

Plain Language Summary of Publication

A plain language summary of how well the single-dose Janssen vaccine works and how safe it is

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Summary

This is a summary of a publication about the ENSEMBLE trial of the Janssen Ad26.COVS.2 vaccine against COVID-19, which was published in the *New England Journal of Medicine* in April 2021. The ENSEMBLE study started in September 2020 and is still ongoing.

The study compared the **effectiveness** of the vaccine to a **placebo** in 43,783 adults from Latin America, South Africa, and the United States. Of those, 19,630 got a single dose of the vaccine.

Compared to the **placebo**, the vaccine prevented:




- 66.9% of **moderate to severe–critical** COVID-19 cases after 14 days
- 66.1% of **moderate to severe–critical** COVID-19 cases after 28 days
- 85.4% of severe COVID-19 cases after 28 days
- 100% of people with severe COVID-19 from needing to go to hospital for treatment

None of the vaccinated **participants** died from COVID-19. There were 5 people who got the **placebo** who died from COVID-19.

The vaccine was similarly effective in people from all age groups and different countries, including South Africa, where most cases were caused by the beta variant of the virus that originated there. The people in the study who got the vaccine who went on to get COVID-19 generally had milder and fewer symptoms than those who got the **placebo**. In most people, the vaccine started working after about 2 weeks.

After receiving the vaccine, some people experienced pain at the injection site, headache, tiredness, muscle pain, and nausea. In most cases, these were **mild** and went away within a few days. Serious side effects were very rare. Blood clots, seizures, and tinnitus were very rare but were more common in the people who got the vaccine than in those who got the **placebo**. At the time of the study, it was not clear if these were caused by the vaccine or not.

How to say (double click to play sound)...

- **SARS-CoV-2:** sars-co-vee-two 
- **Placebo:** pla-see-bo 
- **Adenovirus:** ad-EEN-o-virus 

Glossary

- **Effectiveness** means how well the vaccine works. In clinical trials like this one, this is called efficacy
- The **placebo** looked like the vaccine but was just a salt water injection
- **“Moderate to severe–critical”** COVID-19 means all the cases where **participants** had **moderate or severe–critical** COVID-19
- The **participants** are the people who took part in the study
- When a person gets COVID-19, their symptoms can fall into 4 categories:
 - **Asymptomatic:** this means that they have no symptoms, despite having caught coronavirus
 - **Mild:** this means that they have a few symptoms, but they are not too serious
 - **Moderate:** this means that their symptoms are more serious than those in people with **mild** COVID-19, but less serious than those in people with severe COVID-19. They possibly also have more symptoms than people with **mild** COVID-19
 - **Severe–critical:** this means that their symptoms are very serious and debilitating. They are also likely to have more symptoms than someone with **moderate** or **mild** COVID-19. People with severe COVID-19 might need to go to hospital

Who should read this summary?

This summary is for members of the public to help them understand the study. It may also be helpful for health care professionals. More detailed information and references can be found in the original article. The link to this can be found at the end of this summary.

Who sponsored this study?

This study was co-sponsored by Janssen Research & Development, LLC, an affiliate of Janssen Vaccines & Prevention B.V. and part of the Janssen pharmaceutical companies of Johnson & Johnson, and by the US Federal Government as part of Operation Warp Speed.

Federal funds came from the Office of the Assistant Secretary for Preparedness and Response, the Biomedical Advanced Research and Development Authority, and the National Institute of Allergy and Infectious Diseases (NIAID), which is part of the National Institutes of Health.

Kimbra Edwards and Brandis Pickard (CISCRP) and Elizabeth Perdeaux and Sarah Griffiths (Oxford PharmaGenesis) provided pro bono writing and editorial assistance with this article.

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To answer this question, the researchers grouped the data in different ways. They found that the vaccine was effective at protecting against:

- Different severities of COVID-19
- Moderate to severe–critical COVID-19 in all age groups in the study
- Moderate to severe–critical COVID-19 in different countries
- Needing to stay in hospital for COVID-19 symptoms

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The vaccine was 66.9% effective at protecting against moderate to severe–critical COVID-19 at 14 days after injection.

What is COVID-19?

COVID-19 is the illness caused by the coronavirus called severe acute respiratory syndrome coronavirus 2, or SARS-CoV-2. It affects the lungs and can also affect other organs.

COVID-19 causes more serious symptoms in people who are older or who have conditions such as obesity, diabetes, heart disease, cancer, or severe lung disease.

Like all viruses, coronavirus has changed over time. These new types of coronavirus are called “variants.” Four main variant strains of the coronavirus have emerged since the start of the pandemic. These variants have changes in a part of the coronavirus called the spike protein. Some researchers think that the vaccines might offer less protection from the variant strains.

What is a vaccine?

A vaccine trains the immune system to recognize an infection it has not seen before so that it can fight it off quickly if the person comes into contact with the same infection again.

