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A. Messenger RNA – a novel approach for coronavirus vaccines

In late 2019 a new coronavirus called SARS-CoV-2 appeared in East Asia and rapidly spread around the world. In some people this virus causes an illness called Coronavirus Disease-2019 (COVID-19) that requires hospitalization. As the virus continued to take hold around the world, scientists, policymakers and pharmaceutical companies realized that vaccines would be needed, so they set about creating, testing and manufacturing vaccines for SARS-CoV-2. In this issue of *TreatmentUpdate* we explore some of those vaccines.

Messenger RNA

The first two vaccines approved in Canada, the United States and many high-income countries are made by Moderna and Pfizer-BioNTech.

Scientists with these companies have used a technology not previously used in vaccines called messenger RNA (mRNA). This type of RNA encodes the instructions for making a key piece, or protein, of SARS-CoV-2. When injected into animals or people, cells take up the mRNA and begin to make pieces of SARS-CoV-2. These proteins of the virus enter circulation, where they are noticed by cells of the immune system. The cells of the immune system capture the viral proteins and take them to lymph nodes and lymphoid tissues. There, the viral proteins are displayed to many cells of the immune system.

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One group of immune system cells—B-cells—begins to produce antibodies against the viral proteins. Another group of cells—T-cells, particularly CD8+ cells—learns to recognize the proteins and produces antiviral substances in response. The immune system then creates many copies of these B- and T-cells, and some of them leave lymph nodes and related tissues and enter circulation. When they encounter SARS-CoV-2 in the future, these B- and T-cells can respond with antibodies and antiviral substances and greatly reduce the risk of developing COVID-19.

In large clinical trials with tens of thousands of volunteers, the results of the mRNA vaccines have been nothing short of astonishing. Overall, after two injections of the vaccines, they were able to reduce the risk of developing COVID-19 by 95%. That scientists were able to make highly effective vaccines against a new germ in less than a year is unprecedented in human history.

Obstacles ahead

However, much work remains to be done in the field of SARS-CoV-2 vaccines. At this time, no single company has the manufacturing capacity to produce all the vaccines needed by a region, for example North America, Western Europe or East Asia. Therefore, it is likely that different vaccines will need to be used in these regions, with some people getting the Moderna vaccine and some getting the Pfizer-BioNTech vaccine.

As a result of the manufacturing shortfalls, combined with high demand for the mRNA vaccines, the rollout of the vaccines will be bumpy—with inevitable delays and temporary supply shortages. It may be that most of the people in the regions mentioned may not get vaccinated until the latter half of 2021.

Many unknowns

Studies show that the vaccines are generally safe and highly effective, but there are still areas of uncertainty such as the following:

Safety monitoring

The mRNA vaccines are generally safe, though in very rare cases serious allergic reactions can develop. More information about the safety of the vaccines appears later in this issue of *TreatmentUpdate*. Vaccine manufacturers and regulatory agencies are monitoring the rollout of the vaccines to assess if any other risks appear.

How long will protection conferred by the vaccine last?

Due to the public health emergency caused by the global pandemic, clinical trials with the vaccines lasted for about two to three months before licensure. As a result, no one is certain how long protection afforded by the vaccines will persist. Moderna and Pfizer-BioNTech will continue to monitor thousands of people who have been vaccinated for several years to learn about the duration of protection.

What are the elements of a protective response to the virus?

The immune system likely requires some combination of antibodies and T-cell responses to contain the virus. The relative balance of these two parts of the immune system that is necessary to prevent COVID-19 is not known. For instance, are antibodies more important than T-cell responses?

After vaccination, it is normal for levels of antibodies and antiviral T-cells in the blood to fall. This decline does not necessarily mean that the body has lost protection from SARS-CoV-2. For instance, in many other infections, long-lived cells that remember how to make antibodies and antiviral substances against a germ persist at low levels in the circulation or lymph nodes. These types of cells are called memory B-cells and memory T-cells. When the body encounters a germ—or, in this case, SARS-CoV-2—in the future, these memory cells will be activated and billions of copies will be made. The copies of memory cells can then produce antibodies and antiviral substances at the scale necessary to reduce the risk of developing COVID-19. No one is certain how long this immunological memory will remain effective.

A changing virus

All viruses change or mutate eventually. They make subtle changes to their shape or structure or to the nature of the proteins that they produce. These mutations arise from errors in the manufacture or replication of the virus from infected cells. Some of the mutations confer an advantage: The immune system may have trouble recognizing the virus and/or the antiviral response (antibodies and antiviral chemical signals) may not be as effective as it once

was. The mutations that confer an advantage to the virus tend to be carried forward in future copies of the virus.

