



## WHO Collaborating Centre for Vaccine Safety

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# COVID-19 vaccines and vaccination explained

Videos and podcast for health workers and the public that address common questions about COVID-19 vaccines

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## 1 General questions

### 1.1 How could vaccines be developed at record speed while still maintaining quality and safety?

**Version:** 2021-05-24

**Tags:** *safety, vaccine development, quality*

Before authorization, all vaccines have to go through preclinical and three phases of clinical trials. Although the vaccines are developed at record speed, no compromise is made on ensuring their safety and efficacy.

The following three things have made it possible for the vaccines to be developed so quickly while still being high quality and safe:

- First, by building on scientific and technological progress: Investments in new technologies over the last few years have made it possible for many labs around the world to work with new vaccine platforms, such as mRNA, for other infections. As soon as the necessary information about the virus that causes COVID-19 was available, scientists began designing the mRNA instructions which would allow the host cells to build the unique spike protein of SARS-CoV-2 into an mRNA vaccine.
- Second, by optimizing development and regulatory processes: by conducting trials in parallel rather than sequentially; by early communication and alignment on trial design; by exploring flexibilities such as regulatory review of data on a rolling basis (as soon as they are made available); by promoting regulatory reliance on generated evidence through collaborative approaches, transparency and sharing of information. This way, timelines for development were accelerated for these vaccines by overlapping phases one and two of clinical trials. Regulatory approval was accelerated by ensuring that regulatory agencies were ready and flexible to review each phase quickly so, if all went well, they could approve each next step soon after data from the previous step became available. Sharing of information among regulatory authorities is common practice and this also helps improve and speed up the regulatory process.
- And third, by investing in manufacturing despite the financial risk: Investments were made well before the end of the clinical trials so that it was possible to have millions of doses ready to deploy if the vaccine was licensed.

Rapid development of safe and effective vaccines made possible by:

- new technologies
- parallel clinical trial phases
- rolling regulatory reviews, collaboration and reliance
- up front investments in manufacturing

### 1.2 What are clinical trials and are they enough to prove a vaccine is safe?

**Version:** 2021-05-24

**Tags:** *vaccine safety, vaccine development, clinical trials*

Clinical trials are research studies performed in people to evaluate a medical, surgical, or behavioral intervention. They are the primary way that researchers find out if a new treatment or medical device, including a vaccine, is safe and effective in people.

Clinical trials advance through four phases to test a vaccine, find the appropriate dosage, and look for side effects. If, after the first three phases, researchers find a vaccine to be safe and effective, regulatory agencies can evaluate all the information and may approve it for clinical use while continuing to monitor its effects.

A Phase I trial tests an experimental vaccine on a small group of often healthy people (20 to 80) to judge its safety and side effects.

A Phase II trial uses more people (100 to 300). While the emphasis in Phase I is on safety, Phase II focuses on safety, immunogenicity (the immune response triggered by the vaccine), and efficacy (whether the vaccine prevents the disease). So, this phase gathers data on whether the vaccine generates an immune response in people in various categories of age, ethnicity and gender.

A Phase III trial gathers more information about efficacy and safety, studying different populations and different dosages. The number of subjects usually ranges from several hundred to thousands of people. Phase 3 trial is essential for registration and approval to market of a vaccine. If the regulatory authority agrees that the trial results are positive, it will approve the experimental vaccine.

Phase IV trials take place after approval of use. Effectiveness and safety are monitored in large, diverse populations. Sometimes, the side effects of a vaccine may not become clear until more people have taken it over a longer period of time.

All of these steps are standard in vaccine development, and all of them have been followed in developing COVID-19 vaccines that have received WHO Emergency Use Listing pre-qualification or authorization from stringent regulatory authorities.

Clinical trials:

- test for safety, side effects and efficacy
- involve 100s to 1000s of volunteers
- are evaluated against standard protocols.

### **1.3 How do mRNA vaccines, like Pfizer-BioNTech and Moderna COVID-19 vaccines, work?**

**Version:** 2021-05-24

**Tags:** *mRNA vaccines, how vaccines work, Comirnaty, mRNA-1273, Moderna, Pfizer-BioNTech*

COVID-19 mRNA vaccines instruct our cells to make a harmless piece of what is called the “spike protein.” The spike protein is found on the surface of the virus that causes COVID-19. COVID-19 mRNA vaccines are given in the upper arm muscle. Once the instructions (mRNA) are inside the muscle cells, the cells use them to make the protein piece. After the protein piece is made, the cell breaks down the instructions and gets rid of them. Next, the cell displays the protein piece on its surface. Our immune systems recognize that the protein doesn’t belong there and begin building an immune response by making antibodies, just like what would happen if we were naturally infected with the virus that causes COVID-19.

At the end of the process, our bodies have learned how to protect against future infection. The benefit of mRNA vaccines, like all vaccines, is that vaccinated people gain this protection without ever having to risk the serious consequences of getting sick with COVID-19.

The vaccine cannot give someone COVID-19, because mRNA vaccines do not use the live virus that causes COVID-19. They also do not affect or interact with our DNA in any way.

mRNA vaccines:

- instruct a person’s cells to make the COVID-19 spike protein, which triggers an immune response
- cannot give someone COVID-19
- cannot affect their DNA.

## 1.4 How do vector vaccines work?

**Version:** 2021-05-24

**Tags:** *vector vaccines, how vaccines work*

Viral vector-based vaccines differ from most conventional vaccines in that they don’t actually contain antigens, but rather use the body’s own cells to produce them. They do this by using a modified virus (the vector) to deliver genetic code for antigen, in the case of COVID-19 spike proteins found on the surface of the virus, into human cells. By infecting cells and instructing them to make large amounts of antigen, which then trigger an immune response, the vaccine mimics what happens during natural infection with certain pathogens - especially viruses. This has the advantage of triggering a strong cellular immune response by T cells as well the production of antibodies by B cells.

There are two main types of viral vector-based vaccines. Non-replicating vector vaccines are unable to make new viral particles; they only produce the vaccine antigen. Replicating vector vaccines also produce new viral particles in the cells they infect, which then go on to infect new cells that will also make the vaccine antigen. The COVID-19 viral vector vaccines use non-replicating viral vectors.

Once injected into the body, these vaccine viruses begin infecting our cells and inserting their genetic material – including the antigen gene – into the cells’ nuclei. Human cells manufacture the antigen as if it were one of their own proteins and this is presented on their surface alongside many other proteins. When the immune cells detect the foreign antigen, they mount an immune response against it.

This response includes antibody-producing B cells, as well as T cells, which seek out and destroy infected cells. T cells do this by examining the repertoire of proteins expressed on the surfaces of cells. They have

been trained to recognise the body's own proteins as 'self', so if they notice a foreign protein, such as an antigen from the pathogen, they will mount an immune response against the cell carrying it.

One challenge of this approach is that people may previously have been exposed to the virus vector and raise an immune response against it, reducing the effectiveness of the vaccine. Such "anti-vector immunity" also makes delivering a second dose of the vaccine challenging, assuming this is needed, unless this second dose is delivered using a different virus vector.

COVID-19 viral vector vaccines:

- use non-replicating viral vectors
- insert the vector's genetic material into the human cells
- these cells manufacture the antigen which is then detected by the immune system

### **1.5 How should we respond to claims that the mRNA vaccines could cause a genetic change and that we will see this in the coming decades?**

**Version:** 2021-06-29

**Tags:** *genetic change, genome integration, mRNA vaccines, how vaccines work, Comirnaty, mRNA-1273, Moderna, Pfizer-BioNTech*

The mRNA vaccine is injected into human cells, which then churn out copies of the virus's spike protein. This triggers an immune response inside our bodies. That immune response, which produces antibodies, is what protects us from getting infected if the real virus enters our bodies.

The RNA based vaccines are safe: to produce them involves making genetic material only, not the virus. They teach our cells how to make a protein—or even just a piece of a protein—that triggers an immune response inside our bodies. The mRNA of the vaccine cannot interfere with the human genetic system, a concern which has been raised by some. This is because humans do not have a mechanism to convert the RNA back into DNA. mRNA never enters the nucleus of the cell, which is where our DNA (genetic material) is kept. The cell breaks down and gets rid of the mRNA soon after it is finished using the instructions.

The fast and highly scalable mRNA manufacturing process enables rapid production of many vaccine doses, making it suitable for rapid vaccine development and pandemic vaccine supply.

mRNA is a new platform for vaccines but there is no reason why it should be any less safe than any of the other platforms. There are reasons, theoretically, why it could be safer than other existing platforms, for example, compared to vaccines using attenuated viruses (as there is no risk of the attenuated pathogen reverting to a dangerous form) or viral proteins (as there is no addition of adjuvants/immunostimulants, which can sometimes denature the viral proteins).

mRNA-based vaccines:

- teach our cells how to make a part of a protein
- the cell gets rid of the mRNA soon after
- cannot interfere with the human genetic system



## 1.6 What is a third phase of clinical trials? How many people are usually included? Any particular population groups?

**Version:** 2021-05-24

**Tags:** *vaccine development, clinical trials*

- Clinical trials are a type of research that studies new medical interventions and evaluates their effects on human health outcomes.
- Phase 3 studies involve large groups of volunteers (from several hundred to thousands) to investigate the efficacy of an intervention as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely. Phase 3 studies are often the step right before a new intervention is approved. Participation in any phase of clinical trials is voluntary.
- All COVID-19 vaccines, which received WHO Emergency Use Listing approval and/or stringent regulatory agencies' emergency authorization, have undergone phase 3 clinical trials. Information about various COVID-19 candidate vaccines currently undergoing phase 3 clinical trials is rapidly evolving and can be found on the WHO website.

## 1.8 How do inactivated vaccines work?

**Version:** 2021-05-24

**Tags:** *COVID-19 vaccines, inactivated vaccines, attenuated vaccines*

Whole virus vaccines use a weakened (attenuated) or deactivated form of a pathogen to trigger protective immunity to it. There are two types of whole virus vaccines. Live attenuated vaccines use a weakened form of the virus, which can still grow and replicate, but does not cause illness. Inactivated vaccines contain viruses whose genetic material has been destroyed by heat, chemicals or radiation so they cannot infect cells and replicate, but can still trigger an immune response.

Both are tried and tested vaccination strategies, which form the basis of many existing vaccines – including those for yellow fever and measles (live attenuated vaccines), or seasonal influenza and hepatitis A (inactivated vaccines). Bacterial attenuated vaccines also exist, such as the BCG vaccine for tuberculosis.

Both live attenuated and inactivated vaccines contain the whole or part of the disease-causing pathogen, but the type of immunity they trigger is slightly different.

