

Coronavirus Disease-2019 Vaccine Update

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The need to rapidly develop a vaccine that inhibits Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection and the resulting Coronavirus Disease-2019 (COVID-19) has stimulated significant scientific innovation.¹ In May 2020, the United States (U.S.) Department of Health and Human Services launched Operation Warp Speed, a partnership between government and industry, with the goal of delivering 300 million doses of a safe and effective vaccine by January 2021.² An unapproved vaccine may receive Emergency Use Authorization (EUA) status by the Food and Drug Administration (FDA) during a public health emergency when there are no adequate, approved and available alternatives.³ To receive EUA status, the developers must demonstrate clear and compelling efficacy and safety in a large, well-designed, phase 3 clinical trial. The issuance of an EUA is different than an FDA approval of a vaccine.³ The FDA expects manufacturers whose COVID-19 vaccines are authorized under an EUA to continue their clinical trials to obtain additional safety and efficacy information and pursue approval.³ This newsletter will focus on the vaccine candidates currently under development or authorized for emergency use in the U.S. to reduce infection associated with SARS-CoV-2.

Challenges in Vaccine Development

Over 200 COVID-19 vaccine candidates are under development worldwide.⁴ Vaccine development targeting the SARS-CoV-2 virus poses several challenges.¹ Most of the SARS-CoV-2 vaccine candidates target the receptor-binding domain of the surface spike protein of the coronavirus. The spike protein latches on to cells and unlocks them for virus entry; an antibody that binds to the spike and prevents the virus from getting into cells should stop the virus from causing infection.⁵ Although the coronavirus' spike protein is a promising method to develop immunity, optimizing antigen design to ensure at least 50% efficacy in placebo-controlled trials has been challenging.¹ As with naturally acquired infection, the potential duration of immunity is unknown; similarly, whether single-dose vaccines will confer immunity is uncertain.¹ For novel vaccines, large-scale manufacturing has never been done, so facilities capable of producing large quantities of product must be identified, technologies transferred, and manufacturing processes adapted, all without knowing if the vaccine candidate is viable.¹ Finally, in a high-mortality situation, populations may not accept randomized, controlled trials with placebo groups; although other approaches that address such concerns may be scientifically feasible, they're not as fast, and the results can be harder to interpret.⁶

Messenger RNA Vaccines

Vaccines with the greatest potential for rapid development are RNA-based platforms.¹ Two COVID-19 vaccines (**Table 1**) with FDA EUA as of December 17, 2020 are messenger RNA (mRNA) vaccines. mRNA vaccines can be made quickly because they use a synthetic process and do not require culture or fermentation.¹ To date, there are no mRNA vaccines for any infectious diseases except COVID-19. RNA vaccines function on the premise that mRNA coded for pathogen antigen can be delivered into human cells and result in production of antigen within the cell.² Unlike other vaccines, this triggers an immune response without the introduction of live, killed, or subunit portions of the virus.² The mRNA cannot cause infection, does not alter human DNA, and is broken down by normal processes in human cells. One of the main concerns of utilizing mRNA-based platforms is the potential of synthetically formulated mRNA to cause a severe adverse reaction due to its inherent inflammatory nature.⁴ In addition, mRNA is highly susceptible to extracellular ribonucleases and is rapidly degraded, so it must be encapsulated in a protective lipid system to facilitate delivery into human cells.² Because mRNA is naturally unstable, it must be stored frozen below -20 °C, which complicates the shipping, storage, and administration of mRNA vaccines.⁵ Some companies are working on stabilizing the molecule at higher temperatures by freeze-drying the vaccine.⁵

Viral Vector Vaccines

Two SARS-CoV-2 vaccines under development use non-replicating viral vectors to transport recombinant SARS-CoV-2 spike protein genes into the human cell (**Table 1**).² The infected cells display the coronavirus spike protein on their surfaces, which stimulates the immune system to develop antibodies.⁵ This transient viral DNA protein is not incorporated into the host cell DNA. Clinical use of this strategy has been used in Middle East Respiratory Syndrome (MERS), Zika, and Ebola vaccines.⁴ The Astra-Zeneca vaccine uses a simian adenovirus and the Janssen/Johnson & Johnson vaccine uses a human adenovirus.² Because these adenoviruses do not replicate, a high dose is required, producing about 12 hours of flu-like symptoms as the immune system responds to the vaccine.⁵ The Janssen/Johnson & Johnson vaccine was administered as a single dose in the first phase 3 trial. A second phase 3 trial is using 2 doses of the vaccine to evaluate safety and efficacy.

