

Lauren Westafer, DO, MPH, MS
Disclosures: None
@LWestafer
FOAMcast.org

The FDA has [granted the Pfizer/BioNTech Vaccine \(BNT162b2\) emergency use authorization](#) (EUA) for individuals 12 years of age or older. Details of the Pfizer/BioNTech vaccine can be found in the [EUA review by the FDA](#), and from the [full text in the New England Journal of Medicine](#). The Moderna vaccine details are [here](#), and it was granted EUA by the FDA for adults (12/18), with peer review publication in the [NEJM here](#). Information on the viral vector vaccines (AstraZeneca, Johnson & Johnson) and recombinant protein vaccine (Novavax) can be found at the bottom of the document, the J&J vaccine received FDA EUA 2/27/21.

mRNA vaccine overview

Both the Moderna and Pfizer/BioNTech vaccines utilize messenger RNA (mRNA). The vaccines are administered in 2 doses, a few weeks apart. The vaccines contain a synthetic (produced in a lab) mRNA that is the template for the spike protein from SARS-CoV-2. This means that it does not contain the whole virus.

When the mRNA, which is packed in a lipid layer, enters cells in your body, the cells make the Spike protein from SARS-CoV-2 (and only spike protein). The body's immune system recognizes this protein as foreign and mounts an immune response, including the production of antibodies. *Essentially, the mRNA is a recipe card that goes in your body and makes that one recipe for a few hours.* mRNA breaks down quickly, so it is highly unlikely that it would leave, intact, the cells of your arm where you get in the injection and enter the bloodstream.

mRNA does not alter your DNA. **The mechanism also means there is no risk of people getting the virus from the immunization** (unlike live attenuated viruses such as measles/mumps/rubella and chickenpox vaccines where the risk is low but possible).

Isn't this new technology?

Yes and no. mRNA is not new, our bodies are full of it. Additionally, *this is how viruses replicate in the absence of a vaccine* - they hijack your cellular structures and have your cells make their proteins. So, if you were to be infected with SARS-CoV-2, the virus would do a similar thing; however, instead of producing only the Spike protein, it would produce the whole virus, which would replicate and potentially cause illness.

Study details

Pfizer/BioNTech BNT162b	Moderna mRNA-1273
Randomized to vaccine versus saltwater placebo	
2 doses, 21 days apart	2 doses, 28 days apart
- Most patients were white (82.9%) - Black 9.3%, Latinx 28% - Over age 55 42.2% - Obese 35.1%, chronic lung diseases 7.8%, hypertension 25%. - Pregnant patients were excluded	- Female 47.4% - Median age 53 years (25.3% over age 65) 79.4% were white, 9.7% Black/African American, 20% were Hispanic/Latinx 22.3% had at least 1 high risk condition (Diabetes/liver disease/HIV/significant cardiac disease/chronic lung disease)

How well do the vaccines work?

Pfizer/BioNTech BNT162b		Moderna mRNA-1273	
<u>Both are very effective in preventing COVID-19, particularly after the second dose.</u>			
At 7 days after the second dose in patients who tested negative previously for the virus, there were 8 cases of COVID-19 in the vaccine group and 162 in the placebo group. <u>This resulted in an efficacy of 95% (i.e. prevented 95% of infections)</u>		- Overall, at 14 days after the second dose in patients who tested negative previously for the virus, there were 11 cases of COVID-19 in the vaccine group and 185 in the placebo group. <u>This resulted in an efficacy of 94.1% (i.e. prevented 94.1% of infections).</u> - There were 18 cases not included because they had not yet been finalized. 1 case of COVID-19 in the vaccine arm, 17 in the placebo arm (resulting in similar efficacy)	
<u>The vaccines work better after the second dose, but even a single dose seems to help.</u>			
- Overall efficacy after the first dose was 82%. There were 50 cases in the vaccine group and 275 in the placebo group. - The majority of the cases in the vaccine group (78%) occurred prior to the second dose and it appeared that protection increased 14 days after the first dose		In those receiving only 1 dose, there were 7/996 cases in the vaccine group and 39/1079 in the placebo group (efficacy 80.2% [95% CI 55.2-92.5%]). There were only 2 cases >14 days after dose 1	
<u>In both trials, vaccine efficacy did not appear different based on sex, race, ethnicity, or age</u>			
However, groups of some racial/ethnic minorities are low, so further study should be done to ensure similar efficacy stands.			