Live attenuated vaccines are derived from viruses that have been weakened under laboratory conditions, so that when injected they will infect cells and replicate but cause no or only very mild disease. They may be unsuitable for people with compromised immune systems (e.g. those with HIV) and pregnant women though, because even a weakened virus may trigger disease in these individuals. Also, in very rare cases, live attenuated vaccines can revert to a more pathogenic form, triggering disease in vaccinated individuals or their contacts. This has been seen for vaccine derived poliovirus associated with the oral polio vaccine.

Because these vaccines are simply weakened versions of natural pathogens, the immune system responds as it would to any other cellular invader, mobilizing a range of defenses against it, including killer T cells (which identify and destroy infected cells), helper T cells (which support antibody production) and antibody-producing B cells (which target pathogens lurking elsewhere in the body, e.g. the blood). This immune response continues until the virus is cleared from the body, meaning there is plenty of time for memory cells against the virus to develop. Because of this, live attenuated vaccines can trigger an immune response which is almost as good as being exposed to the wild virus, but without falling ill.

Inactivated virus vaccines also contain the disease-causing virus, or parts of it, but their genetic material has been destroyed. For this reason, they are more stable than live attenuated vaccines, and they can be given to people with compromised immune systems. Even though their genetic material has been destroyed, inactivated viruses usually contain many proteins which the immune system can react to. But because they cannot infect cells, inactivated vaccines only stimulate antibody-mediated responses, and this response may be weaker and less long-lived. To overcome this problem, inactivated vaccines are often given alongside adjuvants (agents that stimulate the immune system) and booster doses may be required.

## 1.9 How do protein-based vaccines work?

**Version:** 2021-05-24

**Tags:** COVID-19 vaccines, protein vaccines

Rather than injecting a whole pathogen to trigger an immune response, subunit vaccines (sometimes called acellular vaccines) contain purified pieces of it, which have been specially selected for their ability to stimulate immune cells. Because these fragments are incapable of causing disease, subunit vaccines are considered very safe. There are several types: protein subunit vaccines contain specific isolated proteins from viral or bacterial pathogens; polysaccharide vaccines contain chains of sugar molecules (polysaccharides) found in the cell walls of some bacteria; conjugate subunit vaccines bind a polysaccharide chain to a carrier protein to try and boost the immune response. Only protein subunit vaccines are being developed against the virus that causes COVID-19.

Other subunit vaccines are already in widespread use. Examples include the hepatitis B and acellular pertussis vaccines (protein subunit), the pneumococcal polysaccharide vaccine, and the MenACWY vaccine, which contains polysaccharides from the surface of four types of the bacteria that causes meningococcal disease joined to diphtheria or tetanus toxoid (conjugate subunit).

Subunit vaccines contain fragments of protein and/or polysaccharide from the pathogen, which have been carefully studied to identify which combinations of these molecules are likely to produce a strong and effective immune response. By restricting the immune system's access to the pathogen in this way, the risk of side effects is minimized. Such vaccines are also relatively inexpensive and easy to produce, and more stable than those containing whole viruses or bacteria.

A downside of this precision is that the antigens used to elicit an immune response may lack molecular structures called pathogen-associated molecular patterns, which are common to a class of pathogen. These

structures can be read by immune cells and recognized as danger signals, so their absence may result in a weaker immune response. Also, because the antigens do not infect cells, subunit vaccines mainly only trigger antibody-mediated immune responses. Again, this means the immune response may be weaker than with other types of vaccines. To overcome this problem, subunit vaccines are sometimes delivered alongside adjuvants (agents that stimulate the immune system) and booster doses may be required.

### **1.10 How do I know which COVID-19 vaccine to choose or recommend?**

**Version:** 2021-05-24

**Tags:** COVID-19 vaccines, emergency use listing (EUL), Pfizer-BioNTech, BNT162b2, Moderna, mRNA-1273, Oxford-AstraZeneca, AZD1222, Janssen, Sinopharm, Sinovac

All COVID-19 vaccines that have received WHO Emergency Use Listing approval and/or stringent regulatory agencies' emergency authorization have fulfilled all regulatory approvals and standards. The WHO Strategic Advisory Group of Experts has issued recommendations on the use of several vaccines and will be reviewing more in the coming months. Slight differences on age upper and lower limits, characteristics and properties of the type of vaccine used (for example mRNA, vector, protein based, live attenuated) and individual co-morbidities (such as polysorbate allergic reactions or immunocompromised individuals) can lean the scale towards one type or other. Therefore, in very particular cases, a risk-assessment and clinical evaluation may need to be performed to determine the most suitable vaccine for specific vaccinees.

### **1.11 What tests or examinations should people get before COVID-19 vaccination?**

**Version:** 2021-05-24

In general, prior testing or examinations of people before COVID-19 vaccination, beyond the usual anamnesis and check-list of potential contraindications, is not recommended. Only in specific circumstances, when potential contraindications may exist, might specific tests be requested by your physician. A pregnancy test before vaccination is not indicated either

## 2 Vaccines and infection

### 2.1 Can people still get COVID-19 after being vaccinated with one or both doses and can they transmit the virus to others?

**Version:** 2021-06-29

**Tags:** mRNA vaccines, transmission, Comirnaty, mRNA-1273, Moderna, Pfizer-BioNTech, Oxford-AstraZeneca, AZD1222, Janssen, Sinopharm, Sinovac

In general, there are several factors to keep in mind:

- Two doses of the Pfizer-BioNTech, Moderna COVID-19, Oxford-AstraZeneca vaccine, Sinopharm, and Sinovac vaccines are recommended to achieve strong and lasting protection, while only one dose is needed for Janssen (Johnson & Johnson) vaccine.
- After receiving the first dose, it takes time for your body to develop protection. So, you can be infected with the virus in the days following vaccination before the vaccine has begun to provide protection.
- Or, you can be infected with the virus without knowing it in the days before you are vaccinated.
- The second dose (except for Janssen (Johnson & Johnson) vaccine which only needs one dose) is also important to help you build the strongest possible defense against developing COVID-19 disease, a more intense but also more mature immune response.
- Vaccination provides protection from COVID-19 disease. However, vaccination may not prevent you from becoming infected with the virus without any symptoms and then transmitting the virus on to others.

For all these reasons, until this pandemic is over it is very important that everyone who gets vaccinated still continues to take precautions like physical distancing, using a mask, cleaning hands and avoiding crowded places.

COVID-19 vaccines:

- are not 100% effective
- cannot prevent disease from prior infection
- are not effective immediately
- may require two doses for optimal protection

### 2.2 Can vaccines alone solve the pandemic?

**Version:** 2021-05-24

**Tags:** mRNA vaccines, public health vaccines, contention measures, physical distancing, mask wearing

The impact of COVID-19 vaccines on the pandemic will depend on several factors, including effectiveness of the vaccines and how many people eventually have access and choose to get vaccinated.

Vaccines will significantly improve the toolkit we have to fight this disease - but they cannot replace it. There is a big leap from vaccines to vaccination, and once we are on track to vaccinate all population groups in every country, we will be much closer to beating this virus. Until we are all protected through vaccination, we will need to continue using all the other tools at our disposal to protect ourselves and communities from this deadly virus.

COVID-19 vaccines:

- will save lives
- will reduce severe disease
- will be in short supply for some time
- are one vital tool among many to fight COVID-19

### 2.3 How much immunization will be needed to reach herd immunity?

**Version:** 2021-06-29

**Tags:** *herd immunity*

- In short: we do not know. To know this, we would need more data on how effective the vaccines are, and how they change the disease severity and transmissibility.
- Also, we should not rely on a single number. An overall high rate of vaccine coverage does not imply that we are all safe. We have seen examples of clusters of measles in subpopulations, even when the overall population had high rates of vaccine coverage.
- COVID-19 vaccines will significantly improve the toolkit we have to fight this disease - but not replace it. The potential impact of vaccines to help us end this pandemic will take time and can only be realized if the vast majority of people join the effort and are vaccinated.
- If we let our guard down too soon by not continuing to wash hands frequently, avoid crowded places and wear a mask where recommended, for example, the arrival of vaccines could open the door for wider community spread of the virus. Until we are all protected through vaccination, we will need to continue using all the other tools at our disposal to protect ourselves and communities from this deadly virus.

### 2.4 Given this virus' characteristics, is it realistic to expect a universal vaccine, instead of an annual one, like the flu vaccine?

**Version:** 2021-05-24

**Tags:** *universal vaccine, vaccine schedule, dosing*

- Influenza viruses are constantly changing and a person's immune protection from influenza vaccination declines over time, hence the need for annual shots for optimal protection.
- We know that SARS-CoV-2 viruses undergo evolution. Some new virus variants may be associated with higher transmissibility, disease severity, risk of reinfection, or a change in antigenic composition resulting in lower vaccine effectiveness.
- WHO and partners undertake a coordinated approach to monitoring and evaluation of variants and their impact on vaccine effectiveness.
- We need to do everything we can to reduce circulation of the virus and delay mutations that may reduce the efficacy of existing vaccines. It also seems increasingly clear that manufacturers will have, and are ready, to adjust to the COVID-19 viral evolution, taking into account the latest variants for future booster shots.

## **2.8 Can a patient with suspected or confirmed COVID-19 infection be vaccinated?**

**Version:** 2021-05-24

**Tags:** *suspicion or confirmed COVID-19 infection*

Vaccination of people with suspected COVID-19 symptoms or with COVID-19 recently confirmed by the laboratory should be postponed until fully recovered and once the isolation period is over.

Similarly, vaccination of people quarantined (for being contacts of a confirmed case) should be postponed until quarantine ends, but no virological or serological diagnostic test is required before vaccination. The reason is to avoid mistakenly attributing symptoms produced by the disease to the administration of the vaccine.

However, current evidence indicates that reinfection is exceptional subsequent to a natural infection. Accordingly, vaccination of people with PCR-confirmed SARS-CoV-2 infection may be delayed for 6 months. In the situation of limited vaccine supply, this will help to prioritize vaccination of people who have not yet had the disease.

In any case, vaccination of confirmed cases in isolation and from close contacts in quarantine should be postponed until the end of such measures.

## **2.13 What will happen if the vaccines are no longer effective against the new variants?**

**Version:** 2021-05-24

We know that SARS-CoV-2 viruses will continue to evolve. Some new virus variants may be associated with biological advantages eventually leading to higher transmissibility, disease severity, risk of reinfection, or a change in antigenic target of vaccines resulting in lower vaccine effectiveness. But this will not happen

suddenly, meaning that vaccine-induced protection is wide and includes both humoral and cellular response. The S protein -the antigen contained in the vaccines- is large, and thus, elicits a wide array of neutralizing antibodies. However, once a critical number of mutations accumulates in the receptor binding domain of the S protein, the neutralizing capacity of the vaccine may get compromised.

WHO and partners are undertaking a coordinated approach to monitor and evaluate variants and their impact on vaccine effectiveness.