The future outcome between the virus and the immune response depends on the type and number of mutations. For instance, a minor mutation probably does not appreciably affect the immune response. However, mutations that confer significant changes to the structure of the virus or enhance the potency of some viral proteins likely have the potential to help the virus evade antibodies and/or T-cells.

The mRNA vaccines made by Moderna and Pfizer-BioNTech are designed to cause cells of the body to produce viral proteins that are in a form that likely enhances the immune system's ability to recognize them. This may mean that, in some cases, some mutations of the virus should still be affected by antibodies and T-cells that have been stimulated by the vaccines.

Since its discovery, SARS-CoV-2 seems to undergo mutations from time to time. Some variants of the virus, such as one called B117, first recognized in the UK, can spread faster (are more infectious) than the original version of the virus. Scientists have found other variants arising in Brazil, South Africa, the U.S. and other countries that may be of concern. Such variants require understanding in laboratory experiments with cells and possibly animals to find out if COVID-19 vaccines can produce a durable and protective response against them.

As other variants of SARS-CoV-2 are likely to appear in the future, public health laboratories need to be monitoring the virus variants in circulation and pharmaceutical companies need to be ready to create either enhancements to existing vaccines or new vaccines as the need arises.

Symptoms or no symptoms

Clinical trials of the first generation of vaccines against SARS-CoV-2 were designed to assess the ability of vaccines to prevent symptoms of disease (COVID-19). These trials were not designed to assess whether the vaccines could prevent infection with SARS-CoV-2. This is an important distinction. Prior to the advent of the vaccines, scientists estimated that 40% to 50% of people who became infected with the virus could have symptom-free infection. Research needs to be done to find out if the mRNA and other vaccines are able to prevent infection with SARS-CoV-2.

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B. The Pfizer-BioNTech vaccine

Clinical trials of the Pfizer-BioNTech vaccine have found that it is generally safe. Local side effects (at the injection site) included pain, swelling and

redness. Local and systemic side effects (including fever, fatigue, headache, joint pain and muscle pain) were usually mild to moderate and temporary. The vaccine was 95% effective at reducing the risk of developing COVID-19 after two injections were given.

How the vaccine works

The Pfizer-BioNTech vaccine contains a piece of microscopic messenger RNA enclosed with fatty molecules. Messenger RNA (mRNA) is a form of genetic information that contains instructions for making copies of a key protein used by SARS-CoV-2, the virus that causes COVID-19. As mRNA contains only instructions for making a piece of the virus, and not the whole virus, the vaccine cannot cause infection with SARS-CoV-2 or COVID-19. Furthermore, the mRNA in the vaccine is taken up by cells and is "read" by cellular machinery called ribosomes. The function of this cellular machinery is to make the proteins encoded by mRNA. The mRNA does not become part of a person's genetic material (DNA) and is eventually broken down. Therefore, the vaccine does not alter a person's genes.

As the ribosomes churn out copies of the viral proteins, these proteins move to the surface of a cell and are released into circulation. Once the viral proteins are in circulation, cells of the immune system capture them and take them back to lymph nodes and lymphoid tissues, where they educate the rest of the immune system about SARS-CoV-2. The immune system makes many copies of cells that learn to attack these proteins. These cells circulate and some remain in lymph nodes and lymphoid tissues. When the body encounters SARS-CoV-2, these cells make millions of copies of themselves and the immune response against the virus becomes amplified.

Study details

The phase II/III clinical trials that Pfizer-BioNTech used to collect data that was submitted for regulatory approval enrolled 43,651 people. Participants were randomly assigned to receive one of the following interventions:

- an intramuscular injection (into the upper arm) of the vaccine on day one, followed by another injection 21 days later
- an intramuscular injection of placebo on day one, followed by another injection 21 days later

People who initially received the vaccine were also given the vaccine on their second shot, and vice versa for placebo.

The average profile of participants upon study entry was as follows:

- 51% men, 49% women
- age distribution: 12 to 15 years – 0.2%; 16 to 55 years – 57%; 56 years and older – 43%; 65 years and older – 22%
- major ethno-racial groups: white – 83%; Hispanic – 27%; black – 9%; Asian – 4% (Note that due to the complexity of the ethno-racial classification system in the U.S., numbers may not total 100.)
- underlying conditions – 46% had at least one underlying condition that increased the risk for COVID-19, including chronic lung disease, diabetes, higher-than-normal blood pressure

Participants were monitored for about two months after vaccination for assessment of effectiveness.

Results

Cases of flu-like symptoms were assessed if they occurred seven days after the second injection. If these cases tested positive for SARS-CoV-2, they were considered to have COVID-19.

