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Topic: Update on COVID-19 Vaccines

Vaccine Overview

There are now two vaccines that have received an authorization for use in the United States from the FDA, one from Pfizer and BioNTech and a second from Moderna. The vaccine developed by AstraZeneca and Oxford University has currently been authorized for emergency use in the United Kingdom and India.

mRNA Vaccines

The vaccines from Pfizer/BioNTech and Moderna use a molecule called **messenger RNA**, or **mRNA**, to stimulate an immune response against SARS-CoV-2. mRNA is normally used in cells to transport genomic information from the DNA in the nucleus of a cell to the main cellular compartment, called the cytoplasm. The components that form mRNA are similar to those of DNA, which are called nucleotides, and the order of the nucleotides determines which protein is produced by cellular machinery. Once a protein has been manufactured, the mRNA is chopped back up into the individual nucleotides and reused.

> **Insertion of a synthetic mRNA into a cell causes the cellular machinery to produce the protein encoded by the artificial mRNA.**

Scientists have been able to use this concept to develop vaccines against SARS-CoV-2. By inserting mRNA that encodes the spike protein of the virus, cells produce the viral protein. Once released from the cells or embedded in the surface of a cell, the immune system contacts the viral protein and launches an immune response. Spike protein was chosen because antibodies to this protein have been shown to be neutralizing in other experiments, and it is readily accessible on the outside of viral particles for interaction with the immune system. **Neutralizing antibodies** prevent a virus from infecting cells in the body and thereby prevent an infection from starting.

Use of mRNA for vaccines has benefits over other types of vaccines, such as vaccines that contain the viral proteins themselves, inactivated virus, or weakened virus. One improvement is that the components of more traditional types of vaccine can take a long time to produce (proteins) or can have biocontainment needs that complicate the production (live virus vaccines). Proteins and virus-based vaccines also require production in live cells, thereby

necessitating growth of large vats of cell cultures. On the contrary, production of mRNA is a quick and inexpensive process, and the molecule can be chemically synthesized without cells while using the body itself to produce proteins from the virus to stimulate the immune system.

The complicating factor for mRNA vaccines, which is also a problem for many other vaccines and drugs, is keeping the mRNA intact and delivering the molecule to the appropriate area of the body to have an effect. Because of the transitory nature of mRNA in the cell under normal circumstances, mRNA is not designed to be stable for long periods of time, and it is quickly broken down in the bloodstream so that it can no longer be used to produce a protein.

To solve this problem, researchers have developed a protective coating for the mRNA. In the case of the Pfizer and Moderna vaccines, the protective coating is a **nanoparticle** made out of lipids (fat molecules). These spherical particles mimic the outer coating of a virus or cell, and keep the mRNA vaccine injected into the bloodstream protected. Additionally, the nanoparticle allows the mRNA to pass through the outer membrane of cells so that cellular machinery can begin production of viral proteins.

Another characteristic that has led to slow adoption of mRNA vaccines in the past is the potential for a strong allergic reaction to mRNA located outside of cells. Because mRNA is typically only used inside of cells, the presence of mRNA in the bloodstream is used by the immune system as an indicator of cells that have broken open due to tissue damage. Therefore, the presence of large amounts of mRNA in the bloodstream can lead to a strong inflammatory response. Modification of the nucleotides used in mRNA vaccines were found to reduce the immune response, and the encapsulation inside the nanoparticles further shields the mRNA until it is inserted into the cells.

Adenovirus Based Vaccines

The SARS-CoV-2 vaccine developed by AstraZeneca and Oxford University (called ChAdOx1nCoV-19 or AZD1222) utilizes a virus rather than nanoparticles to deliver the genetic material from SARS-CoV-2 in the form of DNA (Corum and Zimmer, 2020).

