Results from four AZD1222 (ChAdOx1 nCoV-19) vaccine trials for COVID-19

This is a summary of an article published in *The Lancet* in March 2021

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Trial Sponsor: the University of Oxford

A full list of all the trial sponsors is available at the end of this summary

Thank you

Thank you to the participants who took part in the clinical trials for the COVID-19 vaccine developed by the University of Oxford and AstraZeneca. This vaccine is called ChAdOx1 nCoV-19 or AZD1222. It is referred to in this summary as AZD1222. All of the participants helped the researchers learn more about AZD1222 to prevent COVID-19.

This is a summary of 1 article in *The Lancet* journal that was published in March 2021. The article discusses the results from 4 trials of AZD1222. The purpose of this summary is to help you understand these results. Other trials may provide other information or different results.

AstraZeneca believes it is important to share the trial results. An independent non-profit organisation called CISCRP helped prepare this summary.

Overview

Researchers are studying AZD1222 as a vaccine to prevent the COVID-19 disease caused by the SARS-CoV-2 virus, also called severe acute respiratory syndrome coronavirus 2. The 4 clinical trials described in this summary included 24,422 participants in Brazil, South Africa, and the United Kingdom. Each of these trials compared AZD1222 with a control. The control was either a different vaccine or salt water. Both AZD1222 and the control were given through 2 injections into the muscle of the upper arm. In these trials, 2 different dose levels of AZD1222 were given.

The results show that overall, more than 14 days after the participants received their second injections, AZD1222 was 66.7% effective at preventing symptomatic COVID-19 confirmed by a positive test. The safety of AZD1222 was similar to the controls and what researchers already know about the safety of vaccines in general.

More details about the results of these AZD1222 trials are included later in this summary. You can also find more information about these trials on the websites listed on the last page. When full reports of the trial results are available, they can also be found on those websites.

More results from these trials will be shared when they are available. This includes looking at how AZD1222 affects participants over time and how it affects older participants. Researchers look at the results of many trials to decide which vaccines are most effective and are safest. Other trials may provide new information or different results.

Why was this research needed?

COVID-19 is an infectious disease caused by a type of coronavirus called "SARS-CoV-2", also called severe acute respiratory syndrome coronavirus 2. The global COVID-19 pandemic is having a widespread effect on people's health. COVID-19 has been shown to cause more severe illness in older people than in younger people and more severe illness in those with certain medical problems such as obesity, heart disease, and severe lung disease.

The body's natural defenses are known as the immune system. There are a number of ways in which the immune system fights infections. It makes antibodies and cells called "T cells", which are specific to a germ that causes an infection. A germ might be bacteria, a virus, a parasite, or another microorganism. Most vaccines work by exposing the immune system to a part of a germ or a weakened or dead version of a germ. This teaches the immune system to recognize that germ and to produce the specific antibodies and T cells against it without causing illness. In this way, vaccines stimulate the immune system to produce its own protection against infections. This means the immune system can quickly stop future infections before illness is caused.

AZD1222 was created by the University of Oxford as a vaccine against the SARS-CoV-2 virus that causes COVID-19.

Before a vaccine can be approved for use, researchers do clinical trials in humans to find out how effective and how safe it is. Clinical trials for vaccines need to have a certain minimum number of infections among the trial participants before researchers can review the data and then measure how effective the vaccine is at preventing infection. Trials that are designed this way are known as "event-driven" trials. The effectiveness of a vaccine or treatment at preventing infection during a clinical trial is known as "efficacy".

The World Health Organization (WHO) and the US Food & Drug Administration (FDA) both set out requirements for COVID-19 vaccines before research began. They stated that these vaccines would need to be at least 50.0% effective at stopping infections in the clinical trials. You can find out more about these requirements at the links below:

WHO: https://www.who.int/publications/m/item/who-target-product-profiles-for-covid-19-vaccines

FDA: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19

What is AZD1222?

AZD1222 is a vaccine used to help protect people aged 18 years and older against COVID-19. COVID-19 is caused by a virus called coronavirus (SARS-CoV-2). AZD1222 stimulates the body's natural defenses (immune system). It causes the body to produce its own protection through antibodies and T cells against the virus. This could help protect people against COVID-19 in the future. None of the ingredients in this vaccine can cause COVID-19.