What are the side effects? Adverse events were almost all related to reactogenicity, this is the body's inflammatory response to the vaccine, not a sign of infection. It is important to note that the incidence of many of these adverse events in the saline placebo arm is actually quite high, demonstrating the powerful effect of placebo (or baseline frequency).

	<u>Pfizer/BioNTech</u> n=43,252		<u>Moderna</u> n=30,338		<u>Placebo</u> (both trials)
	18-55 years	>55 years	18-64 years	≥65 years	
Injection site pain	77.8%	66.1%	89.9%	83.2%	~11.7-20%
Fatigue	59.4%	50.5%	67.6%	58.3%	~20-23%
Headache	51.7%	39%	62.8%	46.2%	~24-36%
Muscle aches	37.3%	28.7%	61.6%	47.1%	~8-12%
Joint Pain	21.9%	18.9%	45.5%	35%	~5-11%
Chills	35.1%	22.7%	48.6%	30.9%	~6%
Fever	15.8%	10.9%	17.4%	10%	0.5-1.4%
Lymph node swelling	0.3%		16.2%	8.5%	<1-1.4%
Nausea or vomiting	1.9%	0.7%	21.4%	11.8%	~6.4%

<u>Pfizer/BioNTech</u> n=43,252	<u>Moderna</u> n=30,338
Hypersensitivity reactions: Vaccine 0.63%, Placebo 0.51%	Hypersensitivity reactions: Vaccine 1.5% Placebo 1.1%
Serious adverse events were very rare and about what you would expect to see in the general population regardless of a pharmaceutical trial	
- Vaccine 0.6% (appendicitis 0.04%, myocardial infarction 0.02%, CVA 0.02%) 4 events possibly related to vaccine: shoulder injury (n=1), lymphadenopathy n=1), paroxysmal ventricular arrhythmia (n=1), right leg paresthesia (n=1)) - Placebo 0.5% (pneumonia 0.03%, atrial fibrillation 0.02%)	- Vaccine 1%, Placebo 1% - Bell's Palsy Vaccine 3, Placebo 1 3 likely related serious adverse events (facial swelling in 2 with history of cosmetic injections, 1 case of intractable nausea)
Subsequent monitoring has found a signal for increased rates of myocarditis/pericarditis, particularly in young males (<30) and after the second dose. <u>This podcast goes more in depth</u>	
Deaths were very rare and unrelated to the vaccine	
- Vaccine n=2 [1 of cardiac arrest 62 days after 2nd vaccination, 1 of heart disease] - Placebo n=4 [1 of hemorrhagic stroke, 2 of unknown cause, 1 of heart attack]	- Vaccine n=6 [2 cardiac deaths >75 year olds with cardiac disease; 1 head trauma, 1 70 y/o with cardiac disease 57 days after dose 2; 1 suicide 21 days after dose 1, 1 multiorgan failure after obstructive nephrolithiasis 40 days after dose 2] - Placebo n=7 [3 heart attacks, 1 SIRS in the setting of malignancy, 1 intra-abdominal perforation, 1 unknown cause, 1 of COVID-19]

What about the allergic reactions I heard about? Anaphylaxis has been reported following vaccine administration - but rarely.

<u>Pfizer</u>	<u>Moderna</u>
Between 12/14/20-12/23/20 almost <u>1.9 million Pfizer vaccines</u> were administered. <u>21 cases (0.001%) reported an event consistent with anaphylaxis</u> (~11.1 cases per 1 million doses).	Between 12/19/20-1/10/21 over 4 million first doses of Moderna were administered. <u>10 cases (0.00025%) reported an event consistent with anaphylaxis</u> (~2.5 cases per 1 million doses)
Most (81% Pfizer, 90% Moderna) occurred in individuals with documented history of allergies	
Most occur shortly after immunization (median time to symptoms was 13 minutes in Pfizer, 7.5 minutes in Moderna), although the range extended to 150 minutes with Pfizer and 45 minutes with Moderna	
No deaths in either arm.	

