COVID-19 Vaccines

Introduction

At the end of 2019, a novel coronavirus now known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China. It rapidly spread, resulting in a global pandemic.

In February 2020, the World Health Organization named the disease COVID-19, which stands for coronavirus disease 2019.

Vaccines to prevent SARS-CoV-2 infection are considered the most promising approach for curbing the pandemic and are being vigorously pursued.

As of fall 2020, over 40 candidate vaccines were in human trials and over 150 were in preclinical trials.

Vaccine platforms

SARS-CoV-2 vaccines are being developed using several different platforms. Some of these are traditional approaches, such as **inactivated virus or live attenuated viruses**, which have been used for inactivated influenza vaccines and measles vaccine, respectively. Other approaches employ newer platforms, such as **recombinant proteins** (used for human papillomavirus vaccines) and **vectors** (used for Ebola vaccines). Some platforms, such as RNA and DNA vaccines, have never been employed in a licensed vaccine.

What are RNA vaccines?

RNA vaccines were the first vaccines for SARS-CoV-2 to be produced and represent an entirely new vaccine approach. Once administered, the RNA is translated into the target protein, which is intended to elicit an immune response.

The mRNA remains in the cell cytoplasm and does not enter into the nucleus; mRNA vaccines do not interact with or integrate into the recipient's DNA. These vaccines are produced completely in vitro, which facilitates production. However, since the technology is new, the ability to produce large quantities of RNA vaccines has not been previously tested, and some of the vaccines must be maintained at very low temperatures, complicating storage. Several SARS-CoV-2 RNA vaccines are in late-phase clinical trials.

Vaccine development for SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV) paved the way for rapid development of SARS-CoV-2 vaccines.
The major antigenic target for both SARS-CoV-1 and MERS vaccines was the **large surface spike protein**. An analogous protein is also present in SARS-CoV-2; **it binds to the angiotensin-converting enzyme 2 (ACE2) receptor** on host cells and induces membrane fusion. Based on data from SARS-CoV-1 and MERS-CoV vaccine studies, as well as observations that antibodies binding to the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein can prevent attachment to the host cell and neutralize the virus, **the spike protein became the predominant antigenic target for SARS-CoV-2 vaccine development.**

Approach to vaccination

(Pfizer-BioNTech COVID-19 Vaccine) and (**Moderna COVID-19 vaccine)**

In the United States, the COVID-19 mRNA vaccines BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine) and mRNA 1273 (Moderna COVID-19 Vaccine) have been granted emergency use authorization (EUA) for prevention of COVID-19 in December 2020.
While the safety and effectiveness of this investigational agent for use in the prevention of COVID-19 continues to be evaluated, the vaccine was shown in clinical trials to prevent COVID-19 occurring at least 7 days after the second dose; no significant safety concerns were identified.

Indications

- BNT162b2 **(Pfizer-BioNTech COVID-19 Vaccine**) is indicated for individuals aged 16 years or older.
- mRNA 1273 (**Moderna COVID-19 vaccine**) is indicated for individuals aged 18 years or older.

The choice between these mRNA vaccines is based on **availability**. They have not been compared directly, but they are similar in composition and in their respective phase III trials showed similar efficacy and safety profiles. The differences in **age** ranges included in the indications reflect the different age ranges included in the phase III trials.

Individuals with a history of SARS-CoV-2 infection should still receive one of these vaccines, if indicated; pre-vaccination serologic screening is not recommended. It is reasonable for individuals with recent, documented SARS-CoV-2 infection to delay vaccination for 90 days from the time of infection to allow others to receive vaccine sooner, as the risk of reinfection appears extremely low during this interval.

Mechanism of Action

Promotes active immunization against coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 virus. The nucleoside-modified messenger RNA (mRNA) in the vaccine is embedded in lipid nanoparticles that enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 spike (S) antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the S antigen, which may contribute to protection against COVID-19 disease.

Efficacy: ~95% protective efficacy against symptomatic COVID-19 disease in persons ≥16 years of age without prior evidence of SARS-CoV-2 infection following completion of the 2-dose series.

Dose and administration

•BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine) is administered in two intramuscular doses of 0.3 mL each, given three weeks apart. If more than 21 days have elapsed after the first dose, the second dose can be given as soon as feasible without repeating the series.