How do researchers make AZD1222 and how does it work inside the body?

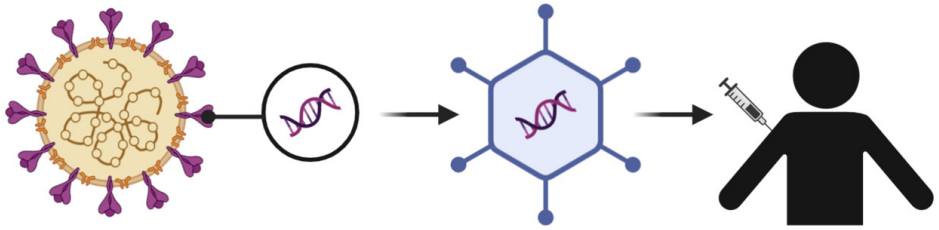
There are many different types of vaccines. The vaccine AZD1222 is a "viral vector" vaccine. This means that genetic information about the protein structure of SARS-CoV-2 is packaged into a harmless and weakened virus called a viral vector for the immune system to process. To make AZD1222, the researchers use a type of common cold virus called "adenovirus" that usually infects chimpanzees but not humans. It has been made so that it is impossible for this virus to grow in humans or change our own DNA.

The information that the researchers put inside the weakened viral vector is the genetic code for the entire SARS-CoV-2 "spike" protein. This is a protein on the outside of the SARS-CoV-2 virus that allows it to enter someone's cells, like a key to a lock. The spike protein is usually the first part of the virus that comes into contact with the immune system when someone gets infected. The vaccine does not contain any other parts of the SARS-CoV-2 virus and cannot cause COVID-19 infection.

The chart below shows how the researchers make AZD1222 and how it works inside the body.

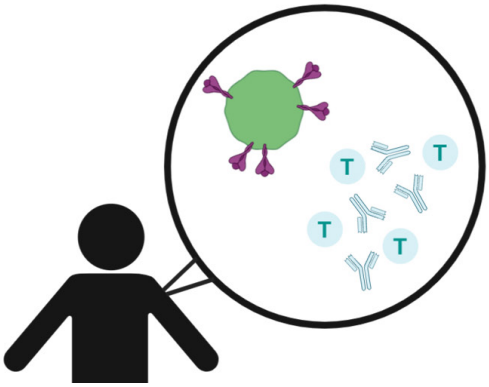
How do researchers make the AZD1222 vaccine?

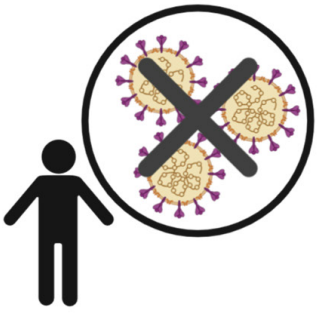
Researchers take genetic information about the **"spike" protein** from **SARS-CoV-2** and put it into a **weakened, harmless virus** to make the AZD1222 vaccine.



How does the AZD1222 vaccine work inside the body?

The AZD1222 vaccine teaches a few of the **body's cells** how to make the **"spike" protein**. This causes the immune system to make **antibodies** and **T cells** that can recognize the "spike" protein and attack it.





Now, the immune system is prepared if the person later catches **SARS-CoV-2**. The immune system will recognize and attack SARS-CoV-2 quickly before it causes illness.

QUESTION: When the vaccine is given, can the "spike" protein or other parts of the weakened viral vector be produced in our body's cells?

ANSWER: Only the "spike" protein is produced in the body's cells that the weakened viral vector in the vaccine has entered. The other parts of the weakened viral vector cannot multiply or grow.

What are the 4 trials that are included in this summary?

The results discussed in this summary come from 4 different AZD1222 clinical trials. These are:

- **COV001**–a Phase 1 and 2 trial in the United Kingdom
- **COV002**–a Phase 2 and 3 trial in the United Kingdom
- **COV003**–a Phase 3 trial in Brazil
- **COV005**–a Phase 1 and 2 trial in South Africa

All of the trials compared AZD1222 with a control. The control injection does not have any of the genetic information about SARS-CoV-2 in it. Researchers use controls to help make sure any effects they see in the participants who receive a vaccine are actually caused by that particular vaccine. Controls also help to rule out effects that may be caused by the injection itself.