Recombinant Protein-Based Vaccines

The Novavax and Sanofi/GlaxoSmithKline (GSK) immunizations include SARS-CoV-2 proteins, but no genetic material (**Table 1**). Since this method is actually producing a unique protein, it is harder to manufacture than other vaccines and requires more time to ensure production meets high-quality standards.

The proteins are recognized by T-cells as target antigens, which generate an immune response. The Novavax product has shown efficacy in initial trials. The Sanofi/GSK vaccine has not produced the desired level of response in subjects over the age of 50 years. A different formulation will begin a phase 2 trial in early 2021. The most promising COVID-19 vaccine candidates developed through Operation Warp Speed are described in **Table 1**.

Table 1. COVID-19 Vaccine Candidates⁷

| Vaccine | How Supplied | Schedule | Storage and Dilution Requirements |
|--|---|------------------------------------|---|
| mRNA Vaccines | | | |
| Pfizer-BioNTech (BNT162b2) Comirnaty® (tozinameran) | 5 doses (30 mcg) in 2.25 mL MDV PF powder | 0.3 mL IM for 2 doses (Days 0, 21) | <ul style="list-style-type: none"> Frozen in ultra-cold storage between -80°C to -60°C (-112°F to -76°F) for 6 months. Once thawed, store refrigerated 2°C to 8°C (36°F to 46°F) for up to 5 days. Once reconstituted, store vials between 2°C to 25°C (35°F to 77°F) and use within 6 hours of dilution. |
| Approved for ≥16 yo under FDA EUA | | | |
| Moderna (mRNA-1273) | 10 doses (100 mcg) in 6.3 mL MDV PF suspension | 0.5mL IM for 2 doses (Days 0, 28) | <ul style="list-style-type: none"> Frozen between -25°C to -15°C (-13°F to 5°F) for 6 months. Refrigerated between 2°C to 8°C (36°F to 46°F) for 30 days. Room temperature between 8°C to 25°C (46°F to 77°F) for up to 12 hours. Once punctured, contents of vial must be administered within 6 hours. |
| Approved for ≥18 yo under FDA EUA | | | |
| Viral Vector Vaccines | | | |
| AstraZeneca-Oxford* (AZD1222) | 10 doses in MDV | 2 doses (Days 0, 28) | <ul style="list-style-type: none"> Refrigerated between 2°C to 8°C for up to 3 months. |
| Janssen/Johnson & Johnson* (Ad26.COV2-S)* | 5 doses in MDV | 1 dose | <ul style="list-style-type: none"> Frozen at -20°C for 2 years Refrigerated between 2°C to 8°C (36°F to 46°F) for up to 3 months. |
| Recombinant Protein Vaccines | | | |
| Novavax (NVX-CoV2373)* | N/A | 2 doses (Days 0, 21) | <ul style="list-style-type: none"> Refrigerated between 2° - 8°C (36 to 46°F) for up to 3 months. |
| Sanofi/GlaxoSmithKline* | N/A | 2 doses (Days 0, 21) | N/A |
| Abbreviations: EUA=Emergency Use Authorization; FDA=Food and Drug Administration; IM=intramuscular; MDV= Multi-dose Vial; mL=milliliters; mRNA=messenger RNA; N/A=Not Available; mcg=micrograms; PF= Preservative Free; yo=Years Old Key: * Approved age range not yet determined | | | |

Efficacy of the BioNTech/Pfizer Vaccine (BNT162b2)

Evidence from one phase 1 randomized controlled trial (RCT)⁸ and one combined Phase 2/3 (RCT)⁹ was evaluated by the FDA for EUA of the Pfizer 30 mcg vaccine. The placebo-controlled, phase 2/3 RCT was conducted at 152 worldwide sites in healthy adults aged 16 years and older (n=43,448).⁹ One hundred thirty clinical trial sites were based in the U.S.⁹ Subjects with stable chronic conditions including human immunodeficiency virus (HIV), hepatitis B virus or hepatitis C virus infections were eligible for trial participation.⁹ However, subjects diagnosed with an immunocompromising condition, treated with immunosuppressive therapy, or with a history of COVID-19 were excluded from the trial.⁹ Pregnant or breast feeding women and people with a history of severe adverse reaction associated with vaccine and/or severe allergic reaction (i.e. anaphylaxis) to any component of the vaccine were also excluded from this study.⁹

