associated with vaccines. It's good to be informed about health choices, but the reality is that Americans have never been healthier than we are today and vaccines have never been safer than they are today. The benefits of vaccines far outweigh the risks. As science continues to advance, we strive to develop safer vaccines and improve delivery to protect ourselves against disease more effectively. This overview focuses on vaccine research, how vaccines are licensed, and how we make sure vaccines are safe. [1, 2, 3].

The National Childhood Vaccine Injury Act

During the mid-1970s, there was an increased focus on personal health and more people became concerned about vaccine safety. Several lawsuits were filed against vaccine manufacturers and healthcare providers by people who believed they had been injured by the diphtheria, pertussis, tetanus (DPT) vaccine. [4] Damages were awarded despite the lack of scientific evidence to support vaccine injury claims. [4] As a result of these decisions, liability and prices soared, and several vaccine manufacturers halted production. A vaccine shortage resulted and public health officials became concerned about the return of epidemic disease. To reduce liability and respond to public health concerns, Congress passed the National Childhood Vaccine Injury Act (NCVIA) in 1986. This act was influential in many ways. [4, 5].

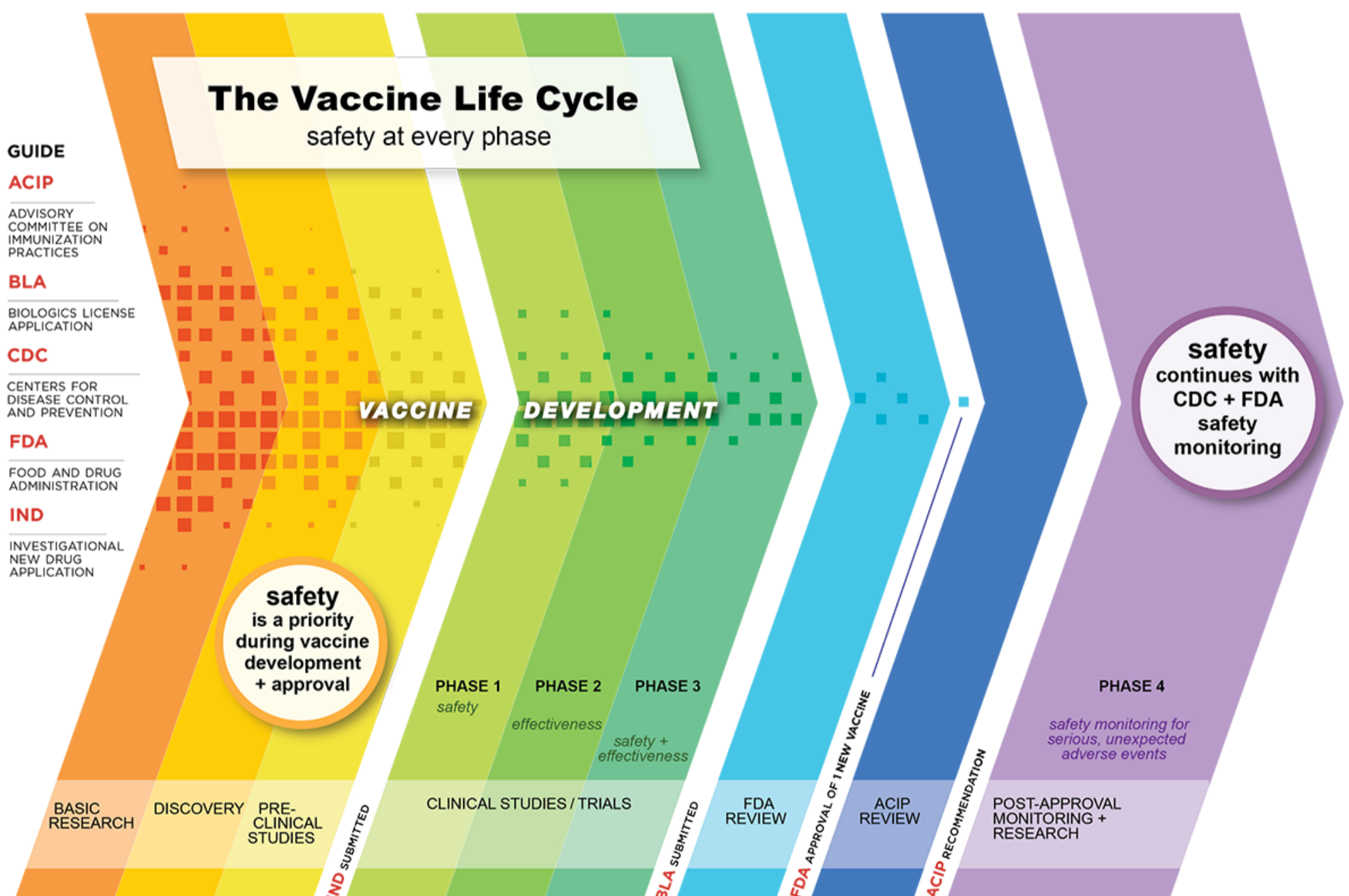
- The National Vaccine Program Office (NVPO) was established to coordinate immunization-related activities between all Department of Health and Human Services (DHHS) agencies, including the FDA, Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), and the Health Resources and Services Administration (HRSA).
- The NCVIA requires healthcare providers who administer vaccines to provide a vaccine information statement (VIS) to the person getting the vaccine or his or her guardian. A VIS must be given with every vaccination, including each dose in a multi-dose series. Each VIS contains a brief description of the disease as well as the risks and benefits of the vaccine. CDC develops VISs and distributes them to state and local health departments as well as individual providers.
- The NCVIA also requires healthcare providers to report certain adverse events (health effects occurring after immunization that may or may not be related to the vaccine) following vaccination to the Vaccine Adverse Event Reporting System (VAERS).