•mRNA 1273 (Moderna COVID-19 vaccine) is administered in two intramuscular doses of 0.5 mL each, given one month apart. If more than 28 days have elapsed after the first dose, the second dose can be given as soon as feasible without repeating the series.

Each vaccine series should be completed with the **same** vaccine initially used; there are no data to support the efficacy and safety of using one of the vaccines for the first dose and the other for the second.

Other non-COVID-19 vaccines should not be administered within 14 days of COVID-19 vaccine administration; there are no data regarding safety and efficacy when these vaccines are co-administered with other vaccines. There is no role for post-vaccination testing for COVID-19 unless clinically indicated.

Dosage Forms Considerations

After dilution with sodium chloride 0.9% injection, each vial of Pfizer-BioNTech COVID-19 Vaccine contains five 0.3 mL doses.

Adverse Reactions

Local reactions

Local reactions include **pain at injection site** (most common), and less commonly, **erythema at injection site** and **swelling at injection site**. Injection site pain was reported more frequently in younger patients (18 to 55 years of age) and was more likely to be moderate in severity compared to patients >55 years. In general, local reactions were mild to moderate in severity and resolved after a mean duration of ~2.5 days (with some cases resolving after ~30 days). The proportion of local reactions did not increase after the second dose.

Onset: Varied; within 7 days after either injection.

Systemic reactions

The most common systemic reactions include **fatigue** and **headache**. Other systemic reaction include **arthralgia** (new/worsened), **myalgia** (new/worsened), **chills**, **fever**, **di arrhea**, **nausea**, and **vomiting**. Frequency and severity of systemic events were higher in younger patients (18 to 55 years of age) than patients >55 years. Frequency and severity were also higher after the second dose compared to the first dose, except for diarrhea and vomiting (similar regardless of dose). In general, systemic reactions were mild to moderate in severity and resolved within a few days after vaccination. An unsolicited systemic reaction possibly attributed to vaccine was **lymphadenopathy.**

Onset: Rapid; within 1 to 2 days after either injection.

Anaphylaxis has been reported with the Pfizer-BioNTech coronavirus disease 2019 (COVID-19) vaccine (mRNA) during vaccination outside of clinical trials. Use the vaccine with caution in persons with history of severe allergic reaction (eg, anaphylaxis) to any other vaccine or injectable therapy (eg, IM, IV, SubQ).

Patient counseling

Vaccine recipients should be advised that side effects are **common and include local and systemic reactions, including pain at the injection site, fever, fatigue, and headache.**

SARS-CoV-2 infection might still occur despite vaccination, and the duration of protection is uncertain; vaccine recipients should be reminded to continue other personal preventive measures to reduce SARS-CoV-2 transmission.

Contraindications and precautions

BNT162b2 and mRNA 1273 are each contraindicated in **individuals with a history of severe allergic reaction to any component of that specific vaccine.**

Because of rare reports of anaphylactoid reactions following administration, the ACIP lists history of severe allergic reaction to any vaccine or injectable therapy as a precaution (but not contraindication) to vaccination.

All individuals should be monitored for immediate vaccine reactions following receipt; individuals with history of anaphylaxis should be monitored for 30 minutes and others for 15 minutes. Vaccines should be administered in settings where immediate allergic reactions, should they occur, can be appropriately managed.

Safety in special populations

Safety of these vaccines has not yet been established in children or pregnant individuals. However, **pregnancy is not a contraindication to vaccine receipt**. The decision to vaccinate individuals 16 years and older who are pregnant or breastfeeding should be made on **a case-by-case basis**, taking into account the individual's preferences, risk of COVID-19, and the unknown fetal effects of the vaccines.

The initiation of breastfeeding does not need to be avoided and breastfeeding does not need to be discontinued in patients who are vaccinated.

Immunocompromised persons (including those with HIV or receiving immunosuppressant therapy) may have a diminished immune response to the vaccine, although data are not currently available to establish vaccine safety and efficacy in these patients, the Centers for Disease Control and Prevention recommends vaccination of immunocompromised patients if there are no contraindications.