Another 83 individuals had non-anaphylaxis allergic reactions (less severe), meaning that overall, 0.005% of people reported any kind of allergic reaction.	Another 43 individuals had non-anaphylaxis allergic reactions (less severe), meaning that overall, 0.001% of people reported any kind of allergic reaction
---	--

This is why the vaccine is administered in a monitored setting, individuals are watched for 15-30 minutes, and people should be instructed to seek medical attention if they develop signs of an allergic reaction.

- The [American College of Allergy, Asthma, and Immunology](#) has released a statement on the concern for allergic reactions.
 - Individuals with common allergies to medications, foods, inhalants, insects, and latex are no more likely than the general public to have an allergic reaction to the Pfizer-BioNTech COVID-19 vaccine
 - The Pfizer-BioNTech COVID-19 vaccine should not be administered to individuals with a known history of a severe allergic reaction to polyethylene glycol as it is a component of this vaccine that is known to cause anaphylaxis
 - It can be given to immunocompromised individuals as it is not a live virus

But we don't know that it prevents the spread of SARS-CoV-2.

This is true. It would also be very difficult to measure on a large scale. You would have to have people tested for SARS-CoV-2 every few days for months and months. It's also not ethical (at least currently in the US) to intentionally infect people with the virus.

- However, given the incredible reduction in COVID-19 cases, it is unlikely that there would be a big effect on COVID-19 cases but not on asymptomatic cases.
- One study ([Corbett et al NEJM 2020](#)) looked at this in monkeys who were given the Moderna vaccine or placebo and then had the virus given in their nose and windpipe to infect their lungs). With the 100-mcg dose of the vaccine, none who received that dose had detectable virus RNA on day 2.
- In the Moderna trial, participants were swabbed on day 29 (second dose). This revealed an additional 15 cases in the vaccine arm and 39 in the placebo arm (if these were included in the efficacy analysis, efficacy would have been 90%.
- These data show some support to the idea that the vaccine would help reduce spread.
- Further, while asymptomatic spread is important as that person may spread to someone with risk factors who could get very sick - if those people are immunized (and thus unlikely to get sick - and all the COVID-19 vaccines appear to significantly prevent severe COVID), then asymptomatic spread essentially becomes unimportant. However, this would only be the case with high levels of herd immunity.

What about pregnancy and breastfeeding? Overview is [here](#)

Although the trials excluded pregnant individuals, subsequent data in thousands of pregnant individuals have shown safety, without any signal of increase in birth defects or pregnancy loss. At Baystate Health, a multidisciplinary working group has created a [decision aid](#) (English/Spanish/Russian) to help pregnant people make an informed choice with their healthcare providers. The American College of Obstetrics and Gynecology (ACOG) released an updated statement on July 30, 2021 that recommends that pregnant and lactating individuals be vaccinated against COVID-19. Additionally, the document reinforces that the claims linking COVID-19 vaccines to infertility are unfounded and have no scientific evidence supporting them, recommending vaccination for all eligible people who may consider future pregnancy. Further, although women < 50 years old may receive any COVID-19 vaccine, there is an increased but very rare risk of thrombosis with thrombocytopenia syndrome after the Janssen/Johnson & Johnson vaccine and they may opt for an mRNA vaccine instead (Pfizer or Moderna). The Society for Maternal-Fetal Medicine (SMFM) supports these statements.

Pfizer/BioNTech	Moderna
• So far >100,000 pregnant people have received a COVID-19 vaccine and reported their pregnancy to the CDC vsafe program • 827 pregnancies have been reported as completed, most of which (86.1%) resulted in a live birth. There was no signal of increased risk of pregnancy loss (miscarriage or stillbirth), congenital abnormalities (birth defects), or pre-term birth • 12.6% were early pregnancy losses, which is the rate we would expect in those who did not receive a vaccine (10-20% of pregnancies result in pregnancy loss under normal conditions)	
Follow up that we have now is too short to conclude anything definitive about pregnancy outcomes.	
	They did a study of the vaccine in rats, which is standard practice for reproductive toxicity. The FDA review of the study concluded that vaccine given prior to mating and during gestation periods at the standard 100 µg dose <i>“did not have any adverse effects on female reproduction, fetal/embryonal development, or postnatal developmental except for skeletal variations which are common and typically resolve postnatally without intervention.”</i>