- Under the NCVIA, the National Vaccine Injury Compensation Program (VICP) was created to compensate those injured by vaccines on a “no fault” basis.
- The NCVIA established a committee from the Institute of Medicine (IOM) to review the literature on vaccine reactions. This group concluded that there are limitations in our knowledge of the risks associated with vaccines. The group looked at 76 health problems to see if they were caused by vaccines. Of those, 50 (66%) had no or inadequate research to form a conclusion. [6, 7] Specifically, the IOM identified the following problems:
 1. Limited understanding of biological processes that underlie adverse events.
 2. Incomplete and inconsistent information from individual reports.
 3. Poorly constructed research studies (not enough people enrolled for the period of time).
 4. Inadequate systems to track vaccine side effects.
 5. Few experimental studies were published in the medical literature.

Significant progress has been made over the past few years to monitor side effects and conduct research relevant to vaccine safety.

The Vaccine Life Cycle: Safety at Every Phase



Safety is a Priority During Vaccine Development and Approval

Before vaccines are licensed by the FDA, they are tested extensively in the laboratory and with human subjects to ensure their safety. First, researchers use computers to predict how the vaccine will interact with the human immune system. Then researchers test the vaccine on animals including mice, guinea pigs, rabbits, and monkeys.

Vaccine development and approval follows the same general pathway as for drugs and other biologics. A sponsor who wishes to begin clinical trials with a vaccine must submit an Investigational New Drug application (IND) to FDA. The IND describes the vaccine, its method of manufacture, and quality control tests for release. Also included are information about the vaccine's

safety and ability to elicit a protective immune response (immunogenicity) in animal testing, as well as a proposed plan for testing the drug on humans. [9]

FDA reviews the IND to ensure a vaccine's use in clinical studies does not place human subjects at unreasonable risk of harm, and adequate informed consent and human subject protections are in place. Participation in these studies is completely voluntary. Many individuals choose to contribute their time and energy for the advancement of science. Before they participate in research, all participants must demonstrate that they understand the purpose of the study and its potential risks. Volunteers agree to receive the vaccine and undergo any medical testing necessary to assess its safety and efficacy. [7].