The distribution of cases of COVID-19 that occurred was as follows:

- people who were vaccinated – 8 cases
- people who received placebo – 162 cases

Researchers calculated that this distribution meant that the vaccine reduced a person's chances of developing COVID-19 by 95%. The vaccine was highly effective in both young and older people.

A subset of participants (8,183 people) who were 18 years and older was closely monitored for safety. In this subset of people, common side effects from the vaccine were as follows:

- pain at the injection site – 84%
- fatigue – 63%
- headache – 55%

- muscle pain – 38%
- chills – 32%
- joint pain – 24%
- fever – 14%

These side effects were generally mild to moderate in intensity. They appeared within the first day of vaccination and tended to resolve within one to two days. The side effects suggest that the immune system is responding to the vaccine.

No deaths were caused by vaccination or placebo.

A relatively small number of people (64) who received the vaccine developed a swollen lymph node(s), usually under the arm. Again, this is likely suggestive that the immune system was responding to the vaccine. It is not clear how long it took for this symptom to resolve.

Hypersensitivity (allergic) reactions

According to the U.S. Food and Drug Administration (FDA), which analysed the data from the clinical trials, there was "a slight numerical imbalance of adverse events possibly representing hypersensitivity-related adverse reactions in [people who received the vaccine] compared to [people who received placebo]." This distribution was as follows:

- vaccine – 137 people (0.63%)
- placebo – 111 people (0.51%)

This suggests that the vaccine has the potential to trigger hypersensitivity reactions in some people. Note that clinical trials of the mRNA vaccines excluded people with a history of severe allergic reactions to vaccines or to an important ingredient in vaccines called PEG (polyethylene glycol). One person who received the Pfizer-BioNTech vaccine developed a serious allergic reaction (anaphylaxis) during the study.

Further information about allergic reactions appears later in this issue of *TreatmentUpdate*.

Changes to lab tests

The only laboratory test abnormalities noted were temporary decreases in a group of immune system cells called lymphocytes. This happened between one and three days after participants received their first dose of the vaccine. These decreases were judged to be mostly mild to moderate and resolved within a week. These changes were not associated with any symptoms. The decreased lymphocyte numbers did not occur after the second vaccination.

Pregnancy

Women of childbearing potential were screened for pregnancy prior to being scheduled for vaccination. Any women who tested positive for pregnancy were excluded from the study. Women who became pregnant after entering the study were excluded from getting a second dose of the vaccine. Subsequently (after the second dose), there were 23 pregnancies distributed as follows:

- vaccine – 12 pregnancies
- placebo – 11 pregnancies

The outcome of these pregnancies is not known at this time.

Given the public health emergency caused by SARS-CoV-2, some physicians and public health authorities may recommend that pregnant women get the vaccine.

Further study needed

As mentioned earlier, Pfizer-BioNTech will continue to monitor participants who were in clinical trials of the vaccine for several years. This is essential to capture data on any new side effects. Extended monitoring is also needed to find out how long protection provided by the vaccine lasts.

According to the FDA, Pfizer-BioNTech will conduct a study to assess the safety and effectiveness of the vaccine in pregnancy.

Vulnerable populations

There was a relatively small number of people with chronic viral infections—hepatitis B and C, HIV—in the study; data from the study suggests that the vaccine works and did not cause problems in these people. Note that doctors caring for people with chronic viral infections are likely to generally recommend the vaccine for these populations, particularly for people who are being treated with medicines for chronic viral infections and whose

health is relatively stable and good. The doctors are likely to do this because the mRNA vaccines do not cause SARS-CoV-2 infection and many people with chronic viral infections have underlying conditions that increase their risk for COVID-19 should they become infected with SARS-CoV-2.

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C The Moderna vaccine

Clinical trials of the Moderna vaccine have found that it is generally safe. Local side effects (at the injection site) included pain, swelling and redness. Local and systemic side effects (including fever, fatigue, headache, joint pain and muscle pain) were usually mild to moderate and temporary. The vaccine was 94% effective at reducing the risk of developing COVID-19 after two injections were given.

How the vaccine works

The Moderna vaccine contains a piece of microscopic messenger RNA enclosed with fatty molecules. Messenger RNA (mRNA) is a form of genetic information that contains instructions for making copies of a key protein used by SARS-CoV-2, the virus that causes COVID-19. As mRNA contains only instructions for making a piece of the virus, and not the whole virus, the vaccine cannot cause infection with SARS-CoV-2 or COVID-19. Furthermore, the mRNA in the vaccine is taken up by cells and is "read" by cellular machinery called ribosomes. The function of this cellular machinery is to make the proteins encoded by mRNA. The mRNA does not become part of a person's genetic material (DNA). Therefore, the vaccine does not alter a person's genes.