In their natural form, the viruses used as a delivery vehicle for DNA in vaccines cause very mild infections, or the virus has been altered to not cause disease. The type of virus that is often used is an adenovirus, because there are a large number of different adenoviruses and there are many that cause only mild infections in humans. The virus used in AZD1222 is an adenovirus that naturally infects chimpanzees, and it has been further modified so that it can enter a cell, but it cannot reproduce inside the cell and continue an infection. The name of the modified virus is ChAdOx1.

Like the Pfizer and Moderna vaccine, the AZD1222 vaccine targets the spike protein of SARS-CoV-2 to cause an immune response, but the sequence for the protein is delivered as DNA. Using DNA instead of mRNA in the vaccine is advantageous because DNA is a more stable molecule than mRNA. Additionally, the virus structure surrounding the DNA protects it more effectively than the nanoparticles used in the mRNA vaccines. Therefore, storage at low temperatures are not required, and AZD1222 is viable when stored at refrigerator temperatures

for at least six months. In fact, the vaccine may be stable for even longer, and longer tests are being performed.

Once injected, AZD1222 sticks to cells in the bloodstream and is absorbed into the cells. Inside the cells, the adenovirus particle comes apart and releases the SARS-CoV-2 DNA for the spike protein. Additional proteins from the adenovirus transport the SARS-CoV-2 DNA into the nucleus of the cell where it is transformed into mRNA and can then be used by the cell to produce SARS-CoV-2 spike proteins. The spike proteins are incorporated into the surface of the vaccinated cells, making the protein accessible to immune cells, such as T cells and B cells. These cells then produce antibodies targeting the spike protein and activate a T cell response.

COVID-19 Vaccines Authorized for Use

The COVID-19 vaccine developed by Pfizer and BioNTech as well as the vaccine developed by Moderna have been granted Emergency Use Authorization (EUA) by the FDA (Oliver et al, 2020).

Based on this recommendation

The **Pfizer/BioNTech vaccine** can be used for people over the age of 16 for the prevention of COVID-19

The **Moderna vaccine** can be used for people over the age of 18 for the prevention of COVID-19

Authorization of the Pfizer-BioNTech COVID-19 vaccine was based on one large, randomized, double-blind, placebo-controlled Phase 2 and 3 clinical trial that enrolled more than 43,000 participants between 16 and 91 years of age. Interim data from this clinical trial from participants with 2 months of observation after receiving the second dose indicate that the Pfizer-BioNTech COVID-19 vaccine was 95.0% effective in preventing symptomatic, laboratory-confirmed COVID-19. The high level of efficacy was observed regardless of age, sex, race, ethnicity, or the presence of chronic medical conditions. Data is not yet available for the efficacy of the vaccine to prevent asymptomatic SARS-CoV-2 infection. The approval committee acknowledged the difficulties from the need for ultracold storage and requirements for handling and administration that could lead to inequities in distribution.

The decision for authorization of the Moderna COVID-19 vaccine was based primarily on one large, randomized, double-blind, placebo-controlled Phase 3 clinical trial that enrolled approximately 30,000 participants aged 18 to 95 years. The interim findings included data from participants with 2 months of observation after the second dose showed that the Moderna vaccine had an efficacy of 94.1% after 2 doses in preventing symptomatic, laboratory-confirmed COVID-19. The high level of efficacy was observed regardless of age, sex, race, ethnicity, or the presence of chronic medical conditions. There was some evidence (categorized as evidence of very low certainty) that the vaccine prevents asymptomatic SARS-CoV-2 infection. The low certainty is due to the lack of longer observation periods of the participants and not from problems in the design of the trial. The vaccine requires long-term storage in a freezer, but it is stable at refrigerator temperatures for up to 30 days after thawing.

Because there is insufficient evidence of whether either vaccine prevents asymptomatic infections or if the vaccines prevent transmission of SARS-CoV-2 at this time, **it will still be necessary to wear a mask in public and follow other health official guidance for social distancing and limiting gatherings after vaccination**.