The immune system is the body’s natural defense against infections caused by germs such as viruses, bacteria, parasites, or other types of microorganisms. When a person gets an infection for the first time, their immune system creates proteins and cells that fight off the infection. These include “antibodies,” “T cells,” and “B cells.” The antibodies, T cells, and B cells recognise proteins on the surface of the germs causing the infection. If that person is infected again with the same or a similar infection, the immune system remembers the infection and makes the right antibodies, B cells, and T cells to fight it off quickly. This is called the immune response.

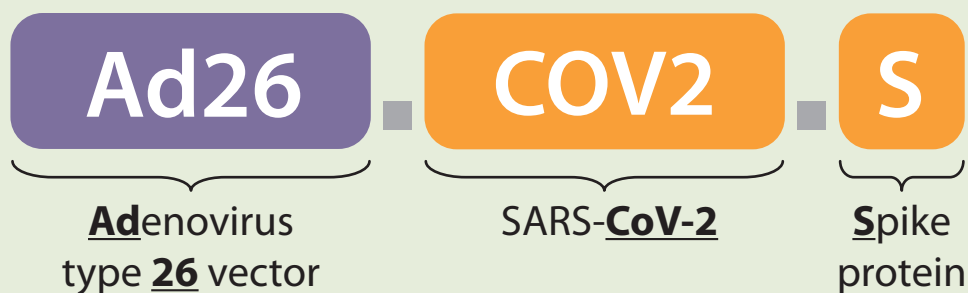
A vaccine uses the body’s immune response to make antibodies, T cells, and B cells against an infection that the body has never been exposed to. This may stop the person from getting ill if they are exposed to the real infection.

What is the Ad26.COVS.S vaccine?

The Ad26.COVS.S vaccine was developed by Janssen Research & Development, LLC, to prevent COVID-19.

The Janssen vaccine, also called Ad26.COVS.S, is made up of 2 parts:

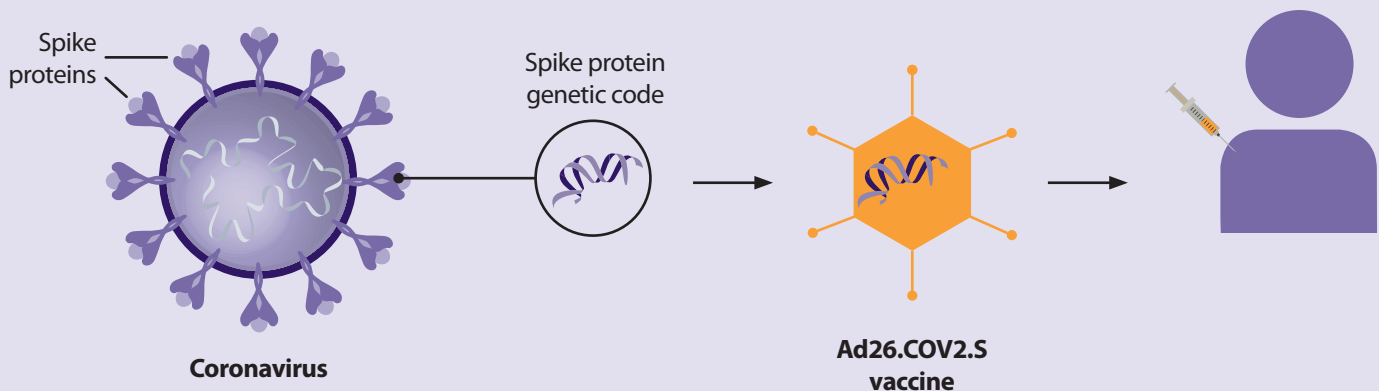
- A modified common cold virus called adenovirus type 26 vector
- The genetic instructions of the coronavirus spike protein



How do researchers make the Ad26.COVS.S vaccine?

This vaccine carries the genetic instructions needed to make a part of the coronavirus called the “spike” protein. The spike protein is on the outside surface of the coronavirus and helps it get into the body’s cells. By itself, the spike protein cannot cause COVID-19.

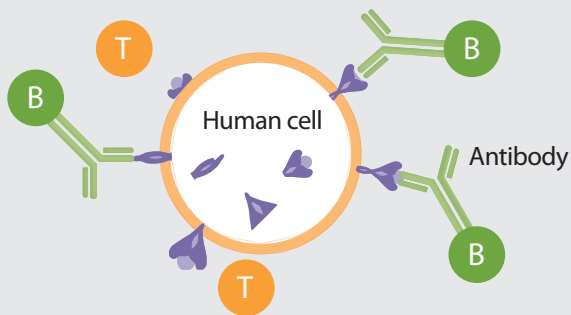
The researchers added the genetic instructions to make the spike protein to a modified form of a common cold virus. This modified common cold virus is called adenovirus type 26. Adenovirus type 26 cannot make copies of itself or cause illness.



How was the vaccine designed to act inside the body?

The vaccine causes some cells within the body to make the coronavirus spike protein for a short time. The immune system makes antibodies, T cells, and B cells in response to the spike protein.