- There's no specific mechanistic cause for concern in pregnancy or lactation, particularly as the mRNA vaccine mimics what happens in any other viral/cold type of infection with the exception that you don't get infected with the virus (or sick with COVID-19). We do know that most vaccines (except live vaccines, which these are not) are safe in pregnancy and many are routinely given in essentially all pregnancies (DTaP/influenza). Vaccines work in the muscle tissue of the arm to generate an immune system response - the components do not go into the bloodstream and thus, don't cross the placenta. However, antibodies have been found in umbilical cord blood after birth in a patient who had received 1 dose of the Moderna vaccine, which may aid in placental protection ([Moderna case report](#))
- The Society for Maternal and Fetal Medicine recommends that the theoretical risk to the fetus is very small and that pregnant and breastfeeding individuals have access to the vaccine and make decisions based on their individual risks and with their healthcare provider (*for more info, check out a podcast [here](#), [Infant risk statement](#)*)
- **Regarding breastfeeding, the vaccine contains a lipid coated mRNA. Because it is so quickly broken down by the body, it is unlikely to leave the cells of the arm, let alone make it into the bloodstream. Even if those things happened, it is highly unlikely it would make it into the milk. Even if it did make it into the milk, the baby would certainly just digest it like any other protein. Consensus is, it is nearly impossible for the vaccine to hurt a breastfed baby; however, it is possible it could help protect them.**

What about children?

The Pfizer vaccine is currently approved for individuals ≥ 12 years old. Current studies are underway for younger children.

How long does protection last?

We don't know yet, since our experience with the virus is so new (so patients haven't been followed long-term). [Doria-Rose et al](#) measured antibody activity against SARS-CoV-2 among 33 healthy adults 180 days after their second dose of the Moderna mRNA-1273 COVID-19 vaccine (209 days or ~7 months after first shot). Overall, antibody response declined somewhat over time but most participants had sustained virus neutralization at 7 months. The long-term durability of the immune response (how long it

lasts) is still being studied. That means we don't yet know if you need a booster shot at some point. We do know that the immune response to the vaccine is not merely limited to antibody production, so simply measuring antibodies does not completely reflect immunity.

Wasn't the process rushed?

Yes, these vaccines were produced very quickly. However, both mRNA vaccines, as well as the AstraZeneca vaccine have gone through Phase I/II/III hurdles - these are the routine steps where they test vaccines in monkeys and in healthy humans to ascertain basic safety, dose, and measure the immune response. No steps were skipped by these vaccine candidates. Most vaccines take quite some time to go through these hurdles - the speed at which the process has played out is likely a result of:

- the incentive - pressure from governments as well as a financial incentive
- the number of cases - unlike a rare disease, COVID-19 has spread uncontrolled in the US and other nations. This means that efficacy is a bit easy to measure (and may have made recruitment easier as well)
- Coordination - months before vaccines were ready, states and hospital systems were coming up with plans for vaccine rollout and coordination of administration.

Further, the sheer size of these studies are enormous. The individual trials each have more patients than all the trials that led to the HPV vaccine's approval.

What if I've had COVID previously?

The [Advisory Committee on Immunization Practices \(ACIP\)](#) states that the studies found that the vaccines are safe in people with a history of prior infection with the virus. Because reinfection is very uncommon in the first 90 days after infection, they recommend waiting until 90 days later to receive the vaccine (but it is not contraindicated to get the vaccine earlier). They recommend against using antibodies (or viral testing) to decide whether or not to get the vaccine.

What if I've previously had Guillain-Barre Syndrome (GBS) or Bell's Palsy?

Yes, you can get the mRNA vaccines according to the [CDC and ACIP](#). These studies of >70,000 individuals found no cases of GBS yet and the incidence of Bell's Palsy was essentially the expected background rate (i.e. the number that typically occurs in the population).

Can I donate blood after receiving a COVID-19 vaccine?

Yes, according to the American Red Cross and the [AABB](#). There is no wait time after the mRNA vaccines (Pfizer/Moderna) but after other types of vaccines, a 2 week wait period may be required. At this time, you are not allowed to donate plasma for the purposes of convalescent plasma after the vaccine.

Will it work on the new variants?

- It depends on the variant. The vaccines appear less effective at preventing asymptomatic and mild infections due to the delta variant but appears to remain effective at preventing severe disease and death (which is what is important).