Allocation of Vaccines

The allocation of the first available doses is determined by state authorities, but a committee, the Advisory Committee on Immunization Practices (ACIP), from the CDC has published recommendations to guide decisions by local officials on the order of vaccination in their area. The ACIP has broken down the distribution into four phases. The United States is currently on Phase 1 of the plan.

Based on the recommendations of the ACIP, healthcare workers and residents and staff of long-term care facilities were designated to have priority for the first vaccinations (Phase 1a).

The ACIP also released recommendations on December 20 for the next groups with priority for vaccination (Dooling, 2020 and Branswell, 2020).

The groups in Phase 1b were included to prevent severe illness and death (people over the age of 75 years) or to preserve societal functioning (frontline essential workers).

Frontline essential workers for Phase 1b were defined as first responders, teachers and other education workers (including day-care workers), food and agriculture workers, correctional facility staff, postal workers, public transit workers, and people who work in manufacturing and in grocery stores. This group is a subset of those designated as “essential” by the Department of Homeland Security.

Phase 1c includes individuals 65 to 74 years and people 16 to 64 with high-risk medical conditions who are more likely to have severe illness or death, and the remaining essential workers designated by the Department of Homeland Security.

Based on estimates, Phase 1a involves approximately 24 million people in the United States, and Phase 1b included an additional 49 million people. At the time of the announcement of the ACIP’s recommendations, it was estimated that more than 500,000 individuals had been vaccinated thus far.

In total, the first three priority groups will cover 202 million people, which is twice the number of vaccine doses expected to be available by the end of February.

Allergic Reactions after Vaccination

There have been reports of severe allergic reactions to both of the COVID-19 vaccines currently available in the United States (Wu, 2020 and De Vrieze, 2020). As of December 21, there were reports of at least eight people having severe allergy-like reactions to the vaccine developed by Pfizer and BioNTech, and on December 24, a man in Boston developed a severe allergic reaction within minutes of receiving the vaccine developed by Moderna.

The component of the vaccine that leads to the immune reactions has not yet been identified, but a group of allergists and immunologists have mentioned a previously observed potential reaction to polyethylene glycol (PEG) that is part of both vaccines. People who have previously been exposed to PEG may have high levels of antibodies against PEG, putting them at risk of an anaphylactic reaction to the vaccine.

For comparison, allergic responses to vaccination typically occur in about one out of one million doses. In the United States, there have been six cases of anaphylaxis among 272,001 people who received the COVID-19 vaccine as of December 19. Pfizer amended their recommendations for administration to include that “appropriate medical treatment and supervision should always be readily available.”

The lack of allergic reactions observed in the clinical trials compared to those observed during distribution of the vaccine may be due to the specifics of the inclusion criteria for the study. The studies for both vaccines excluded people with a history of allergies to components of the COVID-19 vaccines, and Pfizer also excluded those who previously had a severe adverse reaction from any vaccine. People with previous allergic reactions to food or drugs were not excluded, but may have been underrepresented.

Studies of the prevalence of antibodies towards PEG show that at least 72% of people have some amount of antibodies that react to PEG, but most people do not produce enough to cause an allergic reaction. PEG is used in numerous different commercial products and medicines, and is considered to be inert in the body under most conditions. There are a number of drugs that include PEG that have good safety histories, suggesting that PEG in itself may not be the problem. In one clinical trial of a drug with PEG, people who had an allergic reaction were all found to have high levels of antibodies against PEG, but there were also people with high levels of PEG antibodies that did not have a reaction. Also, the level of PEG in the mRNA vaccines is much lower than the amount used in most other drug formulations, and injection into the muscle means that less of the PEG reaches the blood stream compared to other drugs that are administered intravenously.

Overall, the CDC recommends not giving the Pfizer or Moderna vaccines to anyone with a history of severe allergic reaction to any component of the vaccine.

For people who have had a severe reaction to another vaccine or injectable medication, the risks and benefits of vaccination should be carefully weighed, and people who might be at high risk of an anaphylactic reaction should stay at the vaccination site for 30 minutes after their shot so they can be treated if necessary. Physicians also stress that the severe reactions are a rarity in the 1.1 million doses given in the United States by December 25.