As the ribosomes churn out copies of the viral proteins, these proteins move to the surface of a cell and are released into circulation. Once the viral proteins are in circulation, cells of the immune system capture them and take them back to lymph nodes and lymphoid tissues, where they educate the rest of the immune system about SARS-CoV-2. The immune system makes many copies of cells that learn to attack these proteins. These cells circulate and some remain in lymph nodes and lymphoid tissues. When the body encounters SARS-CoV-2, these cells make millions of copies of themselves and the immune response against the virus becomes amplified.

Study details

The phase III clinical trials that Moderna used to collect data that was submitted for regulatory approval enrolled 14,206 people. Participants were randomly assigned to receive one of the following interventions:

- an intramuscular injection (into the upper arm) of the vaccine on day one, followed by another injection 28 days later
- an intramuscular injection of placebo on day one, followed by another injection 28 days later

People who initially received the vaccine were also given the vaccine on their second shot, and vice versa for placebo.

The average profile of participants upon study entry was as follows:

- 53% men, 47% women
- age distribution: 18 to 64 years – 75%; 65 and older – 25%
- major ethno-racial groups: white – 80%; Hispanic – 20%; black – 10%; Asian – 5% (Note that due to the complexity of ethno-racial classification in the U.S., numbers do not total 100.)
- underlying conditions – 19% had an underlying condition that is associated with an increased risk for COVID-19, including chronic lung disease, cardiovascular disease, obesity, diabetes

Results

The distribution of people who developed confirmed COVID-19 two weeks after their second injection was as follows:

- vaccine – 11 cases
- placebo – 185 cases

Researchers calculated that this distribution meant that the vaccine reduced a person's risk of developing COVID-19 by 94%. Among people aged 65 years and older, the efficacy of the vaccine was 86%.

Side effects

Commonly reported side effects were as follows:

- pain at the injection site – 90%
- fatigue – 70%
- headache – 65%
- muscle pain – 62%
- joint pain – 45%
- chills – 42%

In general, most of these side effects were of mild-to-moderate intensity and resolved within a few days.

According to the FDA, more people who received the vaccine (1.1%) vs. placebo (0.63%) developed swollen lymph nodes, usually under the arm. This type of reaction suggests that the immune system was responding the vaccine. It is not clear when this side effect resolved.

No one died from the vaccine (or placebo).

Hypersensitivity reactions

More people who received the vaccine (1.5%) developed hypersensitivity reactions compared to those on placebo (1.1%). According to Moderna, "this imbalance was mainly due to injection site rash and injection site swelling/redness[…]." Still, the findings raise the possibility that in rare cases the vaccine may cause hypersensitivity reactions. No one developed severe hypersensitivity reactions to the vaccine in clinical trials. However, three people who received the Moderna vaccine developed swelling of the lips/face about one and two days after vaccination. All three people had a history of having cosmetic fillers in their face. Unfortunately, the brands and formulations of these fillers are not known.

Note that people who had a history of allergic reactions to vaccines or PEG (polyethylene glycol; an ingredient in the vaccine) were excluded from the study.

Special populations

There were 196 study participants who had what researchers called "liver disease." They did not specify the cause of liver disease, but it is likely that at least some people had chronic viral infections with hepatitis B or C viruses.

There were 176 participants with HIV infection.

In both cases of liver disease and HIV infection no issues of efficacy or safety were reported.

Pregnancy

Women of childbearing potential were screened for pregnancy prior to being scheduled for vaccination. Any women who tested positive for pregnancy were excluded from the study. Women who became pregnant after entering the study were excluded from getting a second dose of the vaccine. Subsequently (after the second dose), there were 13 pregnancies distributed as follows:

- vaccine – 6 pregnancies
- placebo – 7 pregnancies

The outcome of these pregnancies is not known at this time.

Given the public health emergency caused by SARS-CoV-2, some physicians and public health authorities may recommend that pregnant women get the vaccine.

Further study

According to the FDA, Moderna plans to conduct studies to do the following:

- monitor the health of women who are vaccinated and who are or who become pregnant
- monitor participants to assess long-term safety of the vaccine
- further assess the efficacy of the vaccine

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D. Exploring rare and serious allergic reactions to mRNA vaccines for COVID-19

There have been reports of relatively rare serious allergic reactions to both the Pfizer-BioNTech and Moderna mRNA-based vaccines. Readers should bear in mind that while these reports can be alarming, they are rare.

Allergists associated with Massachusetts General Hospital and other leading research institutions in the U.S. have cooperated to try to understand why rare and serious allergic reactions to the mRNA vaccines may occur.