We need to do everything we can to reduce circulation of the virus and delay mutations that may reduce the efficacy of existing vaccines. The virus only evolves through replication and thus, prevention of infection with all available means will reduce the chances that escape variants emerge. Nevertheless, it seems increasingly clear that manufacturers will have, and are ready, to adjust to the COVID-19 viral evolution, taking into account the latest variants for future vaccine developments or booster shots.

## **2.16 How can we ever get back to normal life if the virus mutates faster than scientists can adjust the vaccine?**

**Version:** 2021-05-24

The first priority is to save lives and control the epidemic. To consider the possibility of eliminating or eradicating COVID-19, several factors apply, including how long the vaccine's protection lasts and how effective vaccine programmes will be in achieving high coverage, among other factors.

Even the existence of a highly effective vaccine is no guarantee that we will be able to eliminate or eradicate the virus. One likely scenario in the context of an effective global vaccination programme is that the virus would become an endemic virus with a low level of threat.

In any case, vaccine manufacturers are ready to adapt their vaccines to the new variants. And importantly, the viruses only mutate if they can replicate, and for that they need to infect. Thus, preventing infection by all available means is the best we can do to protect ourselves but also to limit virus evolution.

## **2.17 What will happen if not enough people get vaccinated?**

**Version:** 2021-05-24

The impact of COVID-19 vaccines on the pandemic will depend on several factors, including effectiveness of the vaccines, country preparedness, and how many people get vaccinated.

Vaccines will significantly improve the toolkit we have to fight this disease - but not replace it. While we achieve the optimal vaccine coverage, all the other measures to prevent infection and transmission should be followed.

Importantly, the vaccination strategy recommended by WHO prioritizes vaccination of risk groups: residents of nursing homes and long-term care facilities and those who are at higher risk of severe illness from COVID-19.

Implementation of this strategy will have a great impact on reducing severe COVID-19 disease and deaths even though these groups represent a relatively small proportion of the global population.

## 3 Vaccine efficacy and duration of protection

### 3.1 How quickly does the vaccine work and how long does the protection last?

**Version:** 2021-06-29

**Tags:** *long-term protection, vaccine protection, duration, persistence*

The recommended schedule is two doses Pfizer-BioNTech's, Moderna's, AstraZeneca, Sinopharm and Sinovac COVID-19 vaccines; while one dose only is required for Janssen (Johnson & Johnson) vaccine. It is expected to take 7-14 days after the complete schedule to achieve optimal protection against COVID-19.

How long this protection will last is not yet known. However, it is estimated to be at least 8 months and probably around a year which is at least as long as the protection provided by having had the disease, but with the enormous advantage of not suffering the consequences of it thanks to vaccination. Also, it is expected that the immunity generated by the vaccine is higher than by the disease since the immune response to the vaccine is a more selective and powerful stimulation than the response with natural infection.

Vaccinated volunteers will be monitored in clinical trials during a period of 2 years so that we can collect the necessary information to answer these questions confidently on the characteristics of this protection.

COVID-19 vaccines:

- may require two doses for optimal protection
- are not immediately effective
- generate immunity of uncertain duration
- pose much less risk than natural infection.

### 3.3 Will vaccines be able to eliminate or eradicate COVID-19?

**Version:** 2021-05-24

**Tags:** *elimination, eradication*

- The first priority is to save lives and control the epidemic. To consider the possibility of eliminating or eradicating COVID-19, we would need to see how long the vaccines provide coverage for, and how effective vaccine programmes are in achieving high coverage.
- But even the existence of a highly effective vaccine is no guarantee that we will be able to eliminate or eradicate the virus. The likely scenario in the context of an effective global vaccination programme is that the virus would become an endemic virus with a low level of threat.

### 3.4 How quickly could COVID-19 vaccines stop the pandemic?



**Version:** 2021-05-24

**Tags:** *pandemic, eradication, elimination*

- The impact of COVID-19 vaccines on the pandemic will depend on several factors, including effectiveness of the vaccines, country preparedness, and how many people get vaccinated.
- Vaccines will significantly improve the toolkit we have to fight this disease - but not replace it. There is a big leap from vaccines to vaccination, and once we are on track to vaccinate billions of people across the world, we will be much closer to beating this virus. Until we are all protected through vaccination, we will need to continue using all the other tools at our disposal to protect ourselves and communities from this deadly virus.

### **3.5 If an individual did not develop high antibody titers after vaccination, should he/she be vaccinated again with another vaccine? Is it safe? What should be an interval between two vaccinations?**

**Version:** 2021-05-24

**Tags:** *antibody titres, vaccine failure, safety, intervals*

WHO does not recommend testing for antibodies after any routine or seasonal vaccination. Testing, if available, will significantly complicate the programme and increase its cost. It will also raise issues of the tests' quality and may trigger rumors about quality and safety of vaccines. In addition, the post-vaccination protective immunity of vaccines depends not only on availability and quantity of virus-neutralizing antibodies, but also on cellular immunity.

### **3.6 Am I protected before receiving the second dose of the vaccine?**

**Version:** 2021-06-29

**Tags:** *vaccine protection*

The recommended regimen differs per vaccine, but is in most cases two doses separated by a specified range of days or weeks. Optimal protection against COVID-19 is estimated to be effective after the prescribed number of days following the last recommended dose. For vaccines included in WHO Emergency Use Listing or received stringent authorities' emergency approval, we can assume that anyone is protected from 1-2 weeks after receiving the complete series of vaccination. However, as with any existing vaccine, vaccination with COVID-19 vaccines may not protect all vaccine recipients.

### **3.7 Why is a second dose of some COVID-19 vaccines needed?**

**Version:** 2021-05-24

Two doses of some COVID-19 vaccines are needed to ensure you are getting maximal protection. The extra protection offered by the second dose is very important in order to generate a strong immune memory, to increase the amount of antibodies but also its avidity and neutralization capacity. The second dose will not only reduce your chance of becoming very sick but also extend this protection for a longer period.

### **3.8 Will I need to get a booster shot next year to protect against any new variants?**

**Version:** 2021-05-24

**Tags:** *variants, scape variants, mutation, booster, duration, vaccination*

It is still too early to know whether it will be necessary to periodically receive COVID-19 vaccine booster doses. The data available so far indicate that the duration of protection can reach up to at least 12 months and the coverage against the currently circulating variants of the virus ranges from very high to acceptable.

At present, laboratory tests are still being carried out to determine the exact neutralizing capacity of the currently available vaccines against the new and future variants. At present, the most important aim is to vaccinate with the currently available vaccines as many people as possible.

If at some point booster shots are considered necessary according to the available evidence, the concrete information and recommendations will be communicated accordingly.

- It is not yet known whether COVID-19 vaccine booster doses will be needed to remain protected.

### **3.9 Is a COVID-19 booster shot needed?**

**Version:** 2021-09-20

The rationale for implementing booster doses should be guided by evidence on waning vaccine effectiveness, in particular a decline in protection against severe disease with the onset of breakthrough cases and reinfections, or due to the circulation of a variant of concern of SARS-COV-2 capable of evading the immune response induced by the current vaccine schedules.

According to the WHO, introducing booster doses (namely, a 3rd dose to people who have been vaccinated with 2 doses of the Pfizer-BioNTech, AstraZeneca, or Moderna vaccines, or a 2nd dose to people who have been vaccinated with 1 dose of the Janssen vaccine) should be firmly evidence-driven and targeted to the population groups in greatest need. To date (September 2021), the evidence remains limited and inconclusive on any widespread need for booster doses following a primary vaccination series <sup>1</sup>.

It is important to distinguish between booster doses and a limited fraction of the population who may need an additional dose for primary response. Emerging data suggests that immunocompromised people (e.g. those

<sup>1</sup><https://www.who.int/news/item/10-08-2021-interim-statement-on-covid-19-vaccine-booster-doses>

with solid organ transplants, hemodialysis) should receive one more dose in their primary vaccination series if their immune system has not responded sufficiently to the primary series, as can be the case with most other vaccines in these situations.

In the context of ongoing global vaccine supply constraints, administration of booster doses in highly vaccinated populations will exacerbate inequities by driving up demand and consuming scarce supply while priority populations in some countries, or subnational settings, have not yet received a primary vaccination series. At present, the global priority remains to provide a full vaccination course, which is highly effective in preventing serious disease, hospitalizations and death from currently circulating variants of the virus, to those who have not received any COVID-19 vaccine and to complete the vaccination schedule for those who have not done so yet.

WHO is carefully monitoring the situation and will continue to work closely with countries to obtain the data required to update or modify policy recommendations.

Summary:

- Evidence remains limited and inconclusive on any widespread need for booster doses.
- Immunocompromised people may need a third dose to achieve the same level of immunity as others in the general population.
- The limited supply of vaccines will save the most lives if made available to people who are at appreciable risk of serious disease and have not yet received any vaccine.

### 3.10 Are COVID-19 vaccines effective against new variants of concern of the virus?

**Version:** 2021-09-20

Vaccine efficacy against severe disease remains for all variants of concern, despite some drops in vaccine efficacy against symptomatic or asymptomatic disease.

All viruses, including SARS-CoV-2, the virus that causes COVID-19, change over time. Although most changes have little to no impact on the virus' properties, some may affect how easily it spreads, the associated disease severity, or the performance of vaccines, therapeutic medicines, diagnostic tools, or other public health and social measures.

Variants that pose an increased risk to global public health are defined by WHO as variants of interest (VOIs) or variants of concern (VOCs). A Variant of Interest can become a Variant of Concern if it proves to be a greater threat as demonstrated by international spread, greater disease severity, immune escape or ability to out-compete other strains. The classification of viruses enables the global community to prioritize monitoring and research, and ultimately to inform the ongoing response to the COVID-19 pandemic.

The following have been classified as variants of concern:

- The Alpha variant (B.1.1.7) is known to increase viral transmissibility and was previously the predominant variant in Europe. This variant has been described as having little escape from previous immunity.

- The Beta (B.1.351) variant is less easily neutralized by convalescent plasma obtained from patients infected with previous variants and preliminary evidence suggests reduced efficacy of some vaccines against mild to moderate disease.
- The Gamma (P.1) variant can cause severe disease even in people who have been previously infected, although this information needs to be expanded with further studies. Similarly, moderate escape from the immune response has been described with this variant.
- The Delta (B.1.617.2) variant has shown in animal studies, which have modelled pathogenesis in humans, higher viral loads and greater shedding. Reductions in vaccine neutralizing titres against new VOCs has been observed, although with the Delta variant these decreases are not as great as with some other variants. Immunology of vaccine protection is complex, and although protection may be predicted by antibody responses as measured directly after vaccination, we don't have an absolute correlate, we don't know the role of anamnestic response, the contribution of T-cells, or the vaccine platform dependence on the efficacy. For all these reasons we have to be very careful in the interpretation of the results of studies assessing the impact of a VOC on vaccine protection. However, randomized data are lacking for the Delta variant with most vaccines.