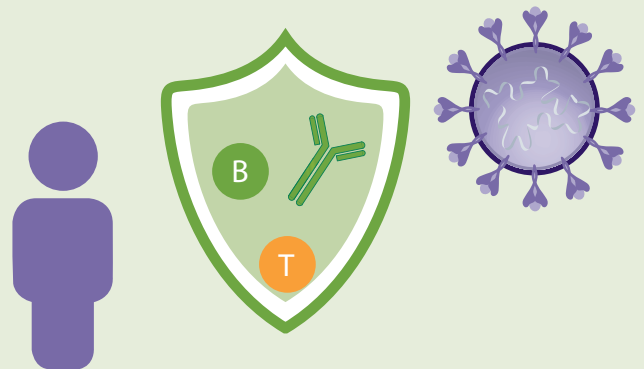
After the vaccine has been injected into the muscle of a person's upper arm, the cells in their body will start making the spike protein for a short time. Pieces of the spike protein then move to the surface of the person's cells. The immune system will recognize these spike protein pieces as something new, which it has not seen before. The immune system will then make antibodies, T cells, and B cells that recognize the spike protein.



How might the vaccine protect someone?

Now the immune system recognizes the spike protein and can react quickly if someone is exposed to the coronavirus.

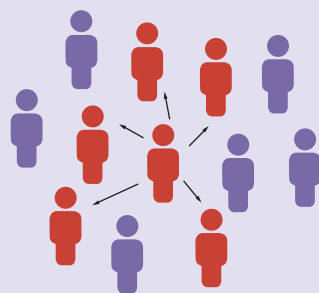
The immune system remembers how to quickly fight off the virus if the person comes into contact with coronavirus. People who do become infected will be less ill with COVID-19 or will not become ill at all. This is called immunity. Researchers think that this may also reduce the spread of the virus.



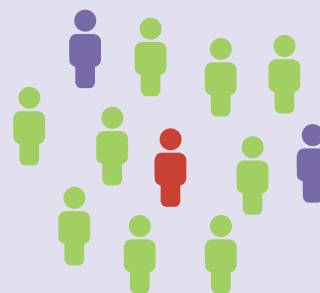
How might coronavirus vaccines help protect a population?

If enough people are vaccinated against the coronavirus, then herd immunity can be reached. This means that coronavirus is less likely to spread, even to the people who are not vaccinated.

- Not vaccinated
- Infected
- Vaccinated



No herd immunity



Herd immunity

Even if herd immunity is not reached, vaccines will help by reducing how seriously people are affected if they catch the coronavirus. Vaccines will also reduce the chances of needing to go to hospital for treatment or dying from coronavirus.

Why was this study done?

The researchers did this study to learn if the Janssen vaccine prevented people from getting COVID-19. This study is also known as the ENSEMBLE study.

The COVID-19 pandemic is having a widespread effect on health and well-being, and vaccines are needed to reduce its impact.

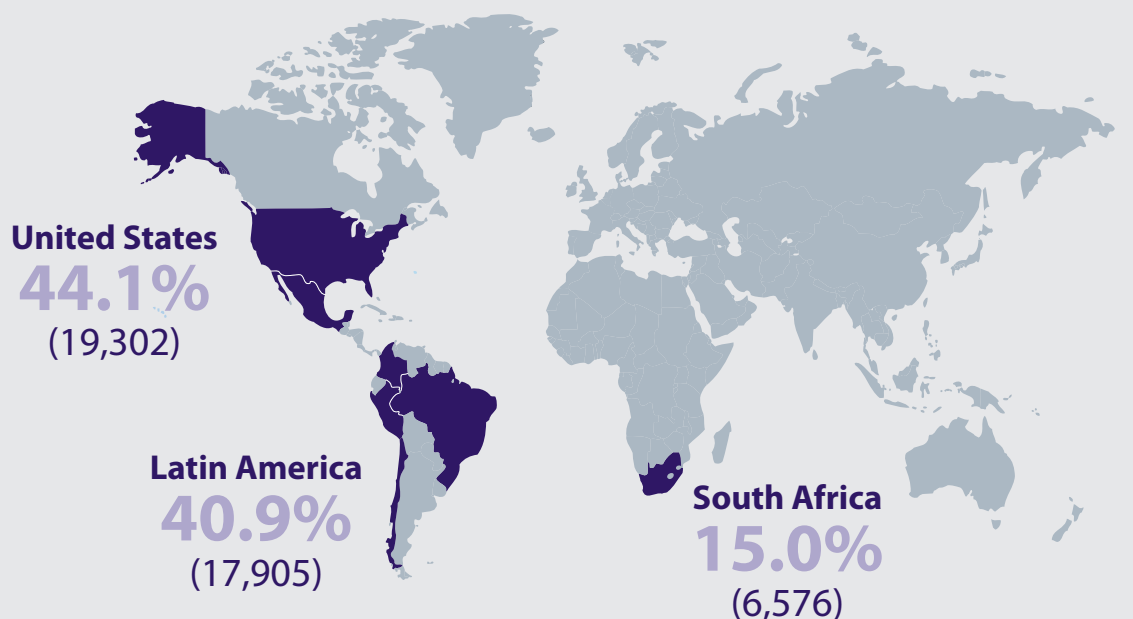
Before a vaccine can be approved for use, researchers must do clinical studies to find out how safe and effective it is. An earlier study had shown that the vaccine was safe in a smaller group of people. In this study, the researchers wanted to learn more about the vaccine's effectiveness and safety in a larger group of people.