Drug Interactions

- Acetaminophen: May diminish the therapeutic effect of Vaccines. Management: Consider avoiding routine prophylactic use of acetaminophen before or during vaccine administration when possible. Acetaminophen is still recommended to treat fevers and/or pain that occurs after vaccination.
- Immunosuppressants: May diminish the therapeutic effect of COVID-19 Vaccine (mRNA).

Monitoring Parameters

Monitor for hypersensitivity and syncope for 15 minutes following administration. Observe patients with a history of anaphylaxis (due to any cause) for 30 minutes after vaccination (CDC 2020). If seizure-like activity associated with syncope occurs, maintain patient in supine or Trendelenburg position to reestablish adequate cerebral perfusion.

Storage

Pfizer company designed, temperature-controlled thermal shippers utilizing dry ice to maintain recommended storage temperature conditions of -70°C±10°C for up to 10 days unopened.

Once a point of use receives a thermal shipper, there are three options for storage:

- Ultra-low-temperature freezers, which are commercially available and can extend shelf life for up to six months.

- The Pfizer thermal shippers, in which doses will arrive, that can be used as temporary storage units by refilling with dry ice every five days for up to 30 days of storage.

- Refrigeration units those are commonly available in hospitals. The vaccine can be stored for five days at refrigerated 2-8°C conditions.

After storage for up to 30 days in the Pfizer thermal shipper, vaccination centers can transfer the vials to 2-8°C storage conditions for an additional five days, for a total of up to 35 days. Once thawed and stored under 2-8°C conditions, the vials cannot be re-frozen or stored under frozen conditions.

Thawing Frozen Vaccine

• Vaccine may be thawed in the refrigerator or at room temperature.
• Refrigerator: Between 2°C and 8°C
- 25 to 195 vials may take 2 to 3 hours to thaw in the refrigerator.
- Fewer numbers of vials will take less time.

• Room temperature (up to 25°C) between 30 minutes and 2 hours

• Vials at room temperature must be mixed within 2 hours or returned to the refrigerator.

• Do NOT refreeze thawed vaccine.

Vaccines in late phase studies

- **NVX-CoV2373 (Novavax)**

  This is a recombinant protein nanoparticle vaccine composed of trimeric spike glycoproteins and a potent Matrix-M1 adjuvant. The vaccine is given intramuscularly in two doses 21 days apart.
  In a phase I/II randomized, placebo-controlled trial of healthy individuals <60 years old, the adjuvanted vaccine induced high binding and neutralizing responses, comparable to those in convalescent plasma from patients who had been hospitalized with COVID-19. CD4 cell responses with a Th1 bias were also detected. Approximately 6 percent of participants experienced severe systemic effects (mainly fatigue, headache, myalgias, and/or malaise) following the second dose.

- **ChAdOx1 nCoV-19/AZD1222 (University of Oxford, AstraZeneca, and the Serum Institute of India)**

  This vaccine is based on a replication-incompetent chimpanzee adenovirus vector that expresses the spike protein. It is given intramuscularly and is being evaluated as a single dose or two doses 28 days apart.

  In a single-blind, randomized controlled phase I/II trial in healthy individuals 18 to 55 years old, in which most of the vaccine recipients received a single dose and a small cohort received an additional booster dose, neutralizing antibody titers 28 days after the last dose were comparable to those detected in convalescent plasma. The levels of antibody titers achieved were higher following two doses; and subsequent studies are evaluating the two-dose regimen. Cellular immune responses were also detected. In a study that included older vaccine recipients (>70 years), the vaccine resulted in similar antibody responses after the second dose as in younger adults.

  In a report of interim results from a multinational phase III randomized trial, this vaccine had 70.4 percent efficacy (95% CI 54.8-80.6) in preventing symptomatic COVID-19 at or after 14 days following the second dose. This effect was assessed after an analysis of 131 confirmed COVID-19 cases (30 in the vaccine group and 101 in the control group) among over 11,000 participants. However, a subgroup of participants inadvertently received a lower vaccine dose for the first of the two vaccine doses, and the vaccine efficacy in this subgroup differed from the rest. Vaccine efficacy was 90.0 percent (95% CI 28.0-78.2) among the 2741 participants who received the lower dose and 62.1 percent (95% CI 41-75.7) among those who received full-dose vaccine. Reasons for this difference are uncertain, although the overlapping confidence intervals indicate that the difference is not statistically significant. Differences in the control administered (meningococcal vaccine for both doses at some study sites versus meningococcal vaccine for one dose with saline for another dose at other sites) and in the interval between administration of the two vaccine doses further contribute to uncertainty about the findings.