Non-COVID vaccines

In general, severe allergic reactions to vaccines are rare. A review of such reactions to vaccines for non-COVID-19 diseases found that they occurred at the rate of about 1 per million people. The risk of severe allergic reactions seemed similar regardless of age and gender.

The allergists noted that the vaccine solution usually contains extra ingredients called excipients, which have the following functions:

- act as preservatives, preventing the growth of bacteria and fungi
- protect the vaccine during transport and storage
- amplify the immune response to the vaccine

Some excipients such as PEG (polyethelene glycol) and the related substance polysorbate help to stabilize the vaccine.

Focus on COVID-19 vaccines

Both the Pfizer-BioNTech and Moderna vaccines contain PEG. The purpose of PEG is to stabilize the mRNA that is at the core of the vaccines. The mRNA is enclosed by tiny fatty particles called lipid nanoparticles. Other COVID-19 vaccines, such as those being developed by AstraZeneca and Janssen, do not use PEG but instead use a related compound called polysorbate 80. Polysorbate 80 and other polysorbates are molecules similar in structure to PEG. Polysorbates are found in many products, including vitamin oils, vaccines and some anticancer drugs.

PEG is also found in some medicines and medical products. These include some medicines for treating constipation (Miralax) and bowel preparation formulations used prior to colonoscopy. A review by the FDA using data collected between 2005 and 2017 found that about four cases of allergic reactions per year were associated with colonoscopy preparations or laxatives. However, the PEG inside the two mRNA vaccines is different from the PEG used in medicines.

Some allergists have speculated that the rare but serious allergic reactions to the Pfizer-BioNTech and Moderna vaccines arise because these vaccines use a formulation of PEG called PEG2000. Furthermore, they add that people who developed serious allergic reactions during clinical trials of the vaccines were sensitized to this formulation of PEG through the use of previous PEG-containing compounds.

Note that the Centers for Disease Control and Prevention (CDC) has developed guidance on helping healthcare providers to recognize signs and symptoms of serious allergic reactions; these appear in our report on that agency's findings, later in this issue of *TreatmentUpdate*. The CDC advises that "persons with an immediate allergic reaction to the first dose of an mRNA COVID-19 vaccine should not receive an additional dose of either of the mRNA COVID-19 vaccines."

Perhaps the most important point that the allergists make is that people with a history of allergic reactions should **not** be pre-treated with antihistamines prior to receiving COVID-19 vaccinations, as these drugs may initially mask serious symptoms of an allergic reaction to these vaccines.

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Banerji A, Wickner PG, Saff R, et al. mRNA vaccines to prevent COVID-19 disease and reported allergic reactions: Current evidence and suggested approach. *Journal of Allergy and Clinical Immunology: In Practice*. 2021; *in press*.

E. Interim CDC analysis of severe allergic reactions in people who received the Pfizer-BioNTech vaccine

Anaphylaxis is a serious allergic reaction that can become life threatening. Here are key points about

anaphylaxis from the U.S. Centers for Disease Control and Prevention (CDC):

> "Early signs and symptoms of anaphylaxis can resemble a mild allergic reaction, and it is often difficult to predict whether initial, mild symptoms will progress to an anaphylactic reaction." The agency also stated that "symptoms of [anaphylaxis] often occur within 15 to 30 minutes of vaccination, though it can sometimes take several hours for symptoms to appear."

Signs and symptoms of anaphylaxis can include the following:

Respiratory
- "sensation of throat closing, stridor (high-pitched sound while breathing), shortness of breath, wheeze, cough"

Gastrointestinal
- "nausea, vomiting, diarrhea, abdominal pain"

Cardiovascular
- "dizziness, fainting, tachycardia (abnormally fast heart rate), hypotension (abnormally low blood pressure)"

Skin/mucosal
- "generalized hives, itching or swelling of lips, face, throat"

The CDC adds that "persons with communication difficulties" should be monitored for the above signs and symptoms, as well as for additional symptoms such as the following:

- flushing
- sudden increase in secretions (from eyes, nose or mouth)
- coughing
- trouble swallowing
- agitation
- acute change in mental status

Allergic reactions to the Pfizer-BioNTech vaccine

The interim CDC analysis is based on the rollout of the first 1,893,360 doses of the vaccine. After assessing reports of adverse events from this data set, the CDC has concluded that there were 21 cases of anaphylaxis. This results in a rate of 4.7 cases per one million doses. This is very rare.

Cases

A brief profile of the 21 people who had severe allergic reactions is as follows:

- age range – 27 to 60 years
- 90% were women (this point is revisited later)
- time to allergic symptoms – some people developed allergic symptoms as quickly as two minutes after their injection while others took as long as 150 minutes.