COV001, **COV002**, and **COV003** were all "single-blind" trials. This means that the researchers, trial doctors, and other trial staff may have known whether the participants were receiving AZD1222 or the control, but the participants did not. In these trials, only the person giving the injection knew whether the participant received AZD1222 or the control.

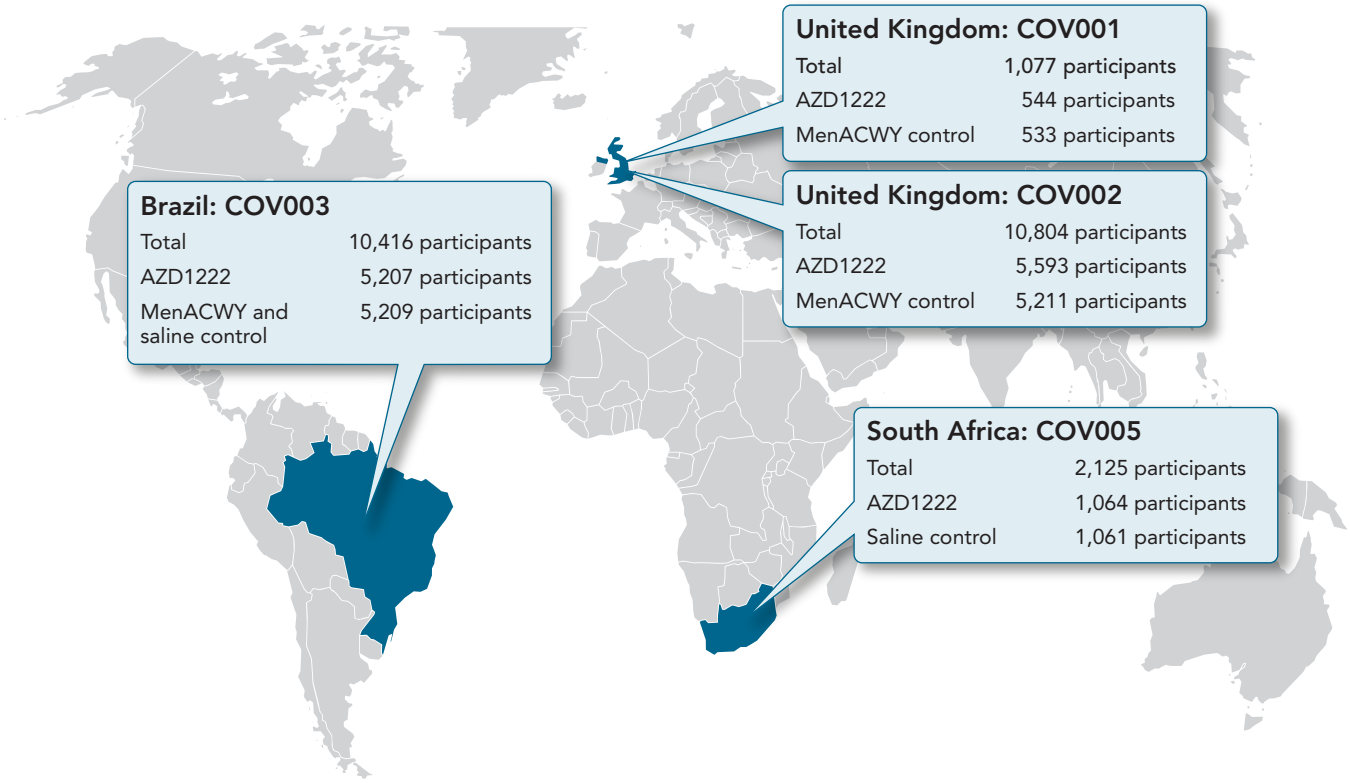
- For the control, COV001 and COV002 used an existing vaccine against meningitis infections called "MenACWY".
- COV003 used the MenACWY vaccine as the control for the first injection. For the second injection, COV003 used an injection of salt water, also known as "saline".

COV005 was a "double-blind" trial. This means that none of the participants, researchers, trial doctors, or other trial staff knew whether the participant was receiving AZD1222 or the control. If it was needed for safety reasons, it was possible for the trial doctors or staff to find out what a participant was receiving.

- For the control, this trial used saline.

