COVID-19: YOUR QUESTIONS ANSWERED

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The American Association of Immunologists (AAI) is pleased to present this short primer on coronavirus disease 2019 (COVID-19). Here, we focus on four key areas:

Vaccine Development **Therapies** **Symptoms** **Prevention**

Because the science regarding coronavirus disease 2019 (COVID-19) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes the disease, is developing, our understanding of the disease is rapidly growing. In response, public health advice is naturally and appropriately evolving. We urge readers to consult the websites of the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and AAI regularly for new, reliable information.

Vaccine Development

The COVID-19 pandemic, caused by SARS-CoV-2 infection, has spread to 223 countries[1], areas or territories with more than 115 million laboratory-confirmed cases and more than 2.5 million deaths.[2] Vaccines are urgently needed to control the pandemic and to help facilitate the return to pre-pandemic normalcy. According to the World Health Organization (WHO), more than seven different vaccines across three platforms are being used in countries around the world[3] and 258 COVID-19 vaccine candidates are in development (76 in clinical evaluation, 16 in phase III or phase IV clinical trials).[4]

In the U.S., three vaccines have already received an Emergency Use Authorization (EUA) from the U.S. Food and Drug Administration (FDA). These vaccines induce immune responses against the SARS-CoV-2 spike protein, a protein needed for the virus to infect cells and therefore a critical target for protective immune responses. The authorized vaccines are:

1. Pfizer-BioNTech COVID-19 vaccine (mRNA vaccine)
2. Moderna COVID-19 vaccine (mRNA vaccine)
3. Johnson & Johnson (Janssen) COVID-19 vaccine (non-replicating viral vector)

The Pfizer-BioNTech and Moderna vaccines rely on mRNA technology. The mRNA vaccine platform enables human cells to produce a harmless version of the SARS-CoV-2 spike protein, thus inducing a protective immune response to SARS-CoV-2. No live virus is involved and recipients cannot get COVID-19 from the vaccine. Both require two shots spaced three weeks (Pfizer) or four weeks (Moderna) apart.[5]

Johnson & Johnson's single-dose vaccine uses adenovirus-vectored technology. This technology uses a harmless, non-replicating version of a common cold virus that enters a cell, which then produces a harmless protein, the SARS-CoV-2 spike protein, and promotes the development of protective antibodies.[6] Recipients cannot get COVID-19 from this altered virus vaccine.

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[1] https://covid19.who.int/table
[2] World Health Organization (WHO) (https://covid19.who.int/)
[3] https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines (as of February 18, 2021)
[4] https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines
[5] https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/Pfizer-BioNTech.html
https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/Moderna.html
[6] https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/janssen.html

Johnson & Johnson's vaccine is the easiest to store so far—it can be stored for up to six months in a normal refrigerator (between 36°F and 46°F). mRNA technology as used in the Moderna and Pfizer vaccines is more fragile compared to adenovirus-vectored vaccine and requires lower temperatures to remain effective. For long term storage, both the Moderna and Pfizer vaccines need to be kept at -4°F. Continuous testing is being done to understand if these vaccines can be stored at less restrictive temperatures, which would make them more accessible. Moderna has recently announced that its vaccine can be stored at normal refrigerator temperatures for up to 30 days.[7]

The Pfizer and Moderna vaccines are reported to be about 95% effective in clinical trials against COVID-19 about two weeks after the second shot. The Johnson & Johnson vaccine has reported an overall efficacy in the U.S. of 72% against any degree of COVID-19 and 85% efficacy against severe/critical COVID-19 by 28 days after vaccination. Importantly, in clinical trials, all three vaccines showed 100% protection against hospitalization and death against the wild type SARS-CoV-2 most common in the U.S. The Johnson & Johnson vaccine has also been found to be effective protection against several variants now circulating in the U.S.[8] While all vaccine manufacturers are testing efficacy of their vaccines against new variants, Pfizer and Moderna have not reported efficacy yet. However, it has been demonstrated that serum from Pfizer or Moderna vaccinees can neutralize the variant viruses in lab experiments, suggesting they will also be reasonably protective against infection.

Side effects for all three vaccines are similar. Some recipients have experienced transient injection site pain and/or flu-like symptoms, including fever, chills, fatigue, headaches, and muscle pain. These side effects are a normal response of the immune system being primed to respond to an actual infection.