The distribution of people in relation to the time to appearance of allergic symptoms was as follows:

- within 2 to 15 minutes – 71%
- within 15 to 30 minutes – 14%
- after 30 minutes – 14%

(The total does not equal 100 due to rounding.)

Most (90%) affected people received injections of epinephrine (adrenaline) after their symptoms appeared.

Four people required hospitalization, three of whom needed admission to an intensive care unit. The remaining 17 people were treated in the emergency department of a hospital.

Complete data were available on 20 of the 21 people (98%). All 20 people recovered and were sent home. No one died.

A history of allergic reactions

The CDC researchers found that 17 people (81%) out of the 21 had "a documented history of allergies or allergic reactions, including to drugs or medical products, foods and insect stings; seven patients (33%) had experienced an episode of anaphylaxis in the past, including one after receipt of a rabies vaccine and another after receipt of an influenza A (H1N1) vaccine."

The CDC did not find a clustering of severe allergic reactions in any particular region.

Non-anaphylactic reactions

The CDC also reported that separately there were 83 cases of allergic reactions not involving anaphylaxis after vaccination. These reactions occurred within the first day of vaccination.

Common symptoms were as follows:

- itchy skin
- rash
- itchy and scratching sensations in the throat
- mild respiratory symptoms (the agency did not define these)

Patients with these allergic symptoms were between 18 to 65 years old. About 90% of these reactions were also in women.

The onset of non-anaphylactic reactions from the time of vaccination ranged from less than one minute to 20 hours. The distribution of the onset of these symptoms after vaccination was as follows:

- within 30 minutes – 85%
- after 30 minutes – 15%

According to the CDC, in 67% of cases of non-anaphylactic reactions "there was a past history of allergies or allergic reactions."

The CDC advises that "persons with an immediate allergic reaction to the first dose of an mRNA COVID-19 vaccine should not receive additional doses of either of the mRNA COVID-19 vaccines."

The issue of gender

Previous reports suggest that, in general, more women experience adverse reactions to flu vaccine than men.

In the rollout of the Pfizer-BioNTech vaccine, 64% of the vaccine patients were women. It is therefore plausible that part of the reason for the over-representation of women in cases of allergic reaction to this vaccine arose in part because most people who received the vaccine were women.

More research is needed to better understand the gendered distribution of vaccine-associated allergic reactions. The CDC's report should be viewed as preliminary and further monitoring and analysis of side effects will be done as more people get the vaccine.

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CDC COVID-19 Response Team and the Food and Drug Administration. Allergic reactions including anaphylaxis after receipt of the first dose of Pifzer-BioNTech COVID-19 vaccine – United States, December 14-23, 2020. *Morbidity and Mortality Weekly Report*. 6 January, 2021.

F. Interim CDC analysis of severe allergic reactions in people who received the Moderna vaccine

Anaphylaxis is a serious allergic reaction that can become life threatening. Here are key points about anaphylaxis from the U.S. Centers for Disease Control and Prevention (CDC):

> "Early signs and symptoms of anaphylaxis can resemble a mild allergic reaction, and it is often difficult to predict whether initial, mild symptoms will progress to an anaphylactic reaction." The agency also stated that "symptoms of [anaphylaxis] often occur within 15 to 30 minutes of vaccination, though it can sometimes take several hours for symptoms to appear."

Signs and symptoms of anaphylaxis can include the following:

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Cardiovascular
- "dizziness, fainting, tachycardia (abnormally fast heart rate), hypotension (abnormally low blood pressure)"

Skin/mucosal
- "generalized hives, itching or swelling of lips, face, throat"

The CDC adds that "persons with communication difficulties" should be monitored for the above signs and symptoms, as well as for additional symptoms such as the following:

- flushing
- sudden increase in secretions (from eyes, nose or mouth)
- coughing
- trouble swallowing
- agitation
- acute change in mental status

Allergic reactions to the Moderna vaccine

The interim CDC analysis is based on the rollout of the first 4,041,396 doses of the vaccine. After assessing reports of adverse events from this data set, the CDC has concluded that there were 10 cases of anaphylaxis. This results in a rate of about 3 cases per one million doses. This is very rare.

Cases

A brief profile of the 10 people who had severe allergic reactions is as follows:

- age range – 31 to 63 years
- all were women (this point is revisited later)
- time to allergic symptoms – some people developed allergic symptoms as quickly as one minute after their injection, while others took as long as 45 minutes.

The distribution of people in relation to the time to appearance of allergic symptoms was as follows:

- within 1 to 15 minutes – 90%
- after 30 minutes – 10%

All affected patients received intramuscular injections of epinephrine (adrenaline) after their symptoms appeared.

Six patients were hospitalized, including five who were admitted to an intensive care unit. Four patients who were in the ICU had to have a flexible plastic tube inserted into their throat so they could breathe.