Rapid development of efficacious COVID-19 vaccines is one of the few true success stories from this pandemic. However, virus variants will continue to flourish as long as virus transmission is ongoing and may therefore threaten the progress made so far and prolong the pandemic. That's why continuous monitoring of the clinical, molecular and vaccine-related behaviour of the virus is a priority.

We must remain vigilant and not let down our guard down. While expanding vaccination and making vaccines available to those at highest risk we must continue public health and social measures, like wearing masks, frequently washing hands and social distancing where needed.

References:

- [https://www.nejm.org/doi/full/10.1056/NEJMSr2105280#article\\_references](https://www.nejm.org/doi/full/10.1056/NEJMSr2105280#article_references)
- [https://www.mscbs.gob.es/en/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/COVID19\\_Actualizacion\\_variantes\\_20210705.pdf](https://www.mscbs.gob.es/en/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/COVID19_Actualizacion_variantes_20210705.pdf)

Summary:

- Vaccines remain very effective in preventing severe disease, caused by circulating virus variants.
- Variants will continue to emerge as long as the virus circulates.
- Both vaccination and public health and social measures to suppress transmission are needed to control the pandemic.

### 3.11 How concerned should we be about other new variants, such as Lambda and Mu?

**Version:** 2021-09-20

Virus variants with genetic changes that are predicted or known to affect virus characteristics and which suggest an emerging risk to global public health are defined by WHO as variants of Interest (VOI). As of

September 2021, WHO has identified and is globally tracking 5 VOIs, of which the most recent additions are Lambda and Mu.

The Lambda (C.37) has been reported in more than 40 countries but most of the reports shared on the global GISAID database include fewer than ten sequences so far.

There are post-vaccination immunology studies (i.e. neutralizing antibody studies) but no vaccine effectiveness studies to date for this variant. The immunology studies include evaluations of Sinovac, Moderna, Pfizer-BioNTech and Janssen vaccines. It is too early to draw definitive conclusions, but there are some reductions in neutralization (less so for the mRNA vaccines than the others). However, the correlate of these reductions in the immune response and the clinical effectiveness is unknown.

WHO will continue to closely monitor the variant, but at present, it does not seem to be spreading rapidly. Even in Peru where it was first detected, reports from the Pan American Health Organization (PAHO) state that the Gamma variant is outcompeting the Lambda variant.

The Mu variant (B.1.621) was classified as a new variant of interest on 30 August 2021. The Mu variant has a constellation of mutations that indicate potential properties of immune escape. Preliminary data show a reduction in the neutralization capacity of convalescent and vaccinee sera, similar to that seen for the Beta variant. More studies are required to understand the phenotypic and clinical characteristics of this variant. Since its first identification in Colombia in January 2021, there have been a few sporadic reports of cases of the Mu variant and some larger outbreaks have been reported in South America and in Europe. The epidemiology of the Mu variant, particularly with the co-circulation of the Delta variant, is being closely monitored.

Summary:

- WHO is closely monitoring newly emerging virus variants as well as identified variants of interest and variants of concern.
- Lambda and Mu variants of interest show potential for reductions in neutralizing capacity, but it is too early to draw definitive conclusions.

### 3.12 To what extent can vaccines prevent people from getting infected with COVID-19?

**Version:** 2021-09-20

COVID-19 vaccines that have been granted Emergency Use Listing by WHO are highly effective at preventing severe disease, hospitalization and death. But post-introduction studies also indicate that these vaccines have demonstrated strong (but less) prevention of both symptomatic and asymptomatic infection. Several studies also show a reduction – about 50% – in risk of transmission to members of the same household, particularly for Pfizer-BioNTech and AstraZeneca vaccines. Accordingly, the vaccines likely reduce transmission, lowering the risk of disease in unvaccinated people, in addition to helping to stop the spread of variants.

This is supported by vaccine effectiveness against symptomatic disease and infections demonstrated by multiple studies with various vaccines, as well as by clinical trials and post-introduction observational studies, demonstrating vaccine effectiveness against asymptomatic infections for some vaccines, such as AstraZeneca, Janssen, Moderna, and Pfizer-BioNTech.



Additionally, some studies have demonstrated reductions in viral load if infected, and shortened duration of viral shedding for some vaccines, such as AstraZeneca, Moderna, Pfizer-BioNTech. For these three vaccines, there is evidence for direct reduction in household transmission, but more studies are needed to support conclusively their ability to reduce transmission.

Summary:

- COVID-19 vaccines are highly effective in preventing severe illness and deaths.
- They also reduce, but do not eliminate, the risk of infection and transmission.

## 4 Co-administration, dose-interval and interchangeability

### 4.3 Is there a maximum limit for the time interval between doses of the mRNA and Oxford-AstraZeneca vaccines?

**Version:** 2021-06-29

**Tags:** *vaccine intervals*

- The recommended interval between doses based on the currently available data from clinical trials is 21 to 28 days. WHO suggests that for mRNA vaccines the interval can be extended up to 12 weeks in exceptional circumstances in which countries that have not yet achieved high vaccine coverage rates in the high priority groups are experiencing a high incidence of COVID-19 cases combined with vaccine supply constraints. For the Oxford-AstraZeneca vaccine in light of the observation that two-dose efficacy and immunogenicity increase with a longer interdose interval, WHO recommends an interval of 8 to 12 weeks between the doses.
- There is no maximum limit to receive the second dose – as with other vaccines, to maximize protection it is best to get both doses within the recommended time interval. It is never too late to get the second dose if a delay cannot be avoided.

### 4.6 Are heterologous (mix and match) vaccine schedules against COVID-19 safe and effective?

**Version:** 2021-09-20

Heterologous vaccine schedules consist of the use of different vaccines (different brand or platform vaccine) as part of the same schedule. Vaccination with heterologous vaccines is a relatively common practice in vaccinology.

While there are currently no data for heterologous priming with other vaccine products, a large number of clinical studies of various vaccine combinations and schedules are currently ongoing.

There are currently limited data on the immunogenicity or efficacy of a ‘mix and match’ regimen. The COVID-19 vaccines with WHO Emergency Use Listing (EUL) have only been assessed as single product regimens. However, based on emerging evidence from conducted studies, the AstraZeneca recommendations have been modified to indicate that either of the mRNA vaccines (Pfizer-BioNTech or Moderna) can be used as a second dose following a first dose with the AstraZeneca vaccine, if a second dose of AstraZeneca vaccine is not available. Based on the basic principles of how vaccines work, WHO is of the view that the mix and match regimens are likely to work. However, we really need to carefully analyze the evidence in each of these vaccine combinations before any other recommendations can be made. WHO will review through its Strategic Advisory Group of Experts on Immunization (SAGE) these data as they become available, and update the recommendations accordingly.

Summary:

- There is currently limited data on the immunogenicity or efficacy of a ‘mix and match’ regimen.

## 5 Safety

### 5.2 How are we going to monitor vaccine safety?

**Version:** 2021-05-24

**Tags:** AEFIs, adverse events, vaccine safety, safety, monitor

Although modern vaccines are safe, the increased number of doses and opportunities for vaccination may lead to vaccine safety concerns. Assured quality vaccines are essential to effective immunization programmes.

Monitoring vaccine safety is a complex and shared responsibility. It can be carried out in many ways: large post-approval clinical trials, record linkage studies that track health care visits following vaccinations, or more targeted follow-up studies such as those using health diaries. However, the cornerstone of surveillance systems in most countries is active and passive reporting schemes that rely on the vigilance of health care providers and the reporting of individual cases of adverse reactions.

As part of safety monitoring we are also looking for vaccine safety “signals” – new events which have not been previously known to be caused by the vaccine. or a potential increase in frequency of a known event in recipients of the vaccine as compared to those who have not received it.

A standardized evaluation instrument known as the causality assessment form has been developed to establish causality. This form assesses different points: biological plausibility, the time elapsed between the vaccine administration and onset of the adverse event, and whether other factors could account for the adverse symptoms. The form concludes with a consensus assessment causality, a commentary about the assessment, and advice for further study or follow-up.

### 5.6 Are adverse effects observed significantly higher following the second dose as opposed to the first dose for the mRNA vaccines?

**Version:** 2021-06-29

**Tags:** AEFIs, adverse events, safety

Reactogenicity and adverse events were generally milder and less frequent in clinical trial participants in the older group ( $\geq 55$  years of age) compared with the younger group (18-55 years of age) and tended to increase after the second dose for the mRNA vaccines. Reactogenicity was mostly mild to moderate and short-lived after dosing for both adult age groups (median onset was 0-2 days after either dose for a median duration of 1 - 2 days).

### 5.8 Can COVID-19 vaccination affect fertility?



**Version:** 2021-05-24

**Tags:** *fertility, pregnancy*

There is no evidence that the immune response to coronaviruses has any impact on fertility in animals or humans, and there is no biological mechanism that has been shown to result in an impact on fertility. There is also no evidence to suggest that COVID-19 vaccines cause infertility. There are no licensed vaccines of any type that cause infertility.

WHO does not recommend pregnancy testing prior to vaccination. WHO does not recommend delaying pregnancy following vaccination.

### **5.9 Why did some EU countries temporarily suspend the use of the Oxford-AstraZeneca vaccine or specific vaccine batches?**

**Version:** 2021-06-29

As a precaution, national health authorities may sometimes temporarily suspend the use of a vaccine batch or a vaccination campaign in the course of the investigation of a severe adverse event or a cluster of adverse events following immunization. In most cases, the investigation will lead to a different explanation and a causal relation between the event and the vaccine will not be found.

Concretely, the detection of a series of thromboembolic cases coincidental in time with vaccination in Austria, in Denmark, or elsewhere in the first quarter of 2021 led to the opening of an investigation and a precautionary suspension of the use in a few countries of the vaccine.

The Pharmacovigilance Risk Assessment Committee of the European Medicines Agency (EMA) taking into account all available evidence and advice concluded that a causal relationship between vaccination with the Oxford-AstraZeneca (Vaxzevria) vaccine and very rare cases of thrombosis together with thrombocytopenia, sometimes accompanied by bleeding, is plausible.

The reported thromboses with thrombocytopenia include venous thrombosis, also in unusual sites such as cerebral venous sinus thrombosis (where blood clots in the brain's venous sinuses prevent blood from draining out of the brain) and splanchnic vein thrombosis (which involves one or more veins in the abdomen), as well as arterial thrombosis. Although such side effects are very rare, the reported case numbers exceeded what is seen in the general population. The majority of these cases occurred within 14 days after vaccination and mostly in women under 60 years of age; some cases had a fatal outcome.

Based on the available data, no specific risk factors were identified. The product information for Vaxzevria has been updated accordingly, and specifies thrombosis in combination with thrombocytopenia as a new very rare side effect (occurring in less than 1 in 10,000 persons).