Rigorous testing and evaluation of a vaccine candidate are required before it is authorized or licensed by the FDA and recommended for use by the Centers for Disease Control and Prevention (CDC). AAI has described these steps in a short primer accessible here: https://www.aai.org/AAISite/media/Public_Affairs/AAI_primer_on_clinical_trial_and_vaccine_development_process_November_2020.pdf

All three vaccines authorized by the FDA are safe and effective. AAI encourages all eligible individuals to receive a COVID-19 vaccine when it is their turn to do so.

[7] https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-longer-shelf-life-its-covid-19-vaccine#:~:text=Using%20standard%20freezer%20temperatures%20of,(%2D4%C2%B0F)%20worldwide

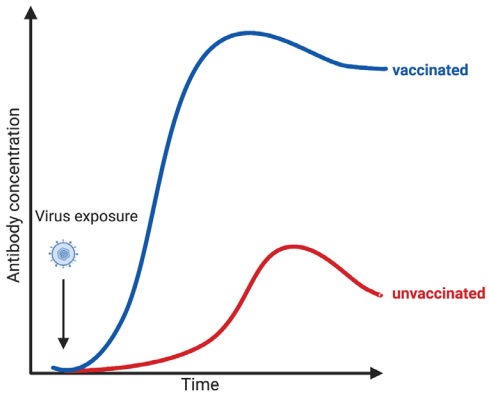
[8] https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/janssen-covid-19-vaccine-frequently-asked-questions

How vaccines work

As pictured to the right, a vaccine prepares the immune system so that it recognizes the virus and knows to combat it. When a person gets exposed to SARS-CoV-2 after vaccination, the immune system will be ready to fight and can more easily block or control the infection, limiting symptoms and transmission. This is why a vaccinated person will have fewer symptoms and may not even get infected as compared to an unvaccinated person.

Because the goal of a vaccine is to induce a rapid and robust immune response to the virus antigen, the vaccine recipient is likely to experience side effects, which can include injection site pain, fatigue, fever, chills, and/or muscle aches. These side effects do not mean that the person is "sick;" they simply mean that the person is having a strong immune response to the vaccine and are a good sign that the vaccine is working!

Induction of immune responses after virus exposure or vaccination:



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Types of immune responses initiated by vaccines

Antibodies vs T-cell immunity: To develop a vaccine against a newly emerging virus, it is important to understand what parts of the anti-viral immune response are necessary for protection. The adaptive immune response has two arms. B cells produce antibodies that can block virus spreading between cells. This is known as humoral immunity. T cells can seek out and kill infected cells, also preventing viral spread. This is known as cellular immunity. Although much remains to be determined regarding immune protection for SARS-CoV-2 infection, emerging data have demonstrated the importance of both humoral and cellular immunity in protection. Research must continue to investigate the details of what immune responses are most effective at controlling infection. If we can determine what a protective response looks like, then we can tailor our second-generation COVID-19 vaccines and/or identify new therapies to better protect the community.

Dosing differences based on individual immune status: Pediatric, geriatric, and immunocompromised patients all present different challenges to vaccination. What is best for one population might not be best for another. Studies are ongoing to determine the ideal combinations and best way to vaccinate every population. Current authorized vaccines have good efficacy in geriatric patients. Pediatric trials are ongoing.

Variant antigen boosters: This advance would enable immune protection from the emergent variant viruses. The rapid development and deployment of these vaccines would ensure the control of the existing variant strains and reduce the chance that "new strains" will prolong the pandemic. Makers of authorized vaccines are already working on developing such boosters and are testing the ability of current vaccines to protect against variants. Basic research is needed to improve pre-clinical models to rapidly test infectivity of new variants, determine protection by current vaccines, and identify new vaccine targets.

Therapies

Over the last year, several therapeutics have been identified for the different stages of COVID-19. Research is well underway, but additional research is needed to understand how to elicit appropriate immune responses to SARS-CoV-2, stop viral replication, and limit disease symptoms. In response to a virus, the immune system needs to activate strongly enough to prevent or stop the infection. This is referred to as inflammation. However, if the immune response is too strong, and there is too much inflammation, tissue damage can occur. A too strong immune response with too much inflammation is associated with the morbidity and mortality of COVID-19. Much work needs to be done to understand how to achieve the correct immune balance in order to better prevent or treat disease. Below, we summarize the limited number of standard of care or authorized effective treatments and the stage of infection or disease when they are most likely to provide benefits.