Complete data were available on nine of the 10 patients. All nine people recovered and were sent home. No one died.

A history of allergic reactions

The CDC researchers found that nine of the 10 patients had a history of allergies or allergic reactions, including to drugs or medical products (such as contrast media used during high-resolution scans) and foods. Five patients had previously experienced anaphylaxis in the past, but none of these episodes was in reaction to a vaccine.

The CDC did not find a clustering of severe allergic reactions in any particular region.

Non-anaphylactic reactions

The CDC also reported that separately there were 43 cases of allergic reactions not involving anaphylaxis after vaccination. These reactions occurred within the first day of vaccination.

Common symptoms were as follows:

- itchy skin
- rash
- itchy sensations in the throat
- sensation of throat closure
- mild respiratory symptoms (the agency did not define these)

Patients with these allergic symptoms were between 22 to 96 years old. About 91% of these reactions were also in women.

The onset of non-anaphylactic reactions from the time of vaccination ranged from less than one minute to 24 hours. The distribution of the onset of these symptoms after vaccination was as follows:

- within 30 minutes – 75%
- after 30 minutes – 25%

According to the CDC, in 60% of cases of non-anaphylactic reactions "there was a past history of allergies or allergic reactions."

The CDC advises that "persons with an immediate allergic reaction to the first dose of an mRNA COVID-19 vaccine should not receive additional doses of either of the mRNA COVID-19 vaccines."

The issue of gender

Previous reports suggest that, in general, more women experience adverse reactions to flu vaccine than men.

In the rollout of the Moderna vaccine, 61% of the people vaccinated were women. It is therefore plausible that part of the reason for the over-representation of women in cases of allergic reaction to this vaccine arose in part because most people who received the vaccine were women.

More research is needed to better understand the gendered distribution of vaccine-associated allergic reactions. The CDC's report should be viewed as preliminary and further monitoring and analysis of side effects will be done as more people get the vaccine.

REFERENCE:

CDC COVID-19 Response Team and the Food and Drug Administration. Allergic reactions including anaphylaxis after receipt of the first dose of Moderna COVID-19 vaccine – United States, December 21, 2020 to January 10, 2021. *Morbidity and Mortality Weekly Report*. 22 January, 2021.

G. Advice from the CDC about anaphylaxis and mRNA COVID-19 vaccines

The Centers for Disease Control and Prevention (CDC) has extensive guidance about the rollout of the COVID vaccine program. A summary of the CDC's advice to vaccination sites is as follows:

- "Ensure that necessary supplies are available to manage anaphylaxis, especially sufficient quantities of epinephrine in pre-filled syringes or auto injectors."
- "Screen potential vaccine recipients to identify persons with contraindications and precautions."
- "Implement post-vaccination observation periods, either 15 or 30 minutes, depending on each patient's previous history of allergic reactions."
- "Ensure that healthcare providers can recognize signs and symptoms of anaphylaxis early."
- "Immediately treat suspected anaphylaxis with intramuscular epinephrine; because of the acute, life-threatening nature of anaphylaxis, there are no contraindications to epinephrine administration. Patients experiencing anaphylaxis should be transported to facilities where they can receive appropriate medical care."
- "All patients should be instructed to seek immediate medical care if they develop signs or symptoms of an allergic reaction after their observation period ends and they have left the vaccination location."
- "Healthcare providers can play an important role in vaccine safety by being vigilant in recognizing and reporting adverse events after immunization."

Resources

Interim Considerations: Preparing for the Potential Management of Anaphylaxis After COVID-19 Vaccination – CDC

Vaccines for COVID-19: Authorized vaccines – Health Canada

REFERENCES:

1. CDC COVID-19 Response Team and the Food and Drug Administration. Allergic reactions including anaphylaxis after receipt of the first dose of Pifzer-BioNTech COVID-19 vaccine – United States, 14-23 December 2020. *Morbidity and Mortality Weekly Report*. 6 January 2021.

2. CDC COVID-19 Response Team and the Food and Drug Administration. Allergic reactions including anaphylaxis after receipt of the first dose of Moderna COVID-19 vaccine – United States, 21 December 2020 to 10 January 2021. *Morbidity and Mortality Weekly Report*. 22 January 2021.

H. The Janssen vaccine for COVID-19: Phase I/II

The vaccines previously reported on in this issue of *TreatmentUpdate* use messenger RNA. However, for its COVID-19 vaccine, the Janssen corporation is using a modified form of a virus called an adenovirus.

About adenoviruses

Adenoviruses are a group of viruses that can cause a range of illness from colds to pink eye to diarrhea to pneumonia.