Vaccine licensing is a lengthy process that can take 10 years or longer. The FDA requires that vaccines undergo three phases of clinical trials with human subjects before they can be licensed for use in the general public:

- **Phase 1** trials are small, involving only 20 to 100 volunteers, and last only a few months. The purpose of phase one trials is to evaluate basic safety and identify very common reactions.
- **Phase 2** trials are larger and involve several hundred participants. These studies last anywhere from several months to two years and collect additional information on safety and efficacy. Data gained from phase two trials can be used to determine the composition of the vaccine, how many doses are necessary, and a profile of common reactions.
- **Phase 3** trials are the next step, unless the vaccine is ineffective or causes health problems, and are expanded to involve several hundred to several thousand volunteers. Typically, these trials last several years. Because the vaccinated group can be compared to those who have not received the vaccine, researchers are able to identify true reactions. [1, 3, 7, 8, 9]

If the clinical trials demonstrate that the vaccine is safe and effective, the manufacturer submits a Biologics License Application (BLA) to FDA requesting two licenses: one for the vaccine (product license), and one for the production plant (establishment license). During the application process, the FDA reviews the clinical trial data and proposed product labeling. In addition, the FDA inspects the plant and goes over manufacturing protocols to ensure vaccines are produced in a safe and consistent manner. Only after the FDA is satisfied that the vaccine is safe is it licensed for use in the general population. [8]

Once FDA licenses a vaccine, the Advisory Committee on Immunization Practices (ACIP) develops recommendations on how to use vaccines to control disease in the United States. ACIP is a group of medical and public health experts. Members of the American Academy of Pediatrics (AAP) and American Academy of Family Physicians (AAFP) are among some of the groups that also bring related immunization expertise to the committee.

The Committee's recommendations are forwarded to CDC's Director for approval. Once the ACIP recommendations have been reviewed and approved by the CDC Director and the U.S. Department of Health and Human Services, they are published in CDC's Morbidity and Mortality Weekly Report (MMWR). The MMWR publication represents the final and official CDC recommendations for immunization of the U.S. population. [10]

Safety Continues with CDC and FDA Monitoring after Approval

Phase 4 safety monitoring and research begins after a vaccine is licensed and recommended for public use. ACIP continues to monitor vaccine safety and effectiveness data even after the vaccine's routine use and may change or update recommendations based on that data. Also, FDA requires all manufacturers to submit samples from each vaccine lot prior to its release. Manufacturers must provide the FDA with their test results for vaccine safety, potency, and purity. Each lot must be tested because vaccines are sensitive to environmental factors like temperature, and can be contaminated during production. The FDA rarely has recalled vaccine lots, for concerns such as mislabeling, contamination during production, and potential manufacturing problems at a production plant. [8, 10]

Vaccine Life Cycle Fact Sheet

Learn more about how vaccine safety works in the United States.

The infographic illustrates the vaccine life cycle as a series of four chevron-shaped stages moving from left to right. Stage 1 (yellow) is 'RESEARCH AND DISCOVERY', involving 'BASIC RESEARCH', 'DISCOVERY AND TARGET IDENTIFICATION', and 'PRE-IND'. Stage 2 (green) is 'VACCINE DEVELOPMENT', involving 'IND', 'INDUSTRY AND ACADEMIC COLLABORATION', and 'INDUSTRY AND ACADEMIC COLLABORATION'. Stage 3 (blue) is 'CLINICAL STUDIES/ TRIALS', involving 'INDUSTRY AND ACADEMIC COLLABORATION', 'INDUSTRY AND ACADEMIC COLLABORATION', and 'INDUSTRY AND ACADEMIC COLLABORATION'. Stage 4 (purple) is 'MONITORING AND RESEARCH', involving 'INDUSTRY AND ACADEMIC COLLABORATION', 'INDUSTRY AND ACADEMIC COLLABORATION', and 'INDUSTRY AND ACADEMIC COLLABORATION'. A central banner reads 'The Vaccine Life Cycle: safety at every phase'. A circular callout in Stage 2 states 'Safety is a priority during vaccine development & approval'. A circular callout in Stage 4 states 'Safety continues with CDC + FDA safety monitoring'. Logos for CDC and FDA are at the bottom left. Text at the bottom right reads 'LEARN MORE: FDA VACCINE DEVELOPMENT + APPROVAL PROCESS: www.fda.gov/vaccine; CDC VACCINE SAFETY MONITORING + RESEARCH: www.cdc.gov/vaccine-safety'. A download link is at the bottom: 'Download vaccine life cycle fact sheet [PDF - 1 page]'.