Who took part in the ENSEMBLE study?

This study included 43,783 adults who were 18 to 100 years old. Of these, 54.9% (24,053) were men and 45.0% (19,722) were women.

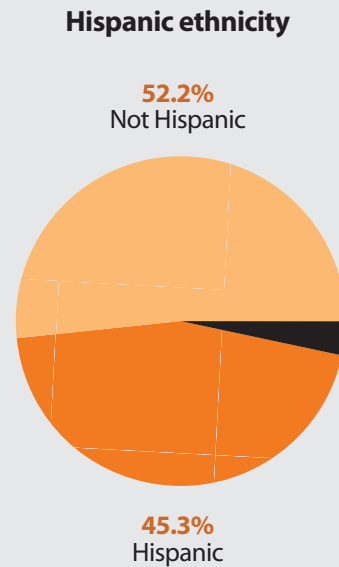
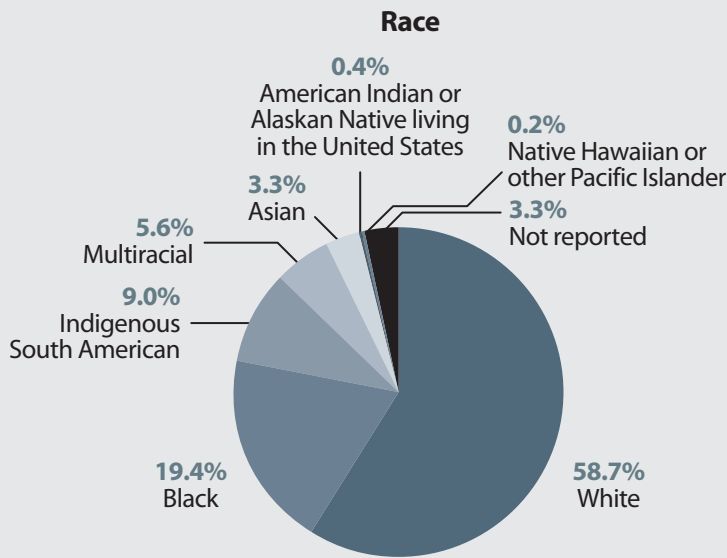
They were from 3 continents and 8 countries:

- Argentina
- Brazil
- Chile
- Colombia
- Mexico
- Peru
- South Africa
- United States

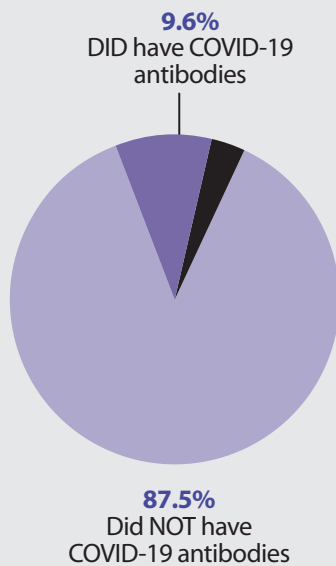


The figures on the next page show:

- **The participants' race**
- **What proportion of the participants identified as Hispanic or not Hispanic**
- **The proportion of participants who had COVID-19 antibodies before they had the vaccine.** The participants who had COVID-19 antibodies had already been exposed to coronavirus at the start of the study
- **The proportion of participants who had at least 1 medical condition** that increased the risk that they would need to go to hospital or could die from COVID-19



COVID-19 antibodies



Medical conditions



The participants were generally well and did not have any COVID-19 symptoms on the day they were due to get the vaccine.

The participants also:

- Did not have any conditions affecting their immune systems
- Did not have known allergies to any of the contents of the vaccine
- Were not taking medications that might change how the vaccine worked

What happened in the ENSEMBLE study?

In this study, the participants got either the Ad26.COVID.S vaccine or the placebo as an injection into the upper arm.

About half of the people who took part in the ENSEMBLE study got a placebo injection. This is an injection that looks like the vaccine but just contains salt water.

This was a “placebo-controlled” study. Researchers use a placebo to help make sure any effects they see in the participants who take the vaccine are actually caused by the vaccine.

This was a “randomized” study. This means that the researchers used a computer program to randomly choose whether the participants got the vaccine or the placebo.