Bottom Line

These vaccines appear effective in preventing the development of COVID-19, particularly after the second dose. People should expect to feel tired, possibly get fevers (although not typically high fevers), and have muscle aches after the vaccine, especially the second dose. However, the severe safety profile appears quite good. We don't have long-term follow up but mechanistically, there isn't a significant concern - just general lack of experience and the unknown. Individuals who are pregnant should be offered the vaccine.

Viral Vector Vaccines

(AstraZeneca and Johnson & Johnson) J&J is currently going before the FDA, [briefing document here](#)

How do viral vector vaccines work?

These vaccines have been referred to as a “Trojan Horse.” These vaccines use a virus that cannot replicate in human cells that have been modified to have a piece of the SARS-CoV-2 spike protein (the portion of the virus that creates an immune response). The vaccines have been used previously (Ebola, trialed in Zikar). The AstraZeneca vaccine uses a non-replicating chimpanzee adenovirus (common cold) and the Johnson & Johnson (J&J) vaccine uses a human common cold virus (adenovirus 26).

Study detail

AstraZeneca	Johnson & Johnson vaccine
Results are from combined trials of 11,636 people. Unlike the Pfizer, Moderna, and J&J studies, the control group in these studies received an active vaccine - a meningococcal vaccine - for one of the doses, and saline for the other. • 2 doses	39,321 participants randomized to single dose COVID-19 vaccine or placebo at the time of the FDA report.

How well do these vaccines work?

AstraZeneca	Johnson & Johnson vaccine (prelim data from press release)
Overall, 70.4% effective in preventing symptomatic COVID-19, which is less than the mRNA vaccines but still decent (particularly given advantages of storage) • Low-dose / standard dose group efficacy was 90% • Standard dose / standard dose group efficacy was 62.1%	Overall, 66.9% effective in preventing moderate to severe COVID-19 28 days after vaccination. • 72% effective in the US • 66% effective in Latin America • 57% in South Africa Efficacy was similar 14 days after vaccination
	Efficacy in preventing severe/critical COVID 85.4%
	Efficacy in preventing covid-19 related hospitalizations: 93.1% at 14 days after vaccination and 100% 28 days after vaccination.

Why might these vaccines not be as effective (at least in all populations)?

One issue with viral vector vaccines is that it is possible that some people have immunity to the vector used. In these cases, the body may mount an immune response to the vector (the adenovirus, for example) rather than the SARS-CoV-2 spike protein. In prior studies, very few people have antibodies to adenovirus 26 (J&J vaccine)

What are the side effects?

	<u>AstraZeneca</u>	Control (meningococcal)	Johnson & Johnson	Placebo
--	------------------------------------	------------------------------------	------------------------------	----------------

		<i>l vaccine)</i>		
Injection site pain	75.3%	54.2%	48.6%	16.7%
Fatigue	62.3%	48.0%	38.2%	21.5%
Headache	57.5%	~44%	28.9%	23.7%
Muscle aches	48.6%	~24%	33.2%	12.7%
Nausea	21.9%	~12.5%	14.2%	9.7%
Fever	9.2%	0.5%	9%	0.6%
Serious adverse events				
Reports of rare, but serious blood clots (cerebral vein thrombosis [CVT]) accompanied by low platelets (termed vaccine-induced thrombotic thrombocytopenia) have been reported with both the AstraZeneca and Johnson & Johnson vaccines. - These events are <i>very very</i> rare. For example, 8 cases of suspected or confirmed VITT have been reported in the >6.8 million doses of Johnson & Johnson vaccine in the United States (~1 in a million doses). - Young adults (18-60) and women seem to be the most vulnerable				
<i>AstraZeneca</i>			<i>Johnson & Johnson</i>	
- Possibly related serious adverse event: One case of transverse myelitis in the vaccine group and one case of fever >40C who recovered and did not require hospitalization - There were 2 cases of transverse myelitis that an independent committee believe unrelated to vaccination (including one in the control group)			Guillain-Barre: 1 unlikely related case (day 16) Pericarditis: 1 possibly related Hypersensitivity reaction: 1 likely related Thrombo-embolic events (vaccine 0.06% vs placebo 0.05%) Most considered unrelated by study investigators. 2 related deep vein thrombosis (1 vaccine, 1 placebo). FDA reported possibly related: 1 transverse sinus thrombosis, 1 PE, 2 DVTs, and 1 episode of hemiparesis Angioedema: vaccine 0.2% vs placebo 0.12% Bell's Palsy: 2 in each group	
Deaths				
<i>AstraZeneca</i>			<i>Johnson & Johnson</i>	
4 non-COVID deaths, all unrelated to the vaccine (3 in the control group, 1 in the vaccine group)			25 deaths (5 vaccine, 20 placebo - including 7 due to COVID-19), all unrelated to study product	

Will these vaccines work on the new variants?