One plausible explanation for the combination of blood clots and low blood platelets is an immune response, leading to a condition similar to one seen sometimes in patients treated with heparin (heparin induced thrombocytopenia).

Both EMA and the Global Advisory Committee on Vaccine Safety (GACVS) clearly state that the benefits of Vaxzevria in preventing COVID-19 continue to outweigh the risks; and there are no recommended changes regarding the use of this vaccine.

### 5.10 Under what circumstances should a COVID-19 vaccine be recalled?

**Version:** 2021-05-24

Although every vaccine goes through three phases of clinical testing before being used, vaccines or vaccine lots (specific batches) can be withdrawn or recalled after being deployed to countries. Vaccine recalls or withdrawals due to safety issues are very rare.

Recalls are usually initiated voluntarily by a vaccine manufacturer, if as part of their continuous monitoring of the quality of vaccine production they find an irregularity affecting a specific batch of vaccines. Sometimes, health authorities may temporarily suspend or withdraw a specific vaccine batch as a precaution while they investigate a severe acute event following immunization or a cluster of adverse events.

In most cases, a person who had been vaccinated with a vaccine from a recalled batch will not need to do anything after the vaccine is recalled. If the vaccine recall is related to a possible safety concern, people who were vaccinated should talk to their doctor if they have any concerns that they may be having a reaction. If a vaccine recall is due to low vaccine effectiveness, people who were vaccinated with a vaccine from that lot or batch might need to be vaccinated again to ensure they are protected against the disease.

### 5.11 What happens if a serious side effect is reported?

**Version:** 2021-05-24

As with any vaccine, it is essential to closely monitor the safety and effectiveness of COVID-19 vaccines as they are delivered. If a problem is reported following vaccination, health authorities will perform a thorough investigation to assess if the reported side effect is causally related to the vaccination.

During these investigations, it is extremely rare that health problems are found to be caused by the vaccine itself. Adverse events are most often found to be coincidental in time with the vaccination and may be entirely unrelated to vaccination. Sometimes they are related to how the vaccine has been stored, transported, or administered.

In the very rare cases where a genuine adverse reaction is suspected or there is an accumulation of reported side effects, the vaccine (or the specific vaccine batch) may be suspended from use. Further investigations will take place to determine what exactly caused the event, and corrective measures will be put in place. WHO works with vaccine manufacturers, health officials and other partners to continuously monitor any safety concerns and potential side effects on an ongoing basis.

### 5.13 Why were children not included in clinical trials?

**Version:** 2021-05-24

The burden of COVID-19 is significantly lower in children as compared to adults, and their role in the transmission of the diseases seems to be less relevant than in other respiratory infections. For these reasons, the development of the vaccines targeting the adult population was the first priority. Now we have learned vaccines are safe and efficacious in adult populations, down-age de-escalation trials will be performed.

Children are a unique population with distinct developmental and physiological differences from adults. Clinical trials in children are essential to develop age-specific, empirically-verified therapies and interventions to determine and improve the best medical treatment available. However, children are an exceptional population about which there are specific ethical and clinical concerns. The vulnerable nature of this population must be considered when balancing the risks of research with the need for safe and validated therapies.

#### **5.14 What do WHO and EMA mean when they say the benefits outweigh the risks of vaccination?**

**Version:** 2021-05-24

WHO and EMA have assessed available data and determined that the benefits of vaccination, namely the tremendous potential to prevent infections and reduce deaths across the world, outweigh the possible but very small risk of suffering any serious adverse event following vaccination.

Concretely in the case of severe thromboembolic events and thrombocytopenia association, irrespective of the existence or not of a causal link with vaccination, the noted frequency is less than 1 per 100.000 doses administered to date<sup>2</sup>.

#### **5.15 Some countries have begun vaccinating teenagers – is this safe, and if so, why aren't all countries lowering the minimum age for vaccination?**

**Version:** 2021-06-29

**Tags:** *adolescents, safety, age, vaccination*

On 10 May 2021, the U.S. Food and Drug Administration extended the emergency use authorization (EUA) for Pfizer-BioNTech COVID-19 vaccine for the prevention of COVID-19 to adolescents aged 12 to 15 years. More recently, the European Medicines Agency has mirrored this recommendation.

Safety and efficacy data available to support EUA in adolescents from 12 years of age include 2260 participants aged 12 to 15 years enrolled in a randomized placebo-controlled clinical trial in the United States<sup>3</sup>. Of these, 1131 adolescent participants received the vaccine and 1129 received a saline placebo. More than half of the participants were followed for safety for at least two months after the second dose.

<sup>2</sup>[https://www.who.int/news/item/16-04-2021-global-advisory-committee-on-vaccine-safety-\(gacvs\)-review-of-latest-evidence-of-rare-adverse-blood-coagulation-events-with-astrazeneca-covid-19-vaccine-\(vaxzevria-and-covishield\)](https://www.who.int/news/item/16-04-2021-global-advisory-committee-on-vaccine-safety-(gacvs)-review-of-latest-evidence-of-rare-adverse-blood-coagulation-events-with-astrazeneca-covid-19-vaccine-(vaxzevria-and-covishield))

<sup>3</sup>Frenck RW Jr et al. Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. N Engl J Med. 2021 May 27. doi: 10.1056/NEJMoa2107456. Epub ahead of print. PMID: 34043894.

The most frequently reported side effects in adolescent clinical trial participants, which generally lasted 1 to 3 days, were injection-site pain, tiredness, headache, chills, muscle pain, fever, and joint pain. With the exception of injection site pain, more adolescents reported these side effects after the second dose than after the first dose. Also, the observed vaccine efficacy was 100% (95% confidence interval, 75.3 to 100).

Having obtained the approval for the vaccine to be used in this age group from 12 to 15 years does not mean a change in the priority groups for vaccination. The priority groups for vaccination according to WHO are those who are most at risk of developing severe disease, including older adults, people with co-morbidities and health workers who are at high risk of contracting the disease and potentially spreading the virus to their patients. The BNT162b2 should be used in adolescents age 12-15 years with comorbidities that put them at significantly higher risk of serious COVID-19 disease, alongside other high-risk groups.

We need to keep in mind that we need a global effort to solve this pandemic and that the priority target groups for vaccination are the same across the world.

- WHO, the FDA and EMA have approved use of Pfizer-BioNTech COVID-19 vaccine for adolescents aged 12-15.
- Prioritization of groups at high risk of contracting or suffering serious illness from COVID-19 should not change.

## 5.16 Could a lump in the neck after receiving Pfizer's or Moderna's mRNA vaccine against COVID-19 be linked to the vaccine?

**Version:** 2021-05-24

**Tags:** *safety, lump, lymphadenopathy, mRNA vaccines, vaccine adverse effects*

The occurrence of lymphadenopathy following vaccination has been described as a rare adverse reaction ( $\geq 1/1000$  to  $< 1/100$ ) following mRNA vaccines. In general, vaccination-related lymphadenopathies are usually in axillary localization, being supraclavicular localization much more infrequent.

An incorrect vaccine administration technique could be influencing the occurrence of supraclavicular lymphadenopathies, as it has been observed that vaccine drainage tends to ascend to the supraclavicular nodes when the vaccine is administered in the area near the shoulder and not in the center of the deltoid triangle<sup>4</sup>.

Supraclavicular lymphadenopathies appearing up to 10 days after vaccination are inflammatory and tend to resolve spontaneously after 7 days from the date of their appearance in most of the cases. No complementary tests (blood tests, biopsies or computed axial tomography) are necessary, nor do they require any specific pharmacological or physical treatment. In case of acute onset of supraclavicular lymphadenopathy after vaccination with a mRNA based COVID-19 vaccine, this possibility of transient and benign self-limited vaccine-related adverse reaction should be considered.

<sup>4</sup>Fernández-Prada M, Rivero-Calle I, Calvache-González A, Martínón-Torres F. Acute onset supraclavicular lymphadenopathy coinciding with intramuscular mRNA vaccination against COVID-19 may be related to vaccine injection technique, Spain, January and February 2021. *Euro Surveill.* 2021 Mar;26(10):2100193. doi: 10.2807/1560-7917.ES.2021.26.10.2100193. PMID: 33706861; PMCID: PMC7953532.

- The occurrence of lymphadenopathy following vaccination has been described as a rare adverse reaction ( $\geq 1/1000$  to  $< 1/100$ ) following mRNA vaccines.

### **5.17 Do mRNA vaccines cause myocarditis as an adverse reaction?**

**Version:** 2021-09-20

Fever, headache, muscle pain and pain at the injection site remain the most common adverse reactions identified following COVID-19 vaccination. However, cases of myocarditis/pericarditis (inflammation of the heart muscle) and pericarditis (inflammation of the membrane surrounding the heart) following COVID-19 vaccination have been reported. While they can lead to serious illness, they are often mild and respond well to conservative treatment. They have typically occurred within days of vaccination, more commonly among younger males and more often following the second dose of COVID-19 mRNA vaccines. It is important to remember that the frequency of myocarditis/pericarditis following natural infection of SARS-COV-2 is much (about six times) higher than in vaccinated subjects.

To date, due to the limited number of cases as well as their favorable prognosis, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency, COVID-19 subcommittee of the WHO Global Advisory Committee on Vaccine Safety (GACVS) and the US Advisory Committee on Immunization Practices (ACIP) have concluded that the benefits of mRNA COVID-19 vaccines in reducing hospitalizations and deaths due to COVID-19 infections continue to outweigh the risks of myocarditis and pericarditis even among young people.

Clinicians should be aware of the rare risk of myocarditis and pericarditis with mRNA vaccines and those most likely to be affected. They should be alert to presentations such as acute chest pain, shortness of breath and palpitations that may be suggestive of myocarditis after vaccination, especially in adolescent or young males. All health professionals are encouraged to report all events of myocarditis and other adverse events observed with these and other vaccines. The GACVS COVID-19 subcommittee will continue to review the safety data from all COVID-19 vaccines and update any advice as necessary.

#### References:

- [COVID-19 subcommittee of the WHO Global Advisory Committee on Vaccine Safety \(GACVS\): updated guidance regarding myocarditis and pericarditis reported with COVID-19 mRNA vaccines](#)
- <https://www.aemps.gob.es/informa/boletines-aemps/boletin-fv/2021-boletin-fv/6o-informe-de-farmacovigilancia-sobre-vacunas-covid-19/#comirnaty>
- <https://www.aemps.gob.es/informa/notasinformativas/medicamentososohumano-3/seguridad-1/2021-seguridad-1/vacunas-frente-a-la-covid-19-actualizacion-sobre-la-evaluacion-de-miocarditis-pericarditis/>

#### Summary:

- Rare cases of myocarditis/pericarditis and pericarditis following COVID-19 vaccination have been reported. They are usually mild and respond well to treatment.
- The reported cases have typically occurred within days of vaccination, more commonly among younger males and more often following the second dose of COVID-19 mRNA vaccines.