For all of the trials, the researchers used a computer programme to randomly choose whether the participants got AZD1222 or the control. This helps make sure the groups are chosen equally and that the types of participants in each group are similar. Researchers do this so that comparing the results of each trial injection is as accurate as possible.

The chart below shows how many participants received AZD1222 or the control.



The main question the researchers wanted to answer in these trials was:

- How effective was AZD1222 more than 14 days after the second injection?

They also wanted to find out:

- How effective was AZD1222 after the first injection?
- What were the safety results of AZD1222?

How did the participants receive the vaccine?

All of the participants in all 4 of the trials received either AZD1222 or the control as an injection into the muscle of the upper arm.

The amount of vaccine in each injection is measured in units called "10^{10} viral particles". A unit of 1×10^{10} viral particles is equal to 10,000,000,000 viral particles.

In **COV001**, the dose level of the AZD1222 injection was 5×10^{10} viral particles. This is known as the standard dose level.

When this trial first started, it was planned that the participants who received AZD1222 would get only 1 injection. After the researchers started looking at the results from the first few participants, they decided that the remaining participants should get a second injection. This was because of the results of 10 participants at the beginning of the trial. In these 10 participants, their immune responses were stronger when they received 2 injections. Those results are in a different medical article and are not in this summary.

In **COV002**, the researchers planned to give the participants the standard dose level of AZD1222.

The researchers realised that about a third of the participants who received AZD1222 had been given a lower dose level of 2.2×10^{10} viral particles for their first injection. This is known as the low dose level.

All of the participants who got AZD1222 in COV002 received the standard dose level for their second injection. The majority of COV002 participants waited at least 12 weeks between each injection.

In **COV003**, all of the participants who got AZD1222 received 2 standard dose level injections. There was an average of less than 6 weeks between each injection.

In **COV005**, almost all of the participants who got AZD1222 received 2 standard dose level injections. There was a very small number of participants who received the low dose level of AZD1222 for 1 of their injections. There was an average of 4 weeks between each injection.

In each of the trials, the participants who received the control got the same number of injections as those who received AZD1222. This was done so that the participants could not tell whether they were receiving AZD1222 or the control.

About the low dose level

There was a discrepancy in the measurement of the vaccine in the initial doses in the COV002 trial, and some doses in the COV005 trial, which resulted in some participants receiving a half dose. The data was reviewed by the independent Data Safety Monitoring Board and the UK regulator, both of whom approved the continuation with no concern and the participants were informed. All other regulatory authorities where the University of Oxford and AstraZeneca had ongoing interactions were also informed.

Who took part in these trials?

The 4 trials included 24,422 male and female participants in Brazil, South Africa, and the United Kingdom. The participants received either AZD1222 or the control between 23 April and 6 December 2020.

The answers to the questions below include information for 17,178 participants who received 2 injections.

How old were the participants when they joined the trials?

	18 to 55 years old	56 to 69 years old	Over 70 years old
COV001 (United Kingdom) AZD1222 (out of 356 participants)	100.0% (356)	0.0% (0)	0.0% (0)
Control (out of 385 participants)	100.0% (385)	0.0% (0)	0.0% (0)
COV002 (United Kingdom) AZD1222 (out of 4,071 participants)	80.6% (3,282)	9.3% (377)	10.1% (412)
Control (out of 4,136 participants)	80.6% (3,334)	9.1% (378)	10.3% (424)
COV003 (Brazil) AZD1222 (out of 3,414 participants)	83.5% (2,850)	14.4% (492)	2.1% (72)
Control (out of 3,339 participants)	84.1% (2,808)	14.0% (466)	1.9% (65)
COV005 (South Africa) AZD1222 (out of 756 participants)	95.1% (719)	4.9% (37)	0.0% (0)
Control (out of 721 participants	94.2% (679)	5.8% (42)	0.0% (0)