Presymptomatic infection or prophylaxis after exposure

- Monoclonal antibodies – purified antibody preparations that bind the spike protein of SARS-CoV-2 and prevent entrance into cells. Requires infusion on an outpatient basis.
    - Bamlanivimab (Eli Lilly) *(Originally granted EUA by the FDA on November 9, 2020)*[9]
    - Casirivimab and imdevimab cocktail (Regeneron) *(Originally granted EUA by FDA on November 21, 2020)*[10]

Mildly symptomatic COVID-19

- Analgesics (over-the-counter and prescription acetaminophen) and nonsteroidal anti-inflammatory drugs (NSAIDs) (over-the-counter and prescription ibuprofen) – reduce cold or flu-like symptoms.
- Monoclonal antibody therapy

Symptomatic COVID requiring medical care

- Remdesivir – This intravenously-delivered drug, originally developed to treat hepatitis and respiratory syncytial virus infection, reduces viral replication by binding to the viral machinery needed for replication. *(Originally granted EUA by the FDA on October 22, 2020)*[11]
- Baricitinib – This orally-delivered arthritis drug inhibits a signaling pathway (JAK) that leads to excessive inflammation and can cause tissue damage. *(Originally granted EUA by FDA on November 19, 2020, in combination with remdesivir)*[12]
- Anticoagulants – This treatment minimizes the likelihood of blood clots, which have been associated with severe COVID-19. *(Originally granted EUA by FDA on August 13, 2020)*[13]
- Dexamethasone or steroid therapy[14] – This orally-delivered drug limits the excessive inflammation that is associated with many of the symptoms of severe COVID-19.
- Tociluzimab[15] – This antibody therapy, approved for arthritis, blocks a factor (IL-6) which amplifies immune responses that can lead to excessive inflammation and can cause tissue damage.

[9,10] https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs

[11, 12, 13] https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs

[14] https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/

[15] https://www.covid19treatmentguidelines.nih.gov/statement-on-tocilizumab/

Late COVID

- Antibiotics and antifungals to treat COVID-19-related secondary infections (e.g., pneumonia)

Post COVID syndrome/"long tail" COVID (ongoing COVID-19 symptoms after primary COVID-19 resolution)

- Analgesics and NSAIDs – reduce ongoing symptoms and inflammation
- Nasal steroids – reduce local inflammation, may help relieve loss of sense of smell

Symptoms

COVID-19 Symptoms in Different Age Groups

- The severity of COVID-19 symptoms increases with age, with the most severe disease commonly observed in the elderly. Disease in children usually results in asymptomatic or mild disease symptoms, thus frequently going unnoticed; however, it is important to note that severe disease can occur in all age groups.[16]
- Common symptoms by age group
  - Children and Youth (<18 years):[17] Most are asymptomatic or only show mild symptoms, however a subset develop a rare but serious disease called multisystem inflammatory syndrome (MIS-C).
    - Cold-like symptoms (fever, cough, shortness of breath)
    - Rash (indicates more severe disease)
  - Adults (18 – 60 years): Mild to moderate symptoms
    - Cold-like symptoms (fever, cough, shortness of breath, aches)
    - Change in taste or smell
    - Vomiting and diarrhea
    - Inability to sleep
  - Elderly (>60 years): moderate to severe symptoms
    - Cold-like symptoms (fever, cough, shortness of breath, aches, sore throat)
    - Fatigue
    - Trouble breathing or shortness of breath
    - Loss of appetite
    - Vomiting and diarrhea

[16] Gandhi RT, Lynch JB, del Rio C. Mild or Moderate Covid-19. New England Journal of Medicine. 2020;383(18):1757-66; Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical Characteristics of Covid-19 in New York City. New England Journal of Medicine. 2020;382(24):2372-4.

[17] Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 Infection in Children. The New England Journal of Medicine. 2020;382(17):1663-5.