- The benefits of mRNA COVID-19 vaccines in reducing hospitalizations and deaths due to COVID-19 infections continue to outweigh the risks of myocarditis and pericarditis even among young people.

## 6 Precautions and contraindications

### 6.2 Can people with allergies be vaccinated with mRNA vaccines?

**Version:** 2021-05-24

**Tags:** allergy, allergic reactions, anaphylaxis, mRNA vaccines, contraindications, precautions, safety

These vaccines are contraindicated in the following cases:

- Severe allergic reaction (eg. anaphylaxis) after a previous dose of a COVID-19 vaccine or due to any of the vaccine components.
- Immediate allergic reaction (any severity) after a previous dose of a COVID-19 vaccine or due to any of the vaccine components (including polyethylene glycol).
- In the case of Moderna vaccine: immediate allergic reaction (any severity) to polysorbate.

A history of any immediate allergic reaction to any other vaccine or injectable therapy (i.e. intramuscular, intravenous, or subcutaneous vaccines or therapies) is considered as a precaution but not a contraindication to vaccination. For such persons, a risk assessment should be conducted to determine the type and severity of reaction and the reliability of the information. Such individuals may still receive vaccination, but they should be counselled about the risks of developing a severe allergic reaction and the risks should be weighed against the benefits of vaccination. Such persons should be observed for 30 minutes after vaccination in health care settings where anaphylaxis can be immediately treated.

Food, contact, or seasonal allergies are not considered reasons for precaution. The vial stoppers are not made with natural rubber latex, and there is no contraindication or precaution to vaccination for persons with a latex allergy. In addition, mRNA vaccines do not contain eggs or gelatin, and there is no contraindication or precaution to vaccination for persons with allergies to these substances.

People with a family history of allergies or anaphylaxis can be vaccinated.

Contraindications for mRNA COVID-19 vaccination are:

- severe allergic reaction to a previous dose
- immediate allergic reaction to a previous dose
- (for Moderna vaccine) immediate allergic reaction to polysorbate

### 6.3 Should a person who experienced an allergic reaction to the 1st dose of COVID-19 vaccine receive a second dose?

**Version:** 2021-05-24

**Tags:** allergy, allergic reactions, anaphylaxis, contraindications, precautions, safety

In general, persons with an immediate allergic reaction to the first dose should not receive additional doses of the same vaccine. For the purposes of this guidance, an immediate allergic reaction to a vaccine or medication is defined as any hypersensitivity-related signs or symptoms, such as anaphylaxis, urticaria, angioedema, respiratory distress (e.g. wheezing, stridor), that occur within hours of administration. However, subject to individual risk-benefit assessment, specialist services for immunization may allow COVID-19 vaccines to be provided under close medical supervision if it is the only available option for persons at high risk of severe COVID-19.

As a small number of anaphylactic reactions have also been reported in vaccinees without a history of severe allergic reactions, WHO recommends that COVID-19 vaccines should be administered only in settings where anaphylaxis can be treated. Until more data and insights are available with regard to severe allergic reactions to COVID-19 vaccination, all vaccinees should be observed for at least 15 minutes after vaccination.

- Immediate or severe reactions after a previous dose are contraindication.
- Administer COVID-19 vaccines only where anaphylaxis can be treated.
- Observe all vaccinees at least 15 minutes after vaccination.

## 6.4 Can immunocompromised people be vaccinated?

**Version:** 2021-06-29

**Tags:** *immunocompromised, immunosuppressive therapy, contraindications, precautions, safety, effectiveness*

Vaccines are considered safe in this population group, although the immune response may be lower than usual in the general population.

Immunocompromised people (including people living with HIV, regardless of the CD4+ count) or people receiving immunosuppressive therapy (including corticosteroids that can be used in the COVID-19 treatment) may have an increased risk of suffering severe COVID-19. Although there are no definitive data on safety and effectiveness of vaccines in these people, they may receive the vaccine if they are part of a group recommended for vaccination and they do not have contraindications for vaccination. On the other hand, until more information is available, no discontinuation of immunosuppressive therapy is recommended.

In the case of vaccines that do not contain live viruses, such as mRNA vaccines and vector vaccines, convalescent plasma or monoclonal antibodies used for COVID-19 treatment would not contraindicate vaccine reception, although to prevent interference with the immune response to the vaccine, it is advisable to delay vaccination at least 90 days.

## 6.5 Is there a maximum age for vaccination?

**Version:** 2021-06-29



**Tags:** *contraindications, precautions, age, vaccines, Comirnaty, mRNA vaccines, vector vaccines, AstraZeneca, Janssen, elderly, frail population*

Vaccination is recommended for older persons without an upper age limit. Persons above the age of 85 years and very frail older persons were not included in the clinical trials. However, the data obtained in a large subset of older people with and without comorbidities suggest that the benefits of vaccination outweigh the potential risks. For very frail older persons with a life expectancy anticipated to be less than 3 months, an individual risk–benefit assessment will need to be conducted.

- Age recommendations differ per vaccine.
- No maximum age has been recommended by producers.

## **6.8 Can breastfeeding women be vaccinated?**

**Version:** 2021-05-24

**Tags:** *breastfeeding, contraindications, precautions, safety, mRNA vaccines, Comirnaty, mRNA-1273, Moderna, Pfizer-BioNTech, vector vaccines, AstraZeneca, Janssen, Sinopharm, Sinovac*

It is not known whether current vaccines are excreted in human milk. However, considering the importance of breastfeeding and the accumulated experience with other inactivated vaccines: breastfeeding should not be interrupted in women who receive the mRNA or vector vaccines, and vaccination should be offered to lactating woman the same as to other adults.

## **6.9 When should a woman planning to get pregnant be vaccinated?**

**Version:** 2021-05-24

**Tags:** *pregnancy*

Pregnant women are at higher risk of severe COVID-19 compared with women of childbearing age who are not pregnant, and COVID-19 has been associated with an increased risk of preterm birth.

WHO does not recommend delaying pregnancy following vaccination nor pregnancy testing prior to vaccination.

## **6.10 Are there any chronic hematological diseases that would be a contraindication for COVID-19 vaccination?**

**Version:** 2021-05-24

Restriction of the use of the vaccine in patients with risk factors for thrombosis is not indicated at this time.

Very rare (less than one in 100.000 vaccinated to date) cases of serious thrombosis associated with thrombocytopenia, sometimes with bleeding and disseminated intravascular coagulation, have been reported including several cases of cerebral venous sinus thrombosis. Most have occurred within 14 days after vaccination. Given the aggregation of cases, the fact that it is a very rare entity and a plausible temporal relationship, EMA has established that these rare cases may be a possible adverse reaction to the vaccine and are object of special attention by physicians. The underlying cause and mechanisms involved in such events is yet to be established. However, we do know that COVID-19 disease is associated, by itself, with an increase in thrombotic events and that such events have been documented in patients with asymptomatic COVID-19 disease<sup>5 6 7</sup>; we also have seen similar conditions would be triggered by an immune response against platelets in heparin-induced thrombocytopenia, resulting in aggregation, thrombosis, and platelet penia. So again, even if this thrombocytopenic thrombotic phenomenon were of an immune nature, restriction of the use of the vaccine in patients with risk factors for thrombosis is not indicated at this time.

A vaccinated person, regardless of the vaccine used, should continue the usual treatment he or she may receive (including any antithrombotic treatment); and no administration of any antithrombotic as a preventive measure, as part of the COVID-19 vaccination, should be considered.

### **6.11 I have had a blood clot in the past or I have a family history of blood clotting. Should I still get vaccinated against COVID-19?**

**Version:** 2021-05-24

You can still get any of the licensed COVID-19 vaccines, including the Oxford-AstraZeneca COVID-19 Vaccine if you have recently had a blood clot, take blood thinning medicine or have a family history of blood clotting. You do not need to cancel or delay vaccination. You should also not receive any antiplatelet or anticoagulant treatment in the days before or after vaccination if it was not previously prescribed by your physician because of your illness. A vaccinated person, regardless of the vaccine used, should continue the usual treatment he or she may receive (including any antithrombotic treatment).

Like everyone who gets the vaccine, you should be aware of the symptoms to look out for and seek urgent medical care if you have any signs or symptoms of blood clotting, such as shortness of breath, chest pain, leg swelling, persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches and blurred vision after vaccination, or who experience skin bruising (petechia) beyond the site of vaccination after a few days, should seek prompt medical attention.

<sup>5</sup>Malas MB, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, Clary B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. *EClinicalMedicine*. 2020;29:100639. <https://doi.org/10.1016/j.eclinm.2020.100639>

<sup>6</sup>Mondal, S., Quintili, A.L., Karamchandani, K. et al. Thromboembolic disease in COVID-19 patients: A brief narrative review. *J intensive care* 8, 70 (2020). <https://doi.org/10.1186/s40560-020-00483-y>

<sup>7</sup>Merrill JT, Erkan D, Winakur J, James JA. Emerging evidence of a COVID-19 thrombotic syndrome has treatment implications. *Nat Rev Rheumatol*2020;16:581-9. doi:10.1038/s41584-020-0474-5. <https://www.nature.com/articles/s41584-020-0474-5>



## **6.12 I am using a hormonal contraception method (oral contraceptives, subdermal implant, skin patches or vaginal ring): should I discontinue this treatment before or after receiving AstraZeneca vaccines?**

**Version:** 2021-05-24

Although it is true that hormonal contraceptives have an associated risk of thrombotic events, withdrawal of these methods is not recommended at any stage of the COVID-19 vaccination process with any of the currently available vaccines.

## 7 Access, allocation and deployment

### 7.1 Who should receive COVID-19 vaccination first in the situation of limited vaccine supply?

**Version:** 2021-05-24

**Tags:** vaccines, prioritization, transmission, high-risk groups

Not everyone can be vaccinated at once, especially in the initial stages when vaccine supplies are limited. Recommendations for how to allocate these limited supplies are based on three goals: to decrease death and serious disease as much as possible, to keep the most critical essential health services functioning; and eventually to reduce the overall disease burden so that further disruption of social and economic functions can be avoided.

This is why healthcare personnel, people aged 60 years and older and residents of long-term care facilities should be offered the first doses of COVID-19 vaccines.

People aged 60 years and older, as well as residents of long-term care facilities, are prioritized because they are at high risk of developing severe disease, of being hospitalized, and of dying from COVID-19.

Healthcare personnel continue to be on the front line of the fight against this deadly pandemic. By providing critical care to those who are or might be infected with the virus that causes COVID-19, healthcare personnel have a high risk of being exposed to and getting sick with COVID-19.