What were the ethnicities of the participants?					
	White	**Black**	**Asian**	**Mixed**	**Other**
COV001 (United Kingdom) AZD1222 (out of 356 participants)	90.7% (323)	0.8% (3)	4.8% (17)	1.7% (6)	2.0% (7)
Control (out of 385 participants)	92.2% (355)	0.3% (1)	4.2% (16)	1.8% (7)	1.8% (6)
COV002 (United Kingdom) AZD1222 (out of 4,071 participants)	91.5% (3,725)	0.6% (23)	5.4% (220)	1.7% (70)	0.8% (33)
Control (out of 4,136 participants)	92.2% (3,815)	0.4% (17)	4.9% (203)	1.6% (66)	0.8% (35)
COV003 (Brazil) AZD1222 (out of 3,414 participants)	66.6% (2,273)	9.9% (337)	2.4% (83)	20.6% (704)	0.5% (17)
Control (out of 3,339 participants)	67.4% (2,249)	10.1% (336)	2.0% (66)	20.1% (670)	0.5% (18)
COV005 (South Africa) AZD1222 (out of 756 participants)	15.1% (114)	67.5% (510)	0.0% (0)	14.9% (113)	2.5% (19)
Control (out of 721 participants	16.8% (121)	64.6% (466)	0.0% (0)	16.2% (117)	2.4% (17)

How many participants were healthcare and social care workers?

	Healthcare and social care workers
COV001 (United Kingdom) AZD1222 (out of 356 participants)	18.8% (67)
Control (out of 385 participants)	16.4% (63)
COV002 (United Kingdom) AZD1222 (out of 4,071 participants)	67.1% (2,731)
Control (out of 4,136 participants)	68.3% (2,825)
COV003 (Brazil) AZD1222 (out of 3,414 participants)	74.0% (2,526)
Control (out of 3,339 participants)	72.6% (2,425)
COV005 (South Africa) AZD1222 (out of 756 participants)	8.5% (64)
Control (out of 721 participants	11.0% (79)

How did the researchers measure COVID-19?

All of the participants were asked to contact their trial doctors if they had any COVID-19 symptoms. In the COV001, COV002, and COV003 trials, the list of COVID-19 symptoms included the 5 main symptoms of COVID-19:

- Fever of 37.8 °C (100 °F) or higher
- Cough
- Shortness of breath
- Loss of smell, also known as "anosmia"
- Loss of taste, also known as "ageusia"

In the COV005 trial, the list of COVID-19 symptoms included the 5 main symptoms of COVID-19 and also included:

- Muscle pain, also known as "myalgia"
- Chills
- Sore throat
- Headache
- Stuffy nose, also known as "nasal congestion"
- Diarrhea
- Runny nose
- Fatigue
- Nausea
- Vomiting
- Loss of appetite

If the participants had any of these symptoms, they were tested for COVID-19. This test was done by a swab of the nose and throat.

In COV002, some of the participants were also given a weekly swab test for COVID-19 throughout the trial, even if they did not have symptoms. This let the researchers check for "asymptomatic" COVID-19, meaning someone who has COVID-19 but has no symptoms.

In all 4 of the trials, independent reviewers looked at the results. These are professionals who do not work for the University of Oxford, AstraZeneca, or any other sponsor, and were not involved in performing the trials. This helps make sure that the results are looked at fairly. Independent reviewers do this for both the results about effectiveness and the results about safety.

What are the results of these trials?

The effectiveness of a vaccine or treatment at preventing infection during a clinical trial is known as "efficacy". Researchers look at the results of many trials to decide which vaccines are most effective and are safest. Other trials may provide new information or different results.

How effective was AZD1222 more than 14 days after the second injection?

To measure the efficacy of AZD1222, the researchers compared:

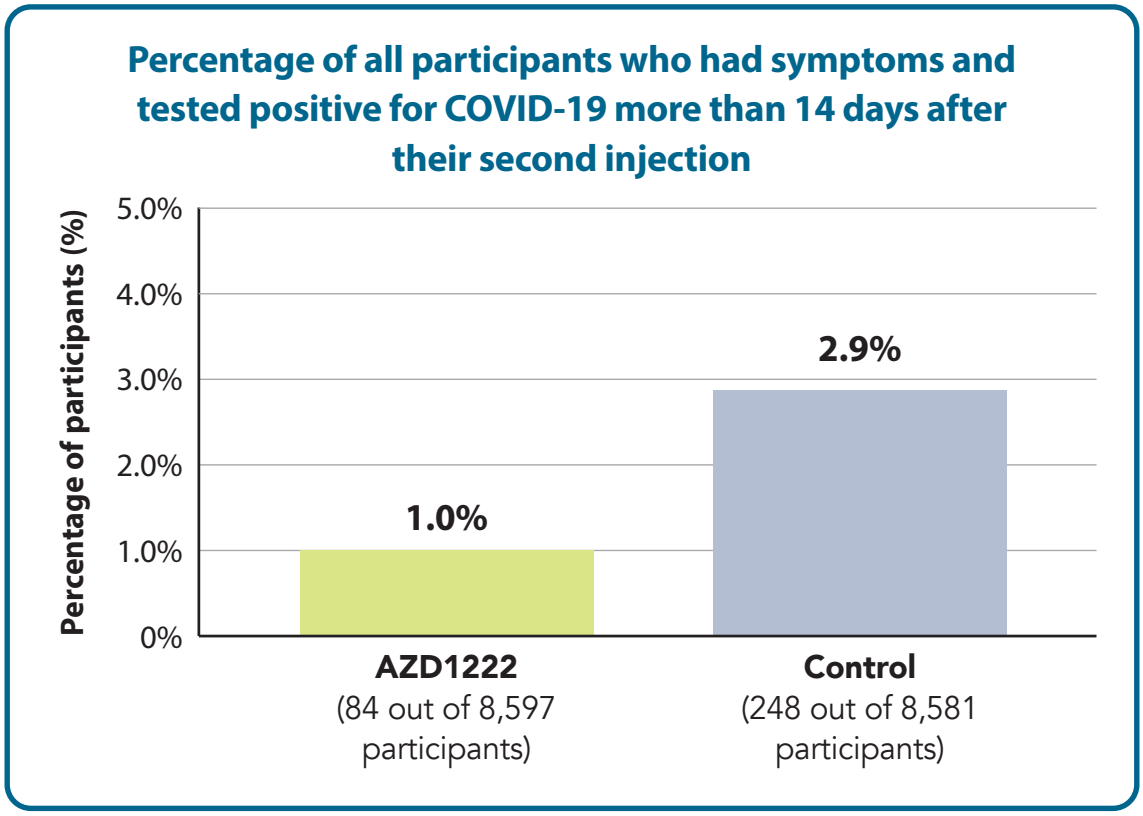
- the number of participants who had symptoms and tested positive for COVID-19 in the AZD1222 groups more than 14 days after their second injection
- the number of participants who had symptoms and tested positive for COVID-19 in the control groups more than 14 days after their second injection

Then, the researchers used a mathematical model to calculate the efficacy as a percentage.

In these 4 trials, 332 total participants had symptoms and tested positive for COVID-19 more than 14 days after their second injection. The researchers found that:

- 1.0% of participants in the AZD1222 groups had symptoms and tested positive for COVID-19. This was 84 out of 8,597 participants.
- 2.9% of participants in the control groups had symptoms and tested positive for COVID-19. This was 248 out of 8,581 participants.

These results are shown in the graph below:



Based on these results, the researchers calculated that overall, AZD1222 was **66.7% effective** in preventing symptomatic COVID-19 infections confirmed by a positive test. This is the overall efficacy of AZD1222.

This means that the AZD1222 vaccine reduced the risk of getting COVID-19 in the clinical trials by **66.7%** compared with the controls.

How effective was AZD1222 after the first injection?

The researchers also wanted to know about the efficacy of AZD1222 after just 1 injection of the standard dose level. In all 4 trials, the researchers compared the number of participants in each group who had symptoms and tested positive for COVID-19 and used the mathematical model to calculate the efficacy. They did this at different time periods after the participants' first injections of the standard dose level.

The table below shows the number of participants who had symptoms and tested positive for COVID-19 at different time periods after their first injection. It also shows the efficacy calculation for each period of time.

Period of time after the participants' first injections	Percentage of participants who had symptoms and tested positive for COVID-19		Efficacy calculation
	AZD1222	Control	
22 to 30 days	0.1% (7 out of 9,257 participants)	0.3% (30 out of 9,237 participants)	76.7%
31 to 60 days	0.1% (6 out of 7,147 participants)	0.3% (22 out of 7,110 participants)	72.8%
61 to 90 days	0.1% (4 out of 2,885 participants)	0.6% (19 out of 2,974 participants)	78.3%
91 to 120 days	0.3% (4 out of 1,369 participants)	0.4% (6 out of 1,404 participants)	31.6%

What are the safety results of AZD1222?

