English

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covid19infovaccines.com

COVID-19 vaccines and vaccination explained

Videos and podcasts for health workers and the public to 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?

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 efifcacy; before authorization, and all vaccines have to go through preclinical and three phases of clinical trials.

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 & reliance.
- Up front investments in manufacturing.

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

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.

Cinical 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's Comirnaty and Moderna's mRNA-1273 vaccines, work?

TAGS: mRNA, vaccines, how vaccines work, Comirnaty, mRNA1273, 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?

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?

TAGS: genetic change, genome integration, mRNA vaccines, how vaccines work, Comirnaty, mRNA1273, 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.

In the SAGE background document, the fast and highly scalable mRNA manufacturing enable 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?

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.

1.7 Which vaccines against COVID should be used?

TAGS: COVID vaccines, emergency use listing (EUL), Pfizer/BioNTech, BNT162b2, Moderna, mRNA-1273, Oxford-Astra-Zeneca, AZD1222 vaccine

- WHO has granted emergency use listing (EUL) for the Pfizer/BioNTech (BNT162b2) and Oxford/Astra Zeneca AZD1222 vaccines.
- WHO is assessing other vaccines currently and is expecting additional dossiers to be submitted from other vaccine producers in future.
- WHO approval is a stamp of quality, safety, efficacy and manufacturing quality. However, national regulatory authorities do have the mandate and the jurisdiction to make these assessments and decisions for use within their own countries.
- Regulatory authorities and independent experts in many countries around the world are reviewing the available data to determine the best possible policy and programmatic approach for their circumstances. WHO's guidance is supporting them in these deliberations.
- Based on WHO EUL approval or stringent regulatory agencies' emergency authorization, the WHO Strategic Advisory Group of Experts has developed recommendations on the use of Pfizer/BioNTech (BNT162b2), Moderna's mRNA-1273 and Oxford-AstraZeneca AZD1222 vaccines.

1.8 How do inactivated vaccines work?

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?

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?

TAGS: COVID vaccines, emergency use listing (EUL), Pfizer/BioNTech, BNT162b2, Moderna, mRNA-1273, Oxford-Astra-Zeneca, AZD1222 vaccine

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 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 comorbidities (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?

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. Vaccine 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?

TAGS: mRNA, vaccines, transmission, Comirnaty, mRNA1273, Moderna, Pfizer-BioNTech

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

- Two doses of the Pfizer–BioNTech or Moderna COVID-19 vaccine are recommended to achieve strong and lasting protection.

- 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 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, we don't know yet whether vaccination will also 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?

TAGS: mRNA, 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?

Keywords-tags: herd immunity

- In short: we do not know. To know this, we would need to know 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 Giving this virus' characteristics, is it realistic to expect a universal vaccine, instead of an annual one, like the flu vaccine?

Keywords-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.

2.5 Has the new variant of SARS-CoV-2 first detected in the United Kingdom been proved to be more dangerous or contagious than other SARS-COV-2 variants?

Keywords-tags: UK variant, SARS-COV-2 variants, mutations

Since many variants are emerging continuously everywhere, it is not possible to measure how transmissible a given variant is with respect to others that have already circulated worldwide or that are circulating today. On the other hand, of the thousands of variants that are emerging on the SARS-CoV-2 genomes, it is reasonable to expect that some variants can eventually achieve biological advantages and be more transmissible, or resistant to treatments or vaccines. Moreover, explanations other than genetic advantages, such as the randomness associated with the model of infection (e.g. super-spreaders events) and social behaviour, can also explain the predominance of a particular strain.

Preliminary analyses have shown a potentially slightly reduced vaccine effectiveness of Oxford-AstraZeneca vaccine against the variant of SARS-CoV-2 first detected in the United Kingdom. Preliminary analyses from the South Africa Phase 1/2a trial indicate minimal protection against mild and moderate disease caused by the variant of SARS-Cov-2 first identified in South Africa (B.1.351) based on a small sample size, but this study was not designed to assess efficacy against severe COVID-19. Similarly, different in vitro studies are assessing the capability of these new strains to evade the vaccine induced immune response of other vaccines, showing a reduced neutralization capacity against the B.1.351 variant. These preliminary findings highlight the urgent need for a coordinated approach for monitoring and evaluation of variants and their impact on vaccine effectiveness.