This was also a “double-blind” study. This means that the participants, study doctors, and researchers did not know whether the participants got the vaccine or the placebo until the data were analyzed.

21,895 participants got a single injection of the Ad26.COVID.S vaccine.

21,888 participants got a single injection of the placebo.

Before the participants got the vaccine



They had their blood tested to see if they had already been exposed to and already had antibodies against SARS-CoV-2.



During the ENSEMBLE study



The participants:

Got either a single injection of the Ad26.COVID.S vaccine or a single injection of the placebo.



Tracked any COVID-19 symptoms using an electronic diary.



Who had potential COVID-19 symptoms used an oximeter to measure their blood oxygen levels and took nasal swabs regularly until their illness went away. At least 1 of the swabs had to be taken by a study doctor or nurse.



Some were asked to keep a diary of any specific symptoms that might be caused by the vaccine. They filled in this diary every day for 1 week and then whenever they had symptoms up to 4 weeks after their injection.



The researchers:

Looked at the participants’ data at 14 days and 28 days after they had their injections.

What were the overall results of the study?

The researchers looked at the data collected as of 22 January 2021, which was 4 months after the trial started. This review is known as a “primary analysis.” The results in this summary are based on this primary analysis.

These results show how well the vaccine worked in this study. The vaccine’s effectiveness might change when it is used in the general population, but the number of participants in this study was large enough to give the researchers a good idea of the vaccine’s true effectiveness.

Was the vaccine effective at reducing the number of moderate to severe–critical COVID-19 cases?

The proportion of participants who got moderate to severe–critical COVID-19 was lower in the participants who got the Ad26.COVS vaccine at 14 and 28 days after getting their injection, compared with the participants who got the placebo.

To answer this question, the researchers looked at the number of participants who became infected with SARS-CoV-2 and developed mild, moderate, or severe–critical COVID-19.

The researchers compared the number of moderate to severe–critical cases of COVID-19 in the participants who got the vaccine and in those who got the placebo. These comparisons were done at 2 time points: 14 days and 28 days after injection. They used this information to calculate the vaccine’s effectiveness as a percentage.

The table below shows the effectiveness of the vaccine at these 2 time points.

	Vaccine	Placebo	Overall percentage effectiveness of vaccine at preventing moderate to severe–critical COVID-19
	Number of confirmed moderate to severe–critical COVID-19 cases (out of 21,895 participants)	Number of confirmed moderate to severe–critical COVID-19 cases (out of 21,888 participants)	
14 days after injection	116 cases	348 cases	66.9%
28 days after injection	66 cases	193 cases	66.1%

The researchers also analyzed the data in a way that accounts for the variability that often exists in clinical study results. They calculated that the actual effectiveness of the vaccine at preventing moderate to severe–critical COVID-19 in the general population could be between 59.0% and 73.4% at 14 days and 55.0% and 74.8% at 28 days after the injection.

How effective was the vaccine at protecting against COVID-19 in different situations?

To answer this question, the researchers grouped the data in different ways. They found that the vaccine was effective at protecting against:

- Different severities of COVID-19
- Moderate to severe–critical COVID-19 in all age groups in the study
- Moderate to severe–critical COVID-19 in different countries
- Needing to stay in hospital for COVID-19 symptoms

Next they looked at the number of COVID-19 cases and how many people needed to stay in hospital for COVID-19 treatment in these different groups to estimate the effectiveness of the vaccine at 28 days after the injection.

The table below shows these results:

	Vaccine (out of 21,895 participants)	Placebo (out of 21,888 participants)	Effectiveness of vaccine 28 days after injection
How effective was the vaccine at protecting against different severities of COVID-19?			
All cases of symptomatic COVID-19	66 cases	195 cases	66.5%
Asymptomatic COVID-19	18 cases	50 cases	65.5%
Mild COVID-19	0 cases	2 cases	Not enough cases to be able to estimate effectiveness accurately
Moderate COVID-19	61 cases	159 cases	62.0%
Severe–critical COVID-19	5 cases	34 cases	85.4%

Take-home message

These results show that the vaccine was particularly effective at protecting against severe COVID-19. The researchers also analyzed the data in a way that accounts for variability that often exists in clinical study results. They calculated that the vaccine could be between 54.2% and 96.9% effective against severe COVID-19 at 28 days after injection in the general population.

How effective was the vaccine in different age groups?

18 to 59 years old	52 cases	152 cases	69.3%
60 years and older	14 cases	43 cases	67.9%

Take-home message

These results show that the vaccine was similarly effective in each age group at 28 days after injection.

How effective was the vaccine at protecting against moderate to severe–critical COVID-19 in different countries?

Worldwide	113 cases	324 cases	65.5%
United States	32 cases	112 cases	72.0%
Brazil	24 cases	74 cases	68.1%
South Africa	23 cases	64 cases	64.0%

Take-home message

Only Brazil, South Africa, and the United States had enough cases for this analysis. The vaccine had similar effectiveness in these 3 countries. The majority of cases in the South African participants were caused by the beta coronavirus variant that was first detected in South Africa. Researchers think the vaccines might be less effective against the variants. In this study, the vaccine showed similar effectiveness at preventing moderate to severe–critical COVID-19 in South African participants as in participants in Brazil and the United States. This suggests that the vaccine was effective against the beta variant that was dominant in South Africa at the time.