At the safety cutoff date, 37,706 participants had a median of 2 months of safety data available after the second dose.⁹ Of these 37,706 participants, 49% were female, 83% were White, 28% were Hispanic, 9% were Black, 4% were Asian, and 21% had at least one coexisting condition.⁹ The median age was 52 years, and 42% of participants were older than 55 years of age.⁹ Among 36,523 subjects with no evidence of prior SARS-CoV-2, there were 8 cases of COVID-19 with onset at least 7 days after the second dose of vaccine among vaccine recipients compared with 162 cases in the placebo arm.⁹ High-quality evidence from this trial showed this vaccine was 95% effective in preventing symptomatic COVID-19 compared to placebo (Relative Risk [RR] 0.05, 95% Confidence Interval [CI] 90.3 to 97.6%).¹⁰

Efficacy of the Moderna Vaccine (mRNA-127)

The phase 3 RCT evaluating the 2-dose Moderna 100 mcg vaccine randomized 30,418 subjects 1:1 to either vaccine or placebo in people 18 years of age and older at 99 U.S. clinical sites.¹¹ Inclusion and exclusion criteria were similar to the Pfizer study except for the range of included ages. Among study participants, 47% were female, 79% were White, 21% were Hispanic, 10% were Black, and 5% were Asian.¹¹ The mean age was 52 years and 25% were 65 years of age and older.¹¹ The median length of follow-up after the second dose was 7 weeks, though ongoing analysis is planned for all patients for 24 months.¹¹ The vaccine was 94.1% effective (95% CI 89.3 to 96.8) in preventing COVID-19 disease at least 14 days after the second vaccine dose with 11 cases of COVID-19 in the vaccine group and 185 in the placebo group.¹¹ At the time of the analysis of these 196 COVID-19 cases, none in the vaccine group and 30 in the placebo group were classified as severe.¹¹

Safety Data with mRNA Vaccines

Depending on vaccine product, age group, and vaccine dose, approximately 80–89% of vaccinated persons develop at least one local symptom and 55–83% develop at least one systemic symptom following vaccination (**Table 2**).¹² Most systemic post-vaccination symptoms are mild to moderate in severity, occur within the first three days of vaccination, and resolve within 1–3 days of onset.¹² The rate of adverse reactions reported with mRNA vaccines is similar to rates observed with the zoster vaccine.¹¹ These symptoms are more frequent and severe following the second dose and among younger persons compared to older persons.¹² Antipyretic or analgesic medications (e.g., acetaminophen, non-steroidal anti-inflammatory drugs) may be taken for the treatment of post-vaccination local or systemic symptoms, if medically appropriate. However, routine prophylactic administration of these medications for the purpose of preventing post-vaccination symptoms is not currently recommended, as information on the impact of such use on mRNA COVID-19 vaccine-induced antibody responses is not available at this time.¹² A 2014 systematic review assessed the evidence for a relationship between prophylactic antipyretic administration and antibody response in children.¹³ Though prophylactic antipyretic administration led to relief of the local and systemic symptoms after primary vaccinations, there was a reduction in antibody responses to some vaccine antigens.¹³

Hypersensitivity-related adverse events were observed in 0.63% of Pfizer and 1.5% of Moderna COVID-19 vaccine clinical trial participants who received the vaccine, compared to 0.51% and 1.1%, respectively, in the placebo groups.¹² Anaphylaxis following vaccination was not observed in the mRNA vaccine clinical trials.¹² However, anaphylactic reactions have been reported following receipt of the Pfizer COVID-19 vaccine during vaccination outside of clinical trials.¹² People who experience anaphylaxis with the first vaccine dose (i.e. they were hospitalized, they needed to use an EpiPen), should not receive a second dose.¹² Unless persons develop a contraindication to vaccination, they should be encouraged to complete the series even if they develop local or systemic symptoms following the first dose to optimize protection against COVID-19.¹² Protection from the vaccine is not immediate and 1-2 weeks is required following the second dose to be considered fully vaccinated.¹² Limited data are currently available regarding the efficacy of a single dose. Patients should be counseled on the importance of completing the two-dose series to optimize protection.¹² The vaccines are not interchangeable and both doses of the series should be completed with the same product.¹² Common and serious adverse effects observed up to 8 weeks after vaccination with the mRNA vaccines are outlined in **Table 2**.