A recent study[1] using a variety of statistical and dynamic modeling approaches, found that the variant is 43 to 90% more transmissible than the predecessor lineage but saw no clear evidence for a change in disease severity, although enhanced transmission will lead to higher incidence and more hospital admissions.

1 Davies NG, Abbott S, Barnard RC, Jarvis CI, Kucharski AJ, Munday JD, Pearson CAB, Russell TW, Tully DC, Washburne AD, Wenseleers T, Gimma A, Waites W, Wong KLM, van Zandvoort K, Silverman JD; CMMID COVID-19 Working Group; COVID-19 Genomics UK (COG-UK) Consortium, Diaz-Ordaz K, Keogh R, Eggo RM, Funk

2.6 Do available vaccines protect against the new SARS-CoV-2 variants?

Keywords-tags: UK variant, SARS-COV-2 variants, Brazil variant, mutations

- The COVID-19 vaccine developed by Pfizer and BioNTech appears to protect against the SARS-COV-2 variant first identified in the United Kingdom (B.1.1.7), according to results of a new study recently published in Science[2]. The study found that a lab-made version of the virus – with all the mutations resembling the B.1.1.7 variant – was neutralized by the volunteer's immune system.
- Another study from Pfizer showed the vaccine to be effective against a key mutation called N501Y, which is present in both the B.1.1.7 variant and the new strain that has emerged in South Africa (B.1.351)[3]. However, another study – which has not yet been peer-reviewed – found that the B.1.351 variant contains mutations that may be resistant to immunity from previous coronavirus infection, which doesn't necessarily mean it could be resistant to vaccines[4].
- Scientists have seen three key mutations in the spike receptor binding domain (RBD) on the variant identified in Manaus, north Brazil (P.1, lineage B.1.1.28). These mutations largely mirror some of those that experts are concerned about in the B.1.351 variant. Although there have been some indications that vaccines will work on these variants, experts say it is still too early to be sure if they will be effective against the new mutations seen on the P1 variant identified in north Brazil.
- In a study published on a preprint server[5], Moderna says its COVID-19 vaccine continues to protect against two of the major mutant strains of SARS-CoV-2 circulating around the world: the B.1.1.7 and the B.1.351. Blood from people vaccinated with the Moderna's mRNA-1273 vaccine did not generate as many immune antibodies against B.1.351 as they did against the non-mutant virus—in fact, this blood contained about six-fold lower levels of antibodies. However, this study states that the level of antibodies still remains high enough to provide sufficient protection against COVID-19 disease.
- Preliminary analyses have shown a potentially slightly reduced vaccine effectiveness of Oxford-AstraZeneca vaccine against the B.1.1.7. Preliminary analyses from the South Africa Phase 1/2a trial (COV005) indicate minimal protection against mild and moderate disease based on a small sample size. However, this study was not designed to assess efficacy against severe COVID-19. These preliminary findings highlight the urgent need for a coordinated approach for monitoring and evaluation on variants and their impact on vaccine effectiveness.
- The Phase III randomized controlled trial[6] of the Janssen COVID-19 vaccine was conducted on three continents during a time of high COVID-19 incidence while viral variants were emerging. In South Africa, 95% of circulating virus was the B.1.351 variant and in Brazil, 69% of the circulating virus was a P1/P2 variant at the time of the trial. Although the Janssen vaccine appeared to be less effective against mild and moderate disease in these regions, it remained strongly protective against severe disease, hospitalizations and deaths. The vaccine efficacy estimates for the Janssen COVID-19 vaccine were 66% for symptomatic laboratory-confirmed COVID-19, 74% for asymptomatic seroconversion, 93% for hospitalization due to COVID-19, and 75% for all-cause death. No deaths due to COVID-19 were identified among vaccine recipients, and 7 deaths due to COVID-19 were identified among placebo recipients.

2 Muik A, Wallisch AK, Sänger