How effective was the vaccine at preventing people from needing to stay in hospital for COVID-19 treatment?

All participants who tested positive for COVID-19 at least 28 days after receiving the injection	0 people	16 people	100.0%
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Take-home message

These results show that the vaccine was very effective at preventing people from needing to stay in hospital due to COVID-19. The researchers also analyzed the data in a way that accounts for variability that often exists in clinical study results. They calculated that, at 28 days after injection, the vaccine is between 74.3% and 100.0% effective at preventing people with COVID-19 from needing to stay in hospital for treatment.

Did the vaccine reduce the number of deaths?

Number of deaths related to COVID-19	0 deaths	5 deaths	Not enough data to be able to estimate effectiveness accurately
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Take-home message

These results suggest that the vaccine may have reduced the number of COVID-19–related deaths in this study. However, more information is needed to know for certain if the vaccine reduces the risk of dying from COVID-19.

Did the vaccine reduce the severity and number of COVID-19 symptoms?

In the participants who got COVID-19, those who got the vaccine generally had less severe and fewer symptoms than the participants who got the placebo.

To answer this question, the researchers identified the participants who got COVID-19 and looked at how severe their symptoms were and how many different COVID-19 symptoms they reported in their diary. The researchers compared these results between the participants who got the vaccine and those who got the placebo.

Compared with the participants who got the placebo, the participants' symptoms in the vaccine group were:

- 24% less severe 1 day after their symptoms started
- 47% less severe 7 days after their symptoms started
- 53% less severe 14 days after their symptoms started

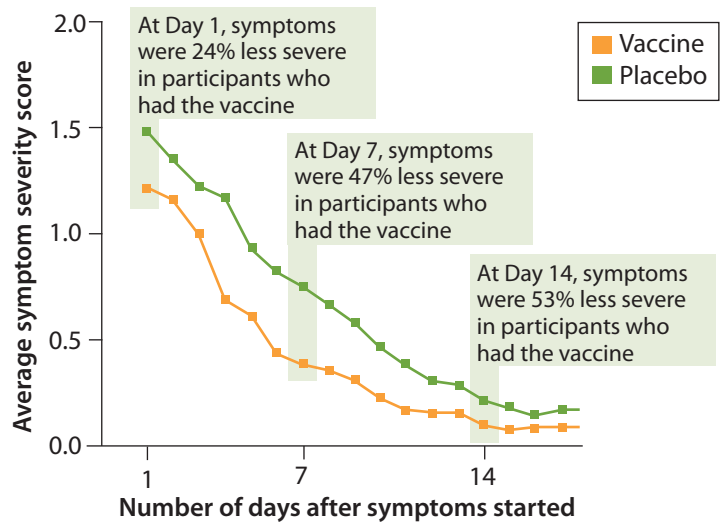
Of the participants who had moderate COVID-19:

- Those who got the vaccine tended to have between 4 and 6 COVID-19 symptoms
- Those who got the placebo tended to have between 7 and 9 COVID-19 symptoms

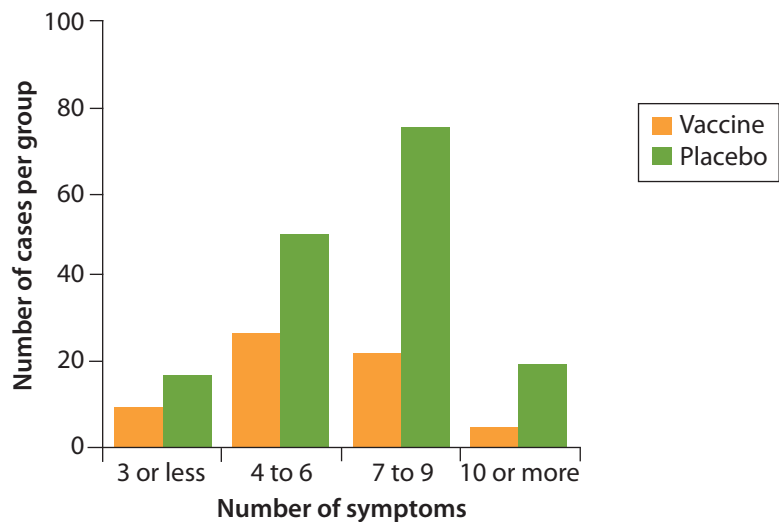
The charts below shows these results:

Symptoms were milder and went away faster in participants who got the vaccine than in those who got the placebo

The participants' symptoms were given a score from 0 to 2, where a higher score means more severe symptoms



Participants who got the vaccine had fewer symptoms than those who got the placebo



How long did it take for the vaccine to start working?