When healthcare personnel get sick with COVID-19, they are also not able to work and provide key services for patients. Healthcare personnel who get COVID-19 can also spread the virus to those they are caring for—including hospitalized patients and residents of long-term care facilities. Many of these individuals may have underlying health conditions that put them at risk for severe COVID-19 illness. Prioritization of medical workers is also supported by the principle of reciprocity; they play critical roles in the COVID-19 response, working under intense and challenging conditions, putting not only themselves but also potentially their households at higher risk for the sake of others.

- Supply of COVID-19 vaccines is limited.
- Need to ensure their most rational and effective use.
- The immediate aim is to reduce deaths and severe disease and maintain essential services.
- First doses must therefore go to those at highest risk: health workers and older adults.

### 7.2 To stop the pandemic, wouldn't it be better to give the first available doses to those most at risk of transmitting the disease rather than to those most at risk of serious infection?

**Version:** 2021-05-24

Not everyone can be vaccinated at once. Recommendations for how to allocate these vaccines are based on three goals: to decrease death and serious disease as much as possible, to keep the most critical essential



health services functioning; and eventually to reduce the overall disease burden so that further disruption of social and economic functions can be avoided.

This is why healthcare personnel, people aged 60 years and older and residents of long-term care facilities should be offered the first doses of COVID-19 vaccines.

In addition, our knowledge on the actual capability to prevent transmission of the currently available vaccines is still limited.

## 8 Regulatory approvals

### 8.1 What does emergency use authorization mean?

**Version:** 2021-06-29

**Tags:** regulatory agencies, emergency use authorization, EUA, WHO prequalification

WHO's Emergency Use Listing (EUL) is a procedure for assessing and listing vaccines with the ultimate aim of making them more readily available to people affected by a public health emergency. It opens the door for countries that do not have robust regulatory systems of their own and need to rely on WHO's robust review process to expedite their own regulatory approval processes to import and administer the vaccine. It also enables UNICEF and the Pan-American Health Organization to procure the vaccine for distribution to countries in need.

WHO has already listed several COVID-19 vaccines for emergency use. WHO and partners are working night and day to evaluate other vaccines that have reached safety and efficacy standards. We encourage even more developers to come forward for review and assessment. It's vitally important that we secure the critical supply needed to serve all countries around the world and stem the pandemic.

WHO Emergency Use Listing:

- aims to expedite access to safe and quality assured vaccines
- enables UN procurement and supports Member States decisions
- involves stringent assessment of clinical trial, manufacturing and regulatory data

### 8.3 Some COVID-19 vaccines in use have not been approved by WHO. Are they safe and effective?

**Version:** 2021-06-29

**Tags:** regulatory agencies, WHO, emergency use authorization

WHO has approved several COVID-19 vaccines for Emergency Use Listing so far. Other vaccines that have not yet been approved by WHO may be under evaluation or may have not been submitted for this specific assessment. Not having completed evaluation and approval by WHO does not necessarily mean that a vaccine is not safe or efficacious, but it precludes its specific recommendation by WHO and its distribution through UN agencies.

WHO Emergency Use Listing enables accelerated access to COVID-19 vaccines for countries seeking to protect healthcare workers and at-risk populations. It is a prerequisite for vaccine supply through the COVAX Facility and it allows countries to expedite their own regulatory approval to import and administer COVID-19 vaccines.

- WHO grants Emergency Use Listing (EUL) to vaccines that it has thoroughly evaluated for safety and efficacy.
- Nationally approved vaccines that do not (yet) have WHO EUL may also be safe and efficacious but WHO has not been able to assess this yet.

## 8.4 Can children be vaccinated against COVID-19?

**Version:** 2021-09-20

On 5 May 2021, Canada became the first country in the world to approve COVID-19 vaccine for emergency use in children aged 12–15 years. After that, the US Food and Drug Administration and European Medicines Agency also approved the Pfizer-BioNTech and Moderna COVID-19 vaccines for adolescents from 12 years of age. There are ongoing studies in children younger than 12 years of age aiming to assess the safety and immunogenicity of COVID-19 vaccines and the optimal dosage/schedule.

Currently mRNA COVID-19 vaccines can be administered safely and efficaciously in adolescents from 12 years of age. WHO's Strategic Advisory Group of Experts (SAGE) has concluded that the Pfizer/BioNTech and Moderna vaccines are suitable for use by people aged 12 and above. Children aged between 12 and 15 who are at high risk may be offered this vaccine alongside other priority groups for vaccination.

While children are less likely to suffer from the direct impact of COVID-19 morbidity and mortality compared with other age groups, they do have a small risk of developing severe illness and complications from COVID-19. More evidence on the short and long term effects of SARS-CoV-2 infection in children as well as the safety profile of vaccines in children and the contribution of vaccination of children to disease transmission control is needed to fully understand the benefits and risks of vaccinating children. In the meantime, vaccination of healthy children should not change the prioritization of well established high-risk groups, anywhere in the world.

References: \* [https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(21\)00384-4/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00384-4/fulltext)

Summary:

- Children aged 12 to 15 who are at high risk may be offered mRNA COVID-19 vaccines alongside other priority groups for vaccination.
- More evidence on the effects of SARS CoV-2 infection in children as well as the safety profile of vaccines in children are needed to fully understand the benefits and risks of vaccinating children.



## **10 mRNA-1273 – Moderna vaccine**



## 11 Vaxzevria – Oxford-AstraZeneca vaccine

### 11.1 How does Vaxzevria, the Oxford-AstraZeneca COVID-19 vaccine work?

**Version:** 2021-05-24

**Tags:** COVID-19 vaccines, vector vaccines, Oxford-AstraZeneca, ChAdOx1

The Oxford-AstraZeneca vaccine is made from a virus (ChAdOx1), which is a weakened version of a common cold virus (adenovirus) that causes infections in chimpanzees. The adenovirus has been genetically changed so that it is impossible for it to cause infection in humans.

Genetic material has been added to this weakened adenovirus, allowing it to make spike proteins from the COVID-19 coronavirus (SARS-CoV-2). These proteins are found on the surface of SARS-CoV-2, the virus that causes COVID-19. They play an essential role in the infection pathway of the SARS-CoV-2 virus.

Vaccinating with this weakened adenovirus, trains the body to recognize SARS-CoV-2 virus and develop an immune response to its spike protein that helps to prevent disease if SARS-CoV-2 virus later enters the body.

COVID-19 vector vaccines:

- are made from a weakened, harmless virus that mimics the COVID-19 virus
- train the body to recognize the spike protein of SARS-CoV-2 virus
- prevent COVID-19 disease

### 11.4 Is Vaxzevria, the Oxford-AstraZeneca vaccine, safe?

**Version:** 2021-05-24

The European Medicines Agency (EMA) has recommended granting a conditional marketing authorisation for Oxford-AstraZeneca COVID-19 Vaccine to prevent coronavirus disease 2019 (COVID-19) in people from 18 years of age and older with no upper age limit. WHO has similarly listed the Oxford-AstraZeneca vaccine for emergency use.

Recently, rare cases of severe thrombosis and thrombocytopenia, some presenting as mesenteric vein or cerebral vein/cerebral venous sinus thrombosis, have been reported in persons who had recently received COVID-19 Oxford-AstraZeneca vaccine, mostly occurring within 14 days after vaccination. The majority of reports involved women under 60, although some of this may reflect greater exposure of such individuals due to targeting of particular populations for vaccine campaigns in different Member States.

The Pharmacovigilance Risk Assessment Committee of the European Medicines Agency taking into account all available evidence and advice concluded that a causal relationship between vaccination with Vaxzevria and very rare cases of thrombosis together with thrombocytopenia, sometimes accompanied by bleeding, is plausible.

The reported thromboses with thrombocytopenia include venous thrombosis, also in unusual sites such as cerebral venous sinus thrombosis (where blood clots in the brain's venous sinuses prevent blood from draining out of the brain) and splanchnic vein thrombosis (which involves one or more veins in the abdomen), as well as arterial thrombosis. Although such side effects are very rare, the reported case numbers exceeded what is seen in the general population.

Based on the available data, no specific risk factors were identified. The product information for Vaxzevria has been updated accordingly, and specifies thrombosis in combination with thrombocytopenia as a new very rare side effect (occurring in less than 1 in 10,000 persons).

Both EMA and GAVCS clearly state that after reviewing the data, the benefits of Vaxzevria in preventing COVID-19 continue to outweigh the risks; and there are no recommended changes regarding the use of this vaccine.<sup>8</sup>

Health care personnel should be alert to the signs and symptoms of thromboembolism and or thrombocytopenia. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches and blurred vision after vaccination, or who experience skin bruising (petechia) beyond the site of vaccination after a few days, should seek prompt medical attention.

### **11.5 Why have some countries not resumed AstraZeneca (Vaxzevria) vaccination campaigns despite WHO, EMA and other regulatory authorities recommending its continued use following investigations of potential side effects?**

**Version:** 2021-05-24

The action taken by some countries to temporarily pause or restrict to certain age groups the use of Oxford-AstraZeneca vaccine (Vaxzevria) has been based mainly on isolated reports -less than 1 in 100.000 doses administered to date- of cerebral sinus vein or mesenteric vein thrombosis occurring together with thrombocytopenia (lowered platelets) shortly after vaccination, a syndrome now called Thrombosis with Thrombocytopenia Syndrome (TTS). This type of thrombosis can also occur naturally in the absence of vaccination, and it can occur in association with COVID-19 disease. This rare adverse event has been linked to the vaccine by EMA and investigation continues. However, EMA concludes that the benefit-risk balance of the vaccine remains positive and vaccination should continue normally.

One in five hospitalized patients with COVID-19 develop thrombosis. On the other hand, the results of the recent AstraZeneca US Phase III trial of Vaxzevria<sup>9</sup> confirms 76% (CI: 68% to 82%) vaccine efficacy against symptomatic COVID-19 and 100% efficacy against severe or critical disease and hospitalization.

<sup>8</sup><https://www.ema.europa.eu/en/news/covid-19-vaccine-astrazeneca-benefits-still-outweigh-risks-despite-possible-link-rare-blood-clots>

<sup>9</sup>Clinicaltrials.gov. A Phase III Randomized, Double-blind, Placebo-controlled Multicenter Study in Adults to Determine the Safety, Efficacy, and Immunogenicity of AZD1222, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19. [Online] Available at: <https://clinicaltrials.gov/ct2/show/NCT04516746?term=NCT04516746&draw=2&rank=1>. Last accessed: March 2021.

Most of the countries have resumed vaccination and continue to use Oxford-AstraZeneca vaccine. Some countries have restricted its use to specific age groups or decided they need more time to continue investigations. These countries may also have access to other COVID-19 vaccines to continue vaccination.