[Download vaccine life cycle fact sheet \[PDF - 1 page\]](#)

While clinical trials provide important information on vaccine safety, the data are somewhat limited because of the relatively small number (hundreds to thousands) of study participants. Rare side effects and delayed reactions might not be evident until the vaccine is administered to millions of people. Therefore, the federal government established the Vaccine Adverse Event Reporting System (VAERS), a surveillance system to monitor adverse events following vaccination. In addition, large-linked databases containing information on millions of individuals, such as the Vaccine Safety Datalink (VSD), have been created to study rare vaccine adverse events. [1, 3]

How CDC Monitors Vaccine Safety


CDC and FDA [monitor the safety of vaccines](#) after they are approved. If a problem is found with a vaccine, CDC and FDA will inform health officials, health care providers, and the public.

CDC uses 3 systems to monitor vaccine safety:

- The [Vaccine Adverse Event Reporting System \(VAERS\)](#): an early warning system, co-managed by CDC and FDA, to monitor for potential vaccine safety problems. Anyone can report possible vaccine side effects to VAERS.
- The [Vaccine Safety Datalink \(VSD\)](#): a collaboration between CDC and 9 health care organizations that conducts vaccine safety monitoring and research.
- The [Clinical Immunization Safety Assessment \(CISA\) Project](#): a partnership between CDC and several medical research centers that provides expert consultation and conducts clinical research on vaccine-associated health risks.

The National Vaccine Injury Compensation Program (VICP)

In very rare cases, a vaccine can cause a serious problem, such as a severe allergic reaction.

In these instances, the [VICP](#)  may provide financial compensation to individuals who file a petition and are found to have been injured by a VICP-covered vaccine. Even in cases in which such a finding is not made, petitioners may receive compensation through a settlement.

Improvements in Vaccine Safety

In the last decades, numerous changes in vaccine production and administration have reduced the number of side effects and resulted in safer vaccines.

- A more purified acellular pertussis (aP) vaccine has been licensed for use and has replaced the whole cell pertussis vaccine used in DTP (diphtheria, tetanus, pertussis vaccine). Several studies have evaluated the safety and efficacy of DTaP as compared to DTP and concluded DTaP is effective in preventing disease, and mild and serious side effects occurred less frequently when the DTaP vaccine was given. [3]
- Changes in the schedule of polio vaccines also have resulted in fewer reports of serious adverse events. In 1997, the Advisory Committee on Immunization Practices recommended a change in the vaccination schedule to include sequential administration of inactivated polio vaccine (IPV) and oral polio vaccine (OPV). [11] This sequential schedule was expected to produce a high level of individual protection against the disease caused by wild polio virus, while reducing by 50 to 70% vaccine-associated paralytic polio (VAPP) that occurs in 8–10 people a year who receive OPV. [11] Today, only IPV is on the recommended childhood immunization schedule.

The Future of Vaccine Safety

The importance of vaccine safety will continue to grow throughout the 21st century. The development and licensure of new vaccines will add to the already robust immunization schedule. Scientists could also perfect new ways of administering immunizations, including edible vaccines and needleless injections. However they are formulated or delivered, vaccines will

remain the most effective tool we possess for preventing disease and improving public health in the future.

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