It took 7 days for the vaccine to protect participants from severe COVID-19. It took 14 days to protect all participants from moderate to severe–critical COVID-19.

To answer this question, the researchers kept track of the number of moderate to severe–critical COVID-19 cases that happened in the participants who got the vaccine and in those who got the placebo.

Then, they looked for when the number of new COVID-19 cases started to slow down in the vaccine group compared with the placebo group. This was considered to be the time it took the vaccine to start working. They did this same comparison for different severities of COVID-19 and in different groups of participants.

The vaccine started to protect against severe COVID-19 cases at 7 days after the injection.

Protection from moderate to severe–critical COVID-19 started at 14 days after the injection in all participants, including those who were greater than 60 years old and who had other conditions that increased their risk of developing severe COVID-19.

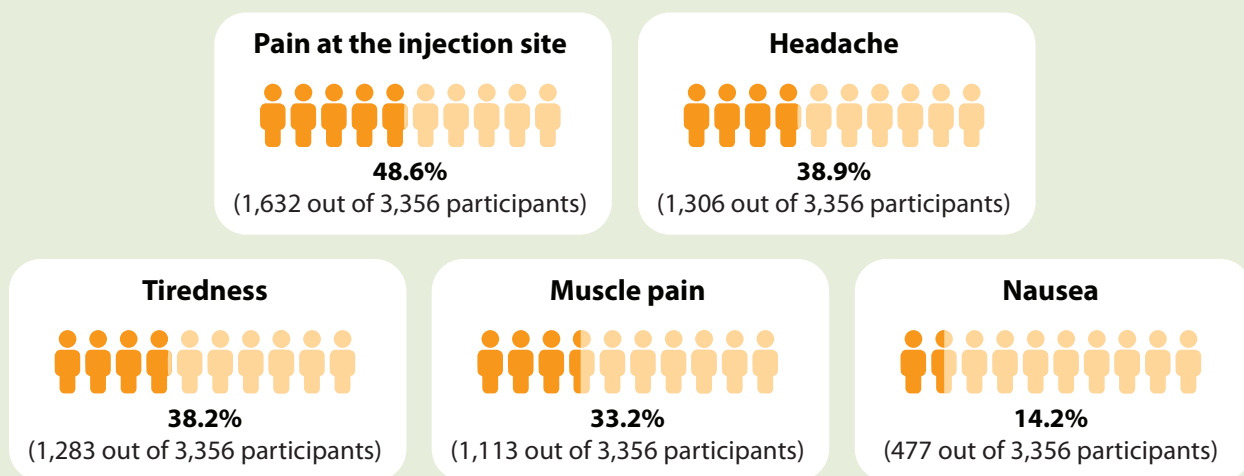
What were the most common side effects that might be related to the vaccine?

In a subgroup of participants who were asked to track their symptoms for 7 days after they got their injection, the most common side effects of the vaccine were pain at the injection site, headache, tiredness, muscle pain, and nausea.

The researchers wanted to find out if the vaccine caused any specific side effects that are thought to be caused by this type of vaccine. To do this, they asked a subgroup of the participants to fill out a diary about these symptoms for the first 7 days after getting their injection. This safety subgroup included:

- 3,356 participants who got the vaccine
- 3,380 participants who got the placebo

The figure below shows the most common side effects in the participants who got the vaccine. In most cases, these side effects were mild and went away within a few days.



Were there any serious side effects?

There were some serious side effects, but they were very rare.

Side effects are considered serious when they require staying in hospital for treatment, cause disability, put the participant’s life at risk, lead to death, or may require treatment to prevent 1 of these. The side effects in this section are called “**serious adverse events**” and “**serious adverse reactions**.”

A **serious adverse event** is any **serious medical problem** that a participant had after their injection. It may or may not have been caused by the injection. A **serious adverse reaction** is a serious medical problem that the **study doctors thought might be related to the vaccine or the placebo**.

Serious adverse events that were not related to COVID-19 happened in:

- 0.4% of the participants who got the vaccine. This was 83 out of 21,895 participants
- 0.4% of the participants who got the placebo. This was 96 out of 21,888 participants

Serious adverse reactions happened in:

- 0.03% of the participants who got the vaccine. This was 7 out of 21,895 participants
- 0.01% of the participants who got the placebo. This was 2 out of 21,888 participants

	Vaccine	Placebo
Serious adverse events	40 in 10,000 participants had a serious adverse event	40 in 10,000 participants had a serious adverse event
Serious adverse reactions	3 in 10,000 participants had a serious adverse reaction	1 in 10,000 participants had a serious adverse reaction

The only serious adverse reaction that occurred in more than 1 participant who got the vaccine was a temporary weakness or lack of movement on 1 side of the face. This is also called Bell’s palsy. This happened in 2 participants.

There were other serious adverse reactions, but they occurred in 1 participant each who got the vaccine.