Incidental Illness after Vaccination

Vaccine researchers also want to make people aware of what is referred to as **incidental illness** that occurs after vaccination (Branswell, 2020).

> **When a negative effect occurs soon after vaccination, it seems logical to attribute it to the vaccine, but the onset of new symptoms is most often due to a new medical event that randomly coincides with administration of a vaccine rather than a response to the vaccine.**

This is especially true in older individuals who are more likely to experience new medical events and who are also being prioritized for vaccination to prevent COVID-19. Both the CDC and FDA have systems in place to monitor potential side effects of drugs and vaccines that have been approved for use so that side effects that were not evident during a clinical trial can be quickly detected and more easily distinguished from incidental illnesses.

Further complicating the issue of the detection of rare side effects are conditions that have unknown triggers, such as Bell's palsy and Guillain-Barré syndrome. Bell's palsy causes temporary paralysis in muscles of the face, and Guillain-Barré syndrome is a form of paralysis that usually is temporary. In the United States, there are 110 new cases of Bell's palsy a day and 274 new cases of Guillain-Barré syndrome each day that occur with no known cause. Both conditions have been observed after administration of several different vaccines, including those for COVID-19, but it has not been possible to show that vaccination was related to the onset of symptoms. However, the normal rate of Guillain-Barré syndrome and Bell's palsy are known in the United States, and researchers will be closely monitoring if the number of people who develop the disease after vaccination is higher than previously recorded.

Progress of Other Vaccines

Sinopharm, a Chinese-based vaccine manufacturer, released a press statement with the Phase 3 results from their vaccine called BBIBP-CorV (Cohen and Normille, 2020). In the statement, the vaccine is reported to have a 79.34% efficacy in preventing COVID-19 and was found to have a good safety profile. However, as often occurs with press statements, there was little additional information describing the trial. A previous press statement of interim results from the section of the trial in the United Arab Emirates reported an efficacy of 86%. Based on the Phase 3 results, Chinese officials approved the vaccine for use.

The vaccine is given in two doses and is comprised of SARS-CoV-2 that has been inactivated by exposure to a compound that chemically modifies the RNA of the virus in a way that makes it unable to create new copies (Corum and Zimmer, 2021). The inactivated virus remains intact, however, and can elicit an immune response, including neutralizing antibodies targeted to the spike protein. This type of vaccine has been used extensively in the past for prevention of polio, rabies, hepatitis A, and other viral infections.

> **Sinopharm reports that it has 100 million doses ready for dispersal, and the company expects to produce 1 billion more doses during 2021.**

Novavax began the Phase 3 trial of its COVID-19 vaccine in the United States and Mexico (Wadman, 2020 and Novavax, 2020). Another section of the trial has enrolled the required number of participants in the United Kingdom. The vaccine is a protein-based vaccine that delivers the SARS-CoV-2 spike protein embedded in a nanoparticle of lipids (fat molecules). The company stressed that the nanoparticles used in their vaccine do not contain PEG, which may be responsible for the allergic reactions reported for the mRNA vaccines (described above). The trial is expected to enroll up to 30,000 participants 18 years of age or older in 115 sites in the United States and Mexico. The vaccine is given in two doses 21 days apart and is stable at refrigerator temperatures.