### **11.6 Were there any underlying conditions or risk factors in the individuals who suffered from Thrombosis with Thrombocytopenia Syndrome (TTS) after AstraZeneca (Vaxzevria) vaccination?**

**Version:** 2021-05-24

No underlying conditions in the individuals who suffered from Thrombosis with Thrombocytopenia Syndrome (TTS) after AstraZeneca vaccination were found, and no underlying conditions contraindicate or pose a special precaution to AstraZeneca vaccination to date. Rare clotting problems like cerebral venous thrombosis are more common among pregnant or postpartum women. Other risk factors for such events include recently starting oral contraceptives, sepsis, cancer, and having an underlying condition that increases the tendency to form clots such as Factor V Leiden deficiency or lupus. However, none of these conditions is associated with thrombocytopenia; these conditions have not been identified as a risk factor for TTS, therefore none of them represents a contraindication for vaccination against COVID-19.

### **11.7 What are the early signals of potential blood clotting events following immunization that people should be aware of?**

**Version:** 2021-05-24

As of April 2021, more than 25 million doses of the AstraZeneca vaccine have been administered in Europe and more than 27 million doses of the Covishield vaccine (AstraZeneca vaccine licensed by Serum Institute of India) have been administered in India. In very rare cases, unusual blood clots associated with thrombocytopenia have been reported within 4-20 of getting the vaccine.

It is important to be aware of the following symptoms if they should occur following vaccination: shortness of breath, chest pain, leg swelling or persistent abdominal pain. Additionally, anyone with neurological symptoms including severe or persistent headaches or blurred vision after vaccination, or who experiences skin bruising (petechia) beyond the site of vaccination after a few days, should seek prompt medical attention.

### **11.8 I have received the AstraZeneca vaccine and I have a headache, should I urgently consult my doctor?**

**Version:** 2021-05-24

Headache is one of the most frequent symptoms that can appear after the administration of any vaccine, not only COVID-19 vaccines. Tiredness, myalgia and shivering are also common. In general, these symptoms subside in the first 24-48 hours after vaccination with or without specific treatment, so immediate consultation with a physician is not necessary.

If the headache is intense, it persists for more than 3 days, increases with movement or when lying down and does not subside with usual analgesics, or if it is accompanied by vascular lesions on the skin (petechiae, hematomas), it should be a reason for urgent consultation at the nearest health center.

### **11.10 If AstraZeneca (Vaxzevria) vaccination can potentially be linked to rare blood clotting events, is it better to wait to be vaccinated against COVID-19 until another vaccine is available?**

**Version:** 2021-05-24

It is safer to accept without delay any vaccine that is offered by national authorities to gain protection from COVID-19 as early as possible.

Before authorizing a vaccine for use in a country the national regulatory authority carefully assesses it for quality, efficacy and safety. AstraZeneca has been reviewed and authorized by WHO, the European Medicines Agency (EMA) and many countries around the world. WHO and EMA also recently reviewed the available safety data following 25 million doses administered in Europe and concluded again that the benefits of the vaccine outweigh any potential risks of side effects, and that the vaccine offers high protection against severe COVID-19 disease.

Global supplies of vaccines against COVID-19 are yet limited and not sufficient to meet demand. In most if not all countries at this time, it is not possible to offer people a choice of COVID-19 vaccine.

### **11.11 What is Vaccine-Induced Thrombosis with Thrombocytopenia Syndrome (TTS)?**

**Version:** 2021-05-24

The United Kingdom, European Union, and Scandinavian countries have reported rare cases of cerebral sinus vein thrombosis (CSVT) and thrombocytopenia in patients who received the AstraZeneca COVID-19 vaccine in the previous 4 to 20 days<sup>10</sup>. It is rare, occurring in anywhere from 1 in every 125,000 to 1 in 1 million people<sup>11</sup><sup>12</sup>; and most of the cases have occurred in women under age 60, although these countries used most of their initial AstraZeneca vaccine supply in this particular age group and may therefore be overrepresented.

The biological mechanism for this syndrome of TTS is still being investigated. At this stage, a 'platform specific' mechanism related to the adenovirus-vectored vaccines is not certain but cannot be excluded.

One plausible explanation for the combination of blood clots and low blood platelets is an immune response, leading to a condition similar to one seen sometimes in patients treated with heparin (heparin induced

<sup>10</sup>Pai M, Grill A, Ivers N, et al. Vaccine induced prothrombotic immune thrombocytopenia VIPIT following AstraZeneca COVID-19 vaccination. Science Briefs of the Ontario COVID-19 Science Advisory Table. 2021;1(17). <https://doi.org/10.47326/ocsat.2021.02.17.1.0>

<sup>11</sup>PINHO AC. COVID-19 Vaccine AstraZeneca: benefits still outweigh the risks despite possible link to rare blood clots with low platelets. European Medicines Agency. Published March 18, 2021. Accessed March 31, 2021. <https://www.ema.europa.eu/en/news/covid-19-vaccine-astrazeneca-benefits-still-outweigh-risks-despite-possible-link-rare-blood-clots>

<sup>12</sup>Updated GTH statement on vaccination with the AstraZeneca COVID-19 vaccine, as of March 22, 2021. Published March 18, 2021. Accessed March 31, 2021. [https://gth-online.org/wp-content/uploads/2021/03/GTH\\_Stellungnahme\\_AstraZeneca\\_3\\_24\\_2021.pdf](https://gth-online.org/wp-content/uploads/2021/03/GTH_Stellungnahme_AstraZeneca_3_24_2021.pdf)



thrombocytopenia). However, since TTS is immune-mediated, an individual with a thrombophilia, a family history of blood clots, or a personal history of arterial or venous clots would likely not be at increased risk of TTS. Accordingly, there are no new contraindications to receiving the AstraZeneca vaccine.

In case TTS is suspected, the recommended treatment might be similar to that of HIT, this is, intravenous gammaglobulin and non-heparin derived anticoagulants.

## 12 Janssen COVID-19 Vaccine (Johnson & Johnson)

### 12.1 How does the Janssen COVID-19 vaccine work?

**Version:** 2021-06-29

COVID-19 Vaccine Janssen is a vector vaccine made up of another virus (an adenovirus type 26) that has been modified to contain the gene for making the SARS-CoV-2 spike protein (glycoprotein (Ad26.COVS-2-S)). This is a protein on the SARS-CoV-2 virus which it uses to enter the body's cells.

Adenovirus type 26 is a nonreplicative human adenovirus. The virus in the vaccine does not cause disease. Vaccinating with this weakened adenovirus trains the body to recognize SARS-CoV-2 virus and develop an immune response against its spike protein that helps to prevent disease if SARS-CoV-2 virus later enters the body.

The adenovirus passes the SARS-CoV-2 gene into the vaccinated person's cells. The cells can then use the gene to produce the spike protein. The person's immune system will recognise the spike protein as foreign and produce antibodies and activate T cells to target it. Later, if the person comes into contact with SARS-CoV-2 virus, the person's immune system will recognise the spike protein on the virus and be ready to defend the body against it.

Janssen COVID-19 vaccine:

- contains a weakened adenovirus that carries the gene to produce the SARS-CoV-2 spike protein
- trains the vaccinated person's body to fight off the SARS-CoV-2 virus

### 12.2 How many doses of Janssen COVID-19 vaccine do I need to be protected?

**Version:** 2021-06-29

Unlike the other vaccines so far approved by the European Medicines Agency, the Janssen COVID-19 vaccine requires only one single 0.5 ml dose to be administered intramuscularly. The maximum protective efficacy is reached from 14 days after vaccination.

There should be a minimum interval of 14 days between the administration of this vaccine and any other vaccine against other health conditions. This recommendation may be amended as data on co-administration with other vaccines become available.

- Janssen COVID-19 vaccine requires only one dose.

### 12.3 Is Janssen COVID-19 vaccine safe and efficacious to use in people 18 years and older?

**Version:** 2021-06-29

A Phase 3, multicenter, randomized, double-blind, placebo-controlled, study (COV3001) of this vaccine was conducted in the United States, South Africa and South America to evaluate the efficacy, safety, and

immunogenicity of a single dose of the vaccine. A total of 21,895 adults received COVID-19 Vaccine Janssen, and 21,888 adults received placebo. Individuals were followed for a median of 58 days. Efficacy against severe COVID-19 at 14 days was 76.7% and at 28 days 85.4%.

- In the phase 3 clinical trial, Janssen COVID-19 vaccine was 76% efficacious against severe COVID-19.

## 12.4 What are the most frequent adverse reactions associated with the use of Janssen COVID-19 vaccine?

**Version:** 2021-06-29

The most common side effects with COVID-19 vaccine Janssen in the clinical trials were pain at the injection site, headache, tiredness, muscle pain and nausea. They were mild or moderate and resolved within 1 or 2 days after vaccination. They affected more than 1 in 10 people.

Rare side effects (that occurred in fewer than 1 in 1,000 people) are hypersensitivity (allergy) and itchy rash. Thrombosis (formation of blood clots in the blood vessels) in combination with thrombocytopenia (low levels of blood platelets) occurred in fewer than 1 in 10,000 people who received the vaccine in the trial.

Allergic reactions, including one case of anaphylaxis (severe allergic reaction), have occurred in people receiving the vaccine. As for all vaccines, COVID-19 Vaccine Janssen should be given under close supervision with appropriate medical treatment available.

- Common side effects following vaccination with Janssen COVID-19 are mild.
- More serious side effects are possible but rare.

## 12.5 Is Janssen COVID-19 vaccine associated with blood clotting events?

**Version:** 2021-06-29

By April 13, 8 cases of thrombotic events associated with thrombocytopenia had been detected among 7,000,000 doses of vaccine administered in the United States. All cases occurred in persons younger than 60 years of age within three weeks of vaccination, mostly in women. Based on currently available evidence, no specific risk factors associated with these blood clotting events have been detected. The European Medicines Agency scientific evaluation continues to support the use of the vaccine, based on its positive risk-benefit ratio. One plausible explanation for the combination of blood clots and low platelets is an abnormal immune response, leading to a condition similar to that sometimes seen in patients treated with heparin called heparin-induced thrombocytopenia, also similar to the one described after vaccination with Vaxzevria (AstraZeneca) vaccine.

- Thrombosis (formation of blood clots in the blood vessels) in combination with thrombocytopenia (low levels of blood platelets) following vaccination with Janssen COVID-19 vaccine is possible but very rare.

## **12.7 Does Janssen COVID-19 vaccine work against new variants of SARS-CoV-2 virus?**

**Version:** 2021-06-29

The WHO Strategic Advisory Group of Experts on Immunization (SAGE) has reviewed all available data on the performance of the vaccine in the settings of the variants of concern. In clinical trials this vaccine has been tested against a variety of SARS-CoV-2 virus variants, including B.1.351 (first identified in South Africa) and P.2 (first identified in Brazil), and found to be effective.

SAGE currently recommends using this vaccine, according to the WHO Prioritization Roadmap, even if variants of concern are present in a country. As new data becomes available, WHO will update recommendations accordingly.

- The available data suggest that COVID-19 Janssen will reduce the risk of severe COVID-19 disease, including in the context of currently identified COVID-19 variants.