There were 3 deaths in the participants who got the vaccine and 16 deaths in the participants who got the placebo. None of the deaths were related to the vaccine or the placebo.

Were there any medical problems that were more common in the participants who got the vaccine?

Yes. Blood clots, seizures, and ringing in the ears were all slightly more common in the participants who got the vaccine than in the participants who got the placebo.

The researchers also studied “adverse events” in all of the participants. These are all of the medical problems that happen during a study that may or may not be related to the vaccine. In particular, the researchers wanted to know if there were any adverse events that were more common in the participants who got the vaccine than in those who got the placebo.

The table that follows shows the adverse events that occurred in more participants who got the vaccine than in those who got the placebo.

Adverse events that happened more often in the participants who got the vaccine

	Vaccine	Placebo
A blood clot causing blocked blood vessels, also called a “thromboembolic event”	0.05% (11 out of 21,895 participants)	0.01% (3 out of 21,888 participants)
Seizures	0.02% (4 out of 21,895 participants)	0.005% (1 out of 21,888 participants)
A ringing in the ear, also called tinnitus	0.03% (6 out of 21,895 participants)	0% (0 out of 21,888 participants)

In 1 of the 14 participants who had a blood clot, the clot was in a vein in the brain, which blocked blood draining from the brain. This caused a bleed in the brain. This participant had been given the vaccine. This participant’s health was followed very closely by the researchers.

At the time of the primary analysis, it was not clear if these adverse events were related to the vaccine or not. As the researchers have reviewed more data, these data have shown that the vaccine may very rarely cause blood clots and low levels of a type of blood cell called platelets. People who have the Janssen COVID-19 vaccine are advised to seek medical attention right away if they have any of the following symptoms in the first weeks after receiving the vaccine:

- Shortness of breath
- Chest pain
- Leg swelling
- Abdominal pain that does not go away
- Headaches that are severe or do not go away, or blurred vision
- Bruise easily or have tiny spots under the skin beyond the site of the injection

All the data collected about medical problems that happen in people who have had the vaccine are monitored very closely by the relevant health authorities.

What do the results of the study mean?

- The vaccine was **66.9%** effective at protecting against moderate to severe–critical COVID-19 at 14 days after injection. At 28 days after injection, the vaccine was **66.1%** effective

At 28 days after the injection:

- The vaccine was **85.4%** effective at protecting against severe COVID-19 symptoms and was up to **100%** effective at preventing people from needing to stay in hospital for treatment for COVID-19
- The vaccine had a similar effectiveness among participants across different age groups and in different countries. The vaccine’s effectiveness was not much lower in South Africa, where the majority of cases were caused by the beta variant. This suggests that the Ad26.COVS vaccine was effective against this variant
- COVID-19 symptoms were less severe in the participants who got the vaccine than in those who got the placebo. In the participants who got moderate COVID-19, those who got the vaccine typically had fewer symptoms than the participants who got the placebo
- In most cases, the vaccine started working about **14 days** after the injection. However, protection against severe COVID-19 started at about **7 days** after receiving the vaccine
- In a subgroup of participants who were asked to track their symptoms for 7 days after they got their injection, the most common side effects of the vaccine were pain at the injection site, headache, tiredness, muscle pain, and nausea. In most cases, these were mild and went away within a few days

- **Serious side effects were very rare.** The only serious adverse reaction that was thought to be caused by the vaccine and occurred in more than 1 participant who got the vaccine was Bell's Palsy
- There were more cases of blood clots, seizures, and tinnitus in the participants who got the vaccine than in those who got the placebo. At the time of the primary analysis, it was unclear if these were related to the vaccine or not

Even though data about the safety and effectiveness of the Ad26.COVID.S vaccine have only been being collected for about 1 year, based on the results of this study and other clinical studies of the vaccine, the Food & Drugs Administration, also called the FDA, authorized the use of the vaccine during the pandemic. This means that people in the United States may be given this vaccine. This is not the same as when a new treatment is normally approved. This means that there is enough data for the FDA to be confident that the benefits of using the vaccine outweigh any potential harms. However, additional data on the safety and effectiveness of the vaccine will continue to be collected from the general population and the people who took part in this study. Based on these data, the vaccine will either ultimately be approved in the US or will no longer be used after the pandemic. In the European Union, the Ad26.COVID.S vaccine has been approved for use against COVID-19.

Where can readers find more information on this study?

The original article discussed in this summary, entitled "Safety and efficacy of single-dose Ad26.COVID.S vaccine against Covid-19," was published in the *New England Journal of Medicine* in 2021. This article is free to read and can be found at: www.nejm.org/doi/full/10.1056/NEJMoa2101544

The full name of the ENSEMBLE study is: A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Assess the Efficacy and Safety of Ad26.COVID.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older.

You can read more about the ENSEMBLE study by visiting www.clinicaltrials.gov and entering the study number NCT04505722 into the search field.

If you participated in the study and have questions about the results or the vaccine, please speak with the study doctor or staff at your study site.

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