This is a summary of the safety results from all 4 trials so far. During the trials, the doctors keep track of the "adverse events" that the participants have. An adverse event is any sign or symptom that participants have during a trial. Doctors keep track of all the adverse events that happen in trials, even if they do not think the adverse events might be related to the trial injections. An adverse event is considered "serious" when it is life-threatening, causes lasting problems, or the participant needs hospital care. Adverse events are "graded" from 1 to 4 based on their severity. The higher the grade, the more severe the adverse event is. Adverse events may or may not be related to the trial injections or procedures in the trial. A lot of research is needed to know whether an adverse event is related to a trial injection.

Independent reviewers looked at the results to help the researchers decide if a sign or symptom is an adverse event or serious adverse event. These are professionals who do not work for the University of Oxford, AstraZeneca, or any other sponsor, and were not involved in performing the trial. This helps make sure that the results are looked at fairly.

How many participants had serious adverse events?

Overall, 1.0% of all participants had a serious adverse event. This was 235 out of 24,244 participants.

- 0.9% of participants who received AZD1222 had a serious adverse event. This was 108 out of 12,282 participants.
- 1.1% of participants who received the MenACWY or saline control had a serious adverse event. This was 127 out of 11,962 participants.

There were 7 participants who died during these trials. None of these deaths were considered to be related to any of the trial injections or procedures.

- 2 deaths were in participants who received AZD1222 and 5 deaths were in participants who received a control.
- 1 death was because of COVID-19. This participant was in a control group.

How many participants had Grade 3 or Grade 4 adverse events?

Overall, 1.5% of participants had a Grade 3 adverse event. This was 375 out of 24,244 participants.

- 1.7% of participants who received AZD1222 had a Grade 3 adverse event. This was 211 out of 12,282 participants.
- 1.4% of participants who received the MenACWY or saline control had a Grade 3 adverse event. This was 164 out of 11,962 participants.

Overall, 0.3% of participants had a Grade 4 adverse event. This was 82 out of 24,244 participants.

- 0.4% of participants who received AZD1222 had a Grade 4 adverse event. This was 48 out of 12,282 participants.
- 0.3% of participants who received the MenACWY or saline control had a Grade 4 adverse event. This was 34 out of 11,962 participants.

What do the results of the trials mean?

Based on these results, the researchers consider AZD1222 to be generally well tolerated and 66.7% effective overall at preventing symptomatic COVID-19 confirmed by a positive test.

These calculations are based on 332 symptomatic COVID-19 infections confirmed by a positive test, out of 17,178 participants. This means the efficacy of AZD1222 is higher than the minimum requirement from the FDA and the WHO.

In general, vaccines are considered to be safe. This is because many years of research has provided data that have been measured and carefully analysed for all vaccines. The safety results for AZD1222 were similar to the controls and the safety results that researchers have seen for other vaccines.

In the future, the researchers would like to find out:

- How effective is AZD1222 in participants who are over 55 years old?
  - Most of the participants in these trials who were over 55 years old joined later than other participants. Because of this, there had not yet been enough infections in this group of participants for the researchers to measure the efficacy.
- For how long does AZD1222 protect participants from COVID-19?

Researchers look at the results of many trials to decide which vaccines are most effective and are safest. This summary shows only the main results from these 4 trials that are in this 1 medical article. Other trials may provide new information or different results.

Where can I learn more about these trials?

This summary is based on a publication called 'Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials'. It was published in *The Lancet* in March 2021. You can read the original article for free at:
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00432-3/fulltext

Earlier results from these trials were also published in *The Lancet* in July 2020, November 2020, and December 2020. You can read these articles for free at:

- https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31604-4/fulltext
- https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32466-1/fulltext
- https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32661-1/fulltext

You can also read more about these trials on the following international trial registration websites:

- For COV001, enter **NCT04324606** in the search field at www.clinicaltrials.gov
- For COV002, enter **NCT04400838** in the search field at www.clinicaltrials.gov
- For COV003, enter **ISRCTN89951424** in the search field at www.isrctn.com
- For COV005, enter **NCT04444674** in the search field at www.clinicaltrials.gov

Disclosures and acknowledgements

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Thank you

Clinical trial participants and their families belong to a large community of people who take part in clinical research around the world. They help researchers answer important health questions and find medical treatments for patients.

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