The J&J vaccine performed pretty well in the the overall population, which included several worrisome variants (nearly the entire South Africa population sequenced had the B.1.351 variant). So, while efficacy was lower in that group, it was still very good at preventing serious/critical COVID-19.

<i>AstraZeneca</i>	<i>Johnson & Johnson</i> 94.5% of SARS-CoV-2 samples from South Africa were due to the B.1.351 ('South Africa') variant.
---------------------------	--

	In Brazil, 69.4% of SARS-CoV-2 samples were due to P.2 variant
	• B.1.351: Vaccine efficacy against severe/critical COVID was 73.1% 14 days after immunization and 81.7% 28 days after vaccination. Efficacy was somewhat reduced for moderate/severe covid 52% 14 days and 64% at 28 days • P.2 efficacy was similar to the US efficacy data

What about transmission?

These data support that the vaccine reduces transmission of SARS-CoV-2. The vaccine was effective in preventing asymptomatic infection (and if you're not infected, you can't transmit the virus)

If these vaccines appear slightly less effective than the mRNA vaccines, is there still a role?

Unlike the mRNA vaccines, the viral vector vaccines do not have to be stored and transported at ultra-cold temperatures. This could make vaccine distribution more efficient/cheaper and make the vaccines accessible in a broader array of environments. Further, only a single dose is required, making overall administration easier and prevention from severe and critical disease remains excellent.

What about pregnancy?

The J&J FDA document reports 8 pregnancies (vaccine 3, placebo 4). There was one spontaneous abortion in the vaccine group, 1 incomplete abortion in the placebo group, 2 elective abortions in the placebo group, and 1 ectopic pregnancy in the vaccine group. A developmental and reproductive toxicity study found that when rats were given 2 times the human dose prior to mating and during gestation, there were no adverse effects on female reproduction, fetal/embryonal development, or postnatal development.

Recombinant Protein Vaccines

(Novavax)

How do recombinant protein vaccines work?

In the lab, they create the spike protein from SARS-CoV-2 (not the rest of the virus). They combine this with an adjuvant, which basically just helps ramp up the immune response to produce a solid response. When this is injected into the arm, the immune system does the same thing it does with the other vaccines - it recognizes the spike protein as foreign and works to remember it (antibodies, etc).

Study details

UK Study	South Africa Study	US Study
15,000 participants 18-84 (27% >65 years old)	>4,400 adult participants beginning Aug 2020	PREVENT-19 is ongoing and has randomized 16,000 people thus far. Results are expected in February.

How well does this vaccine work?

Currently we only have results from a [press release](#)

UK Study	South Africa Study
Symptomatic COVID-19 7 days after 2nd dose in people who were negative for the virus at baseline. Placebo 56 cases, Vaccine 6. Efficacy 89.3% (95% CI 75.2-95.4) 1 severe case (placebo group)	Symptomatic COVID-19 in patients negative for the virus at baseline: Placebo 29, Vaccine 15 Overall efficacy 49.4% (95% CI 6.1-72.8%) In HIV-negative people (94% of participants) the efficacy increased to 60% (95%CI 19.9-80.1%)
<i>The vaccine seems to work well in the UK variant but has reduced efficacy against the South Africa variant</i>	
‘UK variant’ (B.1.1.7) was detected in 51.6% of cases. Efficacy in this group dropped slightly to 85.6% (no CI given)	Of the 44 COVID-19 cases, 27 had been sequenced and nearly all (92.7%) were the ‘South African variant’ (B.351).

Bottom Line: Given vaccine shortages, distribution issues, and delivery logistics associated with the mRNA vaccines, more vaccines are a good sign. Overall, the efficacy looks pretty good in the UK; however, the numbers from South Africa certainly suggest reduced activity of the recombinant protein vaccine against the variant (it works some, but not great). Additionally, due to the size of the studies and the few number of cases included, the confidence intervals are quite wide.