

## The development of vaccines

Stopping the spread of a pandemic like the COVID-19 pandemic necessitates immunizing the population. The availability of vaccines plays a major role in this process. It was assumed that as soon as vaccines were developed, people would quickly get vaccinated and herd immunity would be reached. Meanwhile, enough tested vaccine doses are available, and a majority of the population is vaccinated. According to statistics from Our World in Data, for instance, 63.8 percent of the global population is fully vaccinated, and 12.8 billion total doses of vaccines have been administered. The ratio is lower in South Africa, where 32.8 percent of the people had received the vaccines by October 2022.

Normally, it takes several years to develop and approve vaccines. However, COVID-19 vaccines were developed extremely quickly. Less than one year after the first infections became known, the first vaccines were already approved and administered. All pharmaceuticals including vaccines run through the same phases of development and approval.

### Vaccine development and approval

**1. Isolation and characterization of the pathogen:** First, the pathogen is analyzed. Researchers investigate how the immune system reacts to the parts of the virus and find out what leads to antibodies and how T cells and B cells are produced.

**2. Identification of suitable antigens:** In the second step, researchers determine the antigens for which the vaccine should produce antibodies (see “How the immune system works”).

**3. Development of suitable candidate vaccines:** Now different vaccine types are taken into consideration, for example, inactivated vaccines, viral vector vaccines, or mRNA vaccines. In addition, researchers investigate which additives are needed for production so that the vaccine can be produced, transported, and administered safely and in large quantities. The more knowledge that is available about a pathogen, the faster these steps can be carried out.

In developing the COVID-19 vaccine, researchers built on the experiences and research results with other coronaviruses, for example, the SARS virus of 2003 and the MERS virus of 2012. In addition, they built on the years of research on mRNA, which was in the clinical trial phase as a cancer treatment.

**4. Preclinical trial phase:** Tests are conducted on animals in this phase to determine whether the vaccine triggers the desired immune response toward the pathogen (immunogenicity). In addition, researchers analyze the amount of vaccine that must be administered, how the vaccine spreads in the body, and whether it causes harmful side effects.

**5. Clinical trial – Phase 1:** If the first four steps are successful, clinical trials are initiated to test whether humans also exhibit a sufficient immune response to the pathogen. Ten to 30 volunteers (subjects) participate in the trial for several months. They are divided into two groups. One group is injected with a “placebo” (saline solution), the other group with the vaccine. None of the subjects know whether they have received the vaccine or not. They go on with their normal lives after vaccination, and the researchers wait until trial participants become infected. If a disease occurs very frequently and numerous people around the subjects are infected, then the subjects become infected more quickly than if the disease occurs less frequently.

During development of the COVID-19 vaccine, a very high number of infections surrounded the subjects. Those subjects who received a placebo became infected very quickly. As a result, it was

quickly determined that the vaccine had protected the other subject group very well. The first development phase of the COVID-19 vaccine lasted only a few weeks because the subjects injected with the placebo had become sick very quickly. The researchers thus quickly had results and could move more quickly to phase 2.

**6. Clinical trial – Phase 2:** In the second phase, the tolerability of the vaccine is investigated. About 50 to 500 subjects document all their observed side effects and physical reactions after the vaccine. Here as well, the subjects do not know whether they have received the vaccine with the active ingredient or a placebo. In this phase, researchers also test which dosage produces the best immune response with simultaneously the fewest side effects.

Normally, this phase lasts six months to a year. However, because the number of COVID-19 infections was so high, this phase of vaccine development was completed within a few weeks.

**7. Clinical trial – Phase 3:** The third phase aims to validate the results of the first two phases with a significantly greater number of subjects (300 to 3,000 people). Based on the results of many people, researchers can verify whether a vaccine is effective and safe, and they may possibly discover additional adverse side effects that rarely occur. This phase lasts two to five years. When time is critical, certain steps of clinical trials can be combined, for example, phase 1 with phase 2 or phase 2 with phase 3. This can happen, for instance, when voluntary test subjects participate simultaneously in two phases instead of one. Certain steps in the laboratory can also be combined. During development of the COVID-19 vaccine, the clinical trial phases were conducted with more than 15,000 people in Europe and lasted just a few months.

**8. Vaccines and the regulatory process:** Regulators rigorously evaluate scientific and clinical evidence provided by vaccine manufacturers. Vaccine manufacturers are legally obliged to follow defined standards in the data they provide, and their clinical research and manufacturing operations are subject to regulatory oversight. Either full or summary data from clinical trials are made available following vaccine evaluation. Each vaccine is thoroughly assessed for safety, efficacy, and quality to determine whether it can be approved for use. Regulators use available scientific evidence from preclinical laboratory research, human clinical trials, and manufacturing information to assess benefits and risks of candidate vaccines.

Regulators may seek additional expert advice from independent scientific advisory committees to help inform their decision on whether to approve a vaccine. These committees are made up of experts in science, medicine (including infectious diseases), and public health, and they often include consumer and healthcare professional representatives.

Public health agencies have a different role than regulatory authorities. They develop and deliver vaccination programs, often working with their expert immunization technical advisory committees. This includes prioritizing and designating populations for vaccination with specific vaccines, issuing additional recommendations and providing information more broadly about vaccines and immunization. They also collaborate with regulators to monitor the safety of vaccines after they are approved for use.

Globally, the public can have confidence in the rigor of the process used to scientifically evaluate the safety, efficacy, and quality of vaccines before they are approved for use in the wider population.

**9. Safety evidence prior to potential regulatory authorization:** Safety evidence is an essential part of each regulatory submission for a COVID-19 vaccine. It is gathered during all phases of the

vaccine development process. Robust assessment of safety is carried out in the clinical trials and submitted to regulators for review as part of the approval process.

All adverse events need to be examined and reported in the regulatory submission by the companies for a marketing license. Typically, regulators will require that participants in clinical trials have been followed for at least 1-2 months after receiving their final vaccine dose. Generally, based on previous experience with vaccines, most adverse events occur within such timeframes, though rare adverse events might not be recognized until after wide population use. There will also be longer-term (for example for 6-12 months or more) follow-up of those who participated in the earlier phases of the clinical trials of each vaccine. Many trial participants will also be followed for at least one year to assess the duration of protection and longer-term safety of individual vaccines, and safety data from these longer-term trials will be carefully reviewed by regulators as part of post-approval monitoring of safety.