Transmission of COVID-19[18,19]

The virus SARS-CoV-2 is transmitted within respiratory droplets that are produced when a person breathes, sings, coughs, or sneezes. Transmission from one host to another is via two main mechanisms:

1) Droplet

- Airborne: Larger respiratory droplets exhaled by the infected host make contact with another person, who is usually within six feet of the host
- Contact: Direct contact with a droplet-contaminated surface

2) Aerosol

- Small respiratory particles containing the virus stay suspended in the air (for minutes to hours) and infect another person without close contact with the infected host

Airborne droplet transmission is the major route of infection, though there is some evidence to support a smaller number of cases resulting from aerosol transmission. While restriction of aerosol transmission requires the use of N95 masks, the risk of droplet-based transmission can fortunately be mitigated through use of fabric/surgical masks, social distancing, proper hand washing, and proper ventilation.

COVID-19 Long-Term Effects[20]

- COVID-19 can have long-term effects on the brain, heart, and lung following recovery.
  - Brain: Inflammation of the brain tissue (encephalitis) and lack of oxygen results in cognitive impairment (changes in memory and attention), mood swings, mental health disorders (anxiety, depression, post-traumatic stress disorder), sleep problems, seizures, and increased risk of Alzheimer's and Parkinson's. Further, COVID-19 increases the risk of blood clots and the weakening of blood vessels, making it a risk factor for stroke.
  - Heart: Inflammation of the heart muscle (myocarditis) and/or the covering of the heart (pericarditis) results in damage to heart tissue and an increased risk of heart attack and heart failure.
  - Lung: Inflammation of the lungs results in lung tissue damage, impaired pulmonary function, and an increased risk of pulmonary embolism (blood clots).
- Long-term effects are more likely in susceptible populations, such as the elderly and those with co-morbidities (e.g., cardiovascular disease, diabetes, and mental health illness)

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[18] CDC. How COVID-19 Spreads: CDC; 2021 [updated 1/7/2021. Available from: https://www.cdc.gov/coronavirus/2019-ncov/transmission/index.html.

[19] WHO. Coronavirus disease (COVID-19): How is it transmitted? World Health Organization; 2020 [Available from: https://www.who.int/news-room/q-a-detail/coronavirus-disease-covid-19-how-is-it-transmitted.

[20] Zhou H, Lu S, Chen J, Wei N, Wang D, Lyu H, et al. The landscape of cognitive function in recovered COVID-19 patients. Journal of Psychiatric Research. 2020;129:98-102; Heneka MT, Golenbock D, Latz E, Morgan D, Brown R. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. Alzheimer's Research & Therapy. 2020;12(1):69; The hidden long-term cognitive effects of COVID-19. Harvard Health Publishing. 2020 10/08/2020; Staff MC. COVID-19 (coronavirus): Long-term effects: Mayo Foundation for Medical Education and Research; 2020 [updated 11/17/2020. Available from: https://www.mayoclinic.org/diseases-conditions/coronavirus/in-depth/coronavirus-long-term-effects/art-20490351#:~:text=COVID%2D19%20symptoms%20can,within%20a%20few%20weeks.

Prevention

Immunization to achieve herd immunity (the threshold of immunization required to protect unimmunized individuals from contracting a disease) is the only means of reliable, long term control of COVID-19. In the meantime, there are several mitigation strategies that can limit or prevent further spread of SARS-CoV-2. Below we describe the two major routes of transmission and the most effective methods to prevent virus spread.

1. **Airborne droplet transmission** is infection spread through exposure to virus-containing larger respiratory droplets exhaled by an infectious person. Transmission is most likely to occur when someone is close to the infectious person, generally within about six feet.

   Prevention:

   a. Early/separate hours at businesses for at-risk populations (such as seniors).

   b. Wear a face mask around people you do not live with (immediate household).

   c. Social distancing: Avoid close contact (within six feet) with people outside of your immediate household. Six feet of distancing is the minimum.[21]

   d. Limit unmasked interactions with people outside of household and follow all social distancing and CDC recommendations for face mask use.

   e. Avoid being exposed to someone with COVID-19 for any period of time; if you are taking care of a sick individual, follow your doctors' orders regarding exposure to the person and follow all masking and social distancing recommendations.

2. **Contact droplet transmission** is infection spread through direct contact with an article or surface that has become contaminated.

   Prevention:

   a. Good personal hygiene: Wash hands with soap and water for 20 seconds or use a hand sanitizer that contains at least 60% alcohol.

   b. Limit unmasked physical contact with people outside your immediate household.

   c. Clean and disinfect frequently touched objects and surfaces.

[21] https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html