  In earlier-phase trials, fatigue, headache, and fever were relatively common after vaccine receipt and were severe in up to 8 percent of recipients. In the phase III trial, there were two cases of transverse myelitis in ChAdOx1 nCoV-19 vaccine recipients. One was thought to be possibly related to vaccination and was described as an idiopathic, short-segment spinal cord demyelination; the other was in a participant with previously unrecognized multiple sclerosis and thought to be unrelated to the vaccine.

●Ad26.COV2.S (Janssen)

This vaccine is based on a replication-incompetent adenovirus 26 vector that expresses a stabilized spike protein. It is given intramuscularly and is being evaluated as a single dose. An unpublished report from a phase I/II randomized, double-blind, placebo controlled trial described high rates of neutralizing and binding antibodies after a single vaccine dose in healthy individuals 18 to 85 years old; these responses overlapped with but were slightly lower than those in convalescent plasma. Fewer than one percent reported severe systemic reactions. CD4 cell responses with a Th1 bias were also detected. Adenovirus 26 vectors are used in an Ebola vaccine that is licensed in Europe and in RSV, HIV, and Zika vaccine candidates. Baseline seroprevalence to adenovirus 26 is low in North America and Europe; it is moderately high in sub-Saharan Africa and Southeast Asia, although most seropositive individuals have low neutralizing titers. Nonhuman primate studies suggest that these low titers do not suppress responses to adenovirus 26 vector vaccines.

●Ad5-based COVID-19 vaccine (CanSino Biologics)

This vaccine is based on a replication-incompetent adenovirus 5 vector that expresses the spike protein. It is given as a single intramuscular dose. In early clinical trials, it was immunogenic in healthy adults at 28 days with only mild to moderate local and systemic reactions. However, both pre-existing immunity to adenovirus 5 and older age were associated with lower titers of binding and neutralizing antibodies following vaccination; this may limit its utility in locations where pre-existing immunity is prevalent. The vaccine has been licensed in China for limited use by the military. Prior studies of adenovirus 5 vector HIV vaccine candidates identified an increased risk of HIV acquisition among male vaccine recipients who were uncircumcised and seropositive for adenovirus 5 at baseline. It is uncertain whether these observations are relevant for adenovirus 5 SARS-CoV-2 vaccines.

●Sputnik V (Gamaleya Institute)

This is a vaccine developed in Russia that uses two replication-incompetent adenovirus vectors that express a full-length spike glycoprotein. The vaccine is given intramuscularly as an initial adenovirus 26 vector dose followed by an adenovirus 5 vector boosting dose 28 days later. In an open-label, nonrandomized phase I/II trial, the vaccine was associated with mild to moderate local and systemic reactions, but SARS-CoV-2 humoral and cellular immune responses were detected in the participants. This vaccine was licensed in Russia prior to completion of any efficacy trials. Russian officials reported a

91.4 percent efficacy rate following interim analysis of a phase III trial; however, the validity of this estimate is questionable because it is based on only 39 cases.

●BBIBP-CorV (Sinopharm)

This is an inactivated vaccine based on a SARS-CoV-2 isolate from a patient in China; it has an aluminum hydroxide adjuvant. The vaccine is given intramuscularly in two doses 28 days apart. In phase I/II placebo-controlled randomized trials of healthy individuals 18 to 80 years old, all recipients of two vaccine doses developed neutralizing and binding antibodies; no severe reactions were reported. This vaccine has been licensed in the United Arab Emirates based on interim data from a phase III efficacy data from trial in that country.

●CoronaVac (Sinovac)

This inactivated SARS-CoV-2 vaccine was developed in China; it has an aluminum hydroxide adjuvant. The vaccine is given intramuscularly in two doses 28 days apart. In a phase I/II randomized, placebo-controlled trial, the vaccine appeared safe and immunogenic in healthy individuals aged 18 to 59 years.

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