Adenoviruses as vaccines

For decades scientists have been experimenting with adenoviruses, removing parts of their genetic material that cause disease and replacing them with instructions to make proteins for other viruses. In

this way, the outer layer or form of the adenovirus is used as a carrier for transmitting information to cells. Viruses that are used in this way are called vectors. The adenovirus shell protects the genetic instructions that are the key part of the vaccine.

Modified adenoviruses (with the disease-causing parts removed) are used as vectors because they are very good at both protecting the genetic information they carry and getting this information inside a cell.

Once the modified adenovirus gets its cargo of genetic material inside the cell, the cell begins to produce proteins from another virus chosen by scientists. These proteins are released into circulation, where cells of the immune system encounter them. The cells of the immune system capture the viral proteins and take them to lymph nodes and lymphoid tissues. There, the viral proteins are displayed to many cells of the immune system. One group of immune system cells—B-cells—begins to produce antibodies against the viral proteins. Another groups of cells—T-cells, particularly CD8+ cells—learns to recognize the protein and produces antiviral substances in response. The immune system then creates many copies of these B- and T-cells, and some of them leave lymph nodes and related tissues and enter circulation. When they encounter SARS-CoV-2 in the future, these B- and T-cells can respond with antibodies and antiviral substances and greatly reduce the risk of developing COVID-19.

Adenoviruses have been modified to make vaccines for Ebola virus and also experimental vaccines for HIV and Zika virus.

Adenovirus 26 for COVID-19

The Janssen corporation is using a modified adenovirus called adenovirus 26 into which it has inserted the genetic information to instruct cells to make a protein used by SARS-CoV-2. Antibodies to this protein prevent SARS-CoV-2 from attaching to cells and infecting them.

Phase I/II

The Janssen corporation has released data from a complex phase I/II study of the vaccine that had enrolled about 800 people. In this study, participants received one or two injections of a low-dose or high-dose vaccine or placebo.

Common side effects included the following:

- fever
- fatigue
- headache
- muscle pain
- pain at the injection site

In general, these side effects were mild to moderate, appeared within two days of vaccination and resolved shortly thereafter.

About a month after receiving the first dose of the vaccine, at least 90% of participants had antibodies that attacked SARS-CoV-2. By 57 days after the first dose, this figure had reached 100%. This occurred regardless of the amount of vaccine administered. People who received a second shot of the vaccine had greatly increased antibody levels compared to the time after they had received only one injection.

Scientists found that two weeks after the initial vaccination blood samples from vaccinated people contained T-cells that could recognize SARS-CoV-2.

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3. Custers J, Kim D, Leyssen M, et al. Vaccines based on replication incompetent Ad26 viral vectors: Standardized template with key considerations for a risk/benefit assessment. *Vaccine*. 2021; *in press*.

4. Kremer EJ. Pros and cons of adenovirus-based SARS-CoV-2 vaccines. *Molecular Therapy*. 2020 Nov 4;28(11):2303-2304.

5. Bos R, Rutten L, van der Lubbe JEM, et al. Ad26 vector-based COVID-19 vaccine encoding a prefusion-stabilized SARS-CoV-2 spike immunogen induces potent humoral and cellular immune responses. *NPJ Vaccines*. 2020 Sep 28;5:91.

I. The Janssen vaccine for COVID-19: Interim Phase III results

As this issue of *TreatmentUpdate* went to press, the Janssen corporation released the interim data from its phase III clinical trial.

A total of 44,325 adults were enrolled in Latin America, South Africa and the U.S. Participants were given the vaccine (or placebo) described previously in this issue of *TreatmentUpdate*. The Janssen corporation is using a modified adenovirus called adenovirus 26 into which it has inserted the genetic information to instruct cells to make a protein used by SARS-CoV-2.

Overall, 28 days after vaccination, the vaccine was 66% effective at reducing the risk of developing moderate or severe forms of COVID-19.

No one who received the vaccine died from COVID-19, while five deaths occurred in the placebo group. The efficacy of the vaccine at preventing severe COVID-19 varied from one geographic location to another as follows:

- U.S. – 72% efficacy
- Latin America – 66% efficacy
- South Africa – 57% efficacy

It is possible that the efficacy differed by geography because of the different variants of the virus that are predominant in different places.

Further details may emerge in the future as the full results from phase III are released.

REFERENCE:

National Institutes of Health. Janssen Investigational COVID-19 vaccine: Interim analysis of phase 3 clinical data released. *Press release*. 29 January 2019.

Disclaimer

Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.

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For more than 20 years, CATIE has been there to provide information that enables people to make informed choices about their health and enhances the ability of healthcare providers and other frontline organizations to respond to their clients' needs.

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