Janssen Pharmaceutical Companies of Johnson & Johnson began a Phase 3 clinical trial near the end of September of their adenovirus-based COVID-19 vaccine (NIH, 2020). Importantly, this vaccine requires only a single dose rather than two injections as with the other vaccines that are in use or development. The clinical trial was reported to have full enrollment by the middle of December, 2020, and company officials state that interim Phase 3 data is expected by the end of January, 2021 (Johnson & Johnson, 2020). There is also a second Phase 3 trial underway to investigate the effects of the same vaccine when given as two doses. The Phase 1/2 interim results, which were reported in preprint form, indicate that that 92% of participants aged 18 to 55 produced antibodies targeted to the spike protein of SARS-CoV-2 29 days after inoculation with a single dose (Sadoff et al., 2020). All of the participants over the age of 65 were found to produce antibodies 29 days after vaccination, but there were some questions about the small number of people (only six participants) over 65 included in the interim evaluation. When the groups were combined, 98% of participants in the interim analysis had neutralizing antibodies 29 days after vaccination. There was also a large T-cell response to the vaccine. Because of the added stability as an adenovirus-based vaccine, the vaccine is stable for at least three months at fridge temperatures, and is expected to be stable in normal freezer temperatures for two years based on information from similar vaccines previously developed by Janssen.

Possible Changes to Vaccine Schedules

All of the currently available vaccines require two doses administered around three weeks apart. Scientists and officials in the United Kingdom are considering making sure everyone gets an initial dose before beginning to administer the second dose (Wu and Robbins, 2021). The rationale behind this change would be to get a larger number of people the protection offered by the first dose in order to slow the spread of the new virus variant B.1.1.7. The new variant is thought to be the cause of the recently increased spread of SARS-CoV-2 in the United Kingdom, which has led to cancellation of school across the country and a second nationwide lockdown.

While the efficacy of a single dose of the AstraZeneca vaccine and the Pfizer vaccine is less than that afforded by two doses, some feel it is important to provide at least partial protection to the largest amount of people.

In Britain, doctors have been told to postpone appointments for the second dose of the vaccine and to use the currently available shots for those who are unvaccinated.

Results from the Phase 3 clinical trial indicate that AstraZeneca's vaccine was 73% effective in the period between the first and second dose. There were a number of people in the trial that received their second dose several months apart rather than several weeks, and there was still some protection against COVID-19 in these participants.

The questions that cannot be currently answered about alternative dosing are whether the initial immune response will wane quickly without a booster, and if the increased length of time between doses will lead to a reduction in the overall magnitude of the response.

Another alternative that may have more scientific evidence behind it would be administering two half doses, which would still allow for an increase in the number of doses available. This dosing schedule was found to lead to an identical response for the Moderna vaccine in individuals who were 18 to 55 years old. This dosing schedule does not have the rigorous evidence of a full Phase 3 trial behind it, however, and there would still be a possibility of an incomplete response.

In the United States, researchers and officials report that the number of doses is not the limiting factor for vaccination (Florka et al., 2020). Instead, problems with distribution and adequate staffing of vaccination sites are the bottleneck. The problems are reminiscent of the issues with expanding testing capacity observed at the start of the pandemic. The distribution is being left up to individual states, and there is little direct communication between the federal government and vaccination sites, leading to confusion on timelines and quantities of deliveries.

Most officials report that increasing the number of doses would not increase the speed of getting the whole United States population vaccinated.

Anthony Fauci of the National Institutes of Health told the New York Times that he "would not be in favor" of an alternative dosing schedule, and that "we're going to keep doing what we're doing" (Wu and Robbins, 2021).

The FDA also released a statement warning against the use of alternative vaccine schedules for COVID-19.

In the communication, they state that "suggesting changes to the FDA-authorized dosing or schedules of these vaccines is premature and not rooted solidly in the available evidence" (FDA, 2021). They mention that the values being used in some of the reports are being misinterpreted, and that 98% (Pfizer-BioNTech) and 92% (Moderna) of participants in the Phase 3 trials received two doses of vaccine at the specified times. Those who did not receive a second dose were not observed for the entire study period, making it impossible to "conclude anything definitive about the depth or duration of protection after a single dose of vaccine." FDA officials also emphasize that available evidence suggests that the immune response to COVID-19 is based on the depth and duration of exposure of the immune system in some cases, which is based on observations that people with more severe disease having a larger immune response compared to those with mild or no symptoms.

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