



Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: COVID-19 Vaccine Overview
-November 2020-



Background:

The pandemic caused by the novel SARS-CoV-2 virus has already had a tremendous impact in American Indian and Alaska Native communities. History and prior experience with epidemics of infectious diseases have taught that a combination of standard public health interventions and vaccination can be effective in controlling spread. The global effort to develop and implement a safe and effective COVID-19 vaccine has been underway for many months, including both classical and next generation vaccine platforms.

Discussion:

Examples of successful vaccine development campaigns for epidemic infectious disease are common and range from cholera and rabies vaccines in the nineteenth century to polio and measles vaccines in the twentieth century.¹ Meanwhile, efforts to develop a vaccine for other infectious diseases such as HIV and malaria have not been similarly successful. Yet, the combination of standard public health interventions and an effective vaccine is a promising approach, as recently evidenced by the Ebola outbreak in West Africa in 2013-2016.^{2,3}

Vaccination is a source of active immunity, similar to infection with a disease-causing organism, but ideally without the risk of morbidity and mortality. As a general rule, the more similar a vaccine is to the disease-causing form of the organism, the better the immune response to the vaccine.⁴ COVID-19 vaccine platforms include both classical and next-generation platforms.⁵ Potential vaccine targets for inducing immunity against the SARS-CoV-2 virus are the nucleocapsid protein and the spike protein.

The vast majority of vaccines currently licensed for human use can be divided into virus-based or protein-based vaccines.⁴ The virus-based vaccines can consist of an inactivated virus that is no longer infectious, or live-attenuated virus. Live-attenuated virus vaccines are classically generated by passaging in cell culture until it loses its pathogenic properties and causes only a mild infection upon injection. Protein-based vaccines can consist of a protein purified from the virus or virus-infected cells, recombinant protein or virus-like particles. Virus-like particles consist of the structural viral proteins necessary to form a virus particle, but lack the viral genome and non-structural proteins. Protein-based vaccines require the addition of an adjuvant to induce a strong immune response.

Certain limitations are associated with several of these platforms that make them less amenable to fast vaccine production in a pandemic.⁵ In the case of SARS-CoV-2, large quantities of virus would need to be grown under biosafety level 3 conditions for a whole-inactivated vaccine. Extensive safety testing is required to ensure live-attenuated viruses are safe and do not easily revert to wild type, meanwhile, several recombinant proteins need to be produced simultaneously for virus-like particle vaccines.

Next-generation vaccines offer the advantage of starting development based on viral protein sequence (also known as the viral antigen) alone.⁵ This eliminates the need to depend on the ability to culture the virus, making these platforms highly adaptable and contributing to more rapid vaccine development. For this reason, the majority of COVID-19 vaccine clinical trials currently underway involve a next-generation platform. Viral vector vaccines consist of a recombinant virus (that is, the viral vector), often attenuated to reduce its pathogenicity, in which genes encoding viral antigen(s) have been cloned using recombinant DNA techniques. Vector vaccines can either be replicating or non-replicating. Replicating vector vaccines infect cells in which the vaccine antigen is produced as well as more infectious viral vectors able to infect new cells that will then also produce the vaccine antigen. Non-replicating vector vaccines initially enter cells and produce the vaccine antigen, but no new virus particles are formed. Because viral vector vaccines result in endogenous antigen production, both humoral and cellular immune responses are stimulated. One advantage of these viral vector-based vaccines is therefore that a single dose can be sufficient for protection, as in the case of the vesicular-stomatitis virus-based vaccine against Ebola.

Nucleic acid-based vaccines can consist of DNA or mRNA and can be adapted quickly when new viruses emerge, which is why these were among the very first COVID-19 vaccines to enter clinical trials.⁵ Nucleic acid-based vaccines induce a humoral and cellular immune response, but multiple doses are required. DNA vaccines consist of a synthetic DNA construct encoding the vaccine antigen. Self-replicating RNA vaccines are likely to induce protective immunity using a lower dose, because more vaccine antigen is expressed per cell.

Antigen-presenting cells are an essential component in the immune system's response to a vaccine.⁵ Loading antigen-presenting cells with peptides that would otherwise be produced by vaccination bypasses the first steps after vaccination.

Extra cold-chain requirements for a cell-based vaccine and infusion procedures hamper the deployment of these vaccines on a large scale, even more so since multiple doses are required for an efficient response. COVID-19 vaccines based on all next-generation platforms are currently in clinical trials.

The vaccine development lifecycle includes the exploratory stage, pre-clinical stage, clinical development, regulatory review and approval, manufacturing, quality control, and post marketing surveillance.⁶ Clinical development involves testing a candidate vaccine in healthy volunteers. Phase I clinical trials involve under 100 persons and are most intended to assess safety. Phase II clinical trials involve hundreds of persons and assess whether the vaccine produces an immune response as well as what short-term side effects are experienced. Phase III clinical trials involve thousands of persons in a randomized comparison of treatment and placebo groups intended to assess effectiveness of the vaccine as well as safety. The number of Phase III enrollees is impacted by multiple variables including statistical power needed to show benefit as well as evaluation of vaccine effects in subgroups (such as age demographics and racial/ethnic minorities). The number of subgroup enrollees likewise determines the ability to analyze safety and outcomes with a reasonable degree of certainty. Following regulatory approval and licensing, the CDC Advisory Committee on Immunization Practices evaluates the vaccine for potential inclusion on the U.S. Recommended Immunization Schedule.

Thereafter a critical stage is post-marketing surveillance to ensure safety as thousands or millions of persons are vaccinated, and involves multiple tools.⁶ This includes passive surveillance via reports to the Centers for Disease Control and Prevention (CDC) Vaccine Adverse Event Reporting System as well as active sentinel surveillance via the Food and Drug Administration's (FDA) Post-Licensure Immunization Safety Monitoring system. The Vaccine Safety Datalink is a collaboration between CDC and several healthcare organizations which utilizes databases of medical records to track vaccine safety. The Clinical Immunization Safety Assessment is a collaboration between the CDC, subject matter experts, and various clinical research centers which conducts clinical vaccine safety research involving complex cases of possible vaccine side effects in specific patients. In addition, formal Phase IV post-licensure studies may also be conducted.

Findings:

The U.S. federal response to COVID-19 includes an accelerated logistics program designed to meet the unique challenges of the pandemic. Operation Warp Speed is a partnership among components of the Department of Health and Human Services, including the CDC, FDA, the National Institutes of Health, the Biomedical Advanced Research and Development Authority, and the Department of Defense. Operation Warp Speed's goal is to produce and deliver 300 million doses of safe and effective vaccines with the initial doses available by January 2021, as part of a broader strategy to accelerate the development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics (collectively known as countermeasures).

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the [NPTC website](#).

References:

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2. World Health Organization. Coronavirus disease (COVID-19) pandemic. Available at: www.who.int.
3. Bausch D. [West Africa 2013 Ebola: From virus outbreak to humanitarian crisis](#). *Curr Top Microbiol Immunol*. 2017; 411:63-92.
4. U.S. Centers for Disease Control and Prevention. [Principles of Vaccination](#). Last update: June 29, 2020.
5. Van Riel D, de Wit E. [Next-generation vaccine platforms for Covid-19](#). *Nat Mater*. 2020; 19(8):810-12.