Table 2. COVID-19 mRNA Vaccine Safety¹²

| Vaccine | Common Adverse Effects | Serious Adverse Effects |
|--|--|---|
| Pfizer-BioNTech (BNT162b2) | Injection Site Pain (84%) Fatigue (63%) Headache (55%) Muscle Pain (38%) Chills (32%) Joint Pain (24%) Fever (14%) | <ul style="list-style-type: none"> ▪ SAEs: 0.0% to 4.6% ▪ More frequent after second dose ▪ Fewer SAEs if >56 yo (≤2.8%) vs. ≤55 yo (≤4.6%) |
| Moderna (mRNA-1273) | Injection Site Pain (92%) Fatigue (69%) Headache (63%) Muscle Pain (60%) Joint Pain (45%) Chills (43%) | <ul style="list-style-type: none"> ▪ SAEs: 1% to 4.8% ▪ More frequent after second dose ▪ Fewer SAEs if ≥ 65 yo |
| Abbreviations: NR= Not Reported; SAEs = Severe Adverse Effects; yo = Years Old | | |

Vaccine Safety Reporting Methods

To continuously monitor the safety of the new COVID-19 vaccines, the FDA and CDC are collaborating on safety surveillance using existing vaccine safety monitoring infrastructure, including the Vaccine Adverse Event Reporting System (VAERS), Vaccine Safety Datalink, and Clinical Immunization Safety Assessment Project. Adverse events that occur in a recipient following COVID-19 vaccination should be reported to VAERS. Reporting is encouraged for any other clinically significant adverse event even if it is uncertain whether the vaccine caused the event.¹² Information on how to submit a report to VAERS is available at <https://vaers.hhs.gov> or by calling 1-800-822-7967.

In addition, CDC has developed a new, voluntary smartphone-based tool, V-SAFE, which is an after-vaccination health checker for people who receive COVID-19 vaccines. V-SAFE will use text messaging and web surveys from CDC to check in with vaccine recipients for health problems following COVID-19 vaccination. The system also will provide telephone follow up to anyone who reports medically significant adverse events. Reports to V-SAFE indicating a medically significant health impact, including pregnancy, are followed up by the CDC/V-SAFE call center to collect additional information to complete a VAERS report, if appropriate.¹²

Pearls for Patient Education

- RNA vaccine technology is new, but not unknown, as RNA vaccines have been studied for more than a decade for influenza and rabies.¹⁴
- Vaccine trials were large studies, with over 30,000 volunteers of various ages, races, and underlying diseases.¹⁴

- COVID-19 mRNA vaccines have been rigorously tested for safety before being authorized for use in the U.S. in large clinical trials and data review by the FDA.¹⁴
- RNA vaccines do not impact human DNA or genetic makeup. Human cells use mRNA every day to make many types of life sustaining proteins.¹⁴
- RNA vaccines do not enter the cell nucleus. They are not live vaccines and do not carry a risk of causing disease in the vaccinated person.¹⁴

COVID-19 Resources

- The CDC provides [Interim Clinical Considerations](#) for the administration of mRNA COVID-19 vaccines.
- Additional health provider resources for COVID-19 vaccine patient education can be accessed at the [CDC Website](#).
- Vaccine information and a Providers Communication Toolkit are available at the [OHA COVID-19 Healthcare Partner Resources](#) page.
- The OHA has also developed resources in Spanish at the [Vacnuncovid](#) page.

Conclusions

Two new COVID-19 mRNA vaccines received EUA by the FDA in late December 2020. The need for rapid development of vaccines to provide worldwide protection from the SARS-CoV-2 virus necessitated combined phase 2 and 3 clinical trials to expedite safety and efficacy assessments for these novel products. Initial data shows over 94% efficacy for both vaccines, and collection of long-term data is ongoing. Both vaccines are safe with expected mild to moderate symptoms (injection site pain, fever, headache, myalgia) lasting 1 to 3 days post immunization. At this time, data are not available to determine how long the mRNA vaccines will provide protection, nor is there evidence that these vaccines prevent transmission of SARS-CoV-2 from person to person.³ Additional vaccines using 2 different platforms, viral vector and recombinant proteins, are currently in phase 3 trials with results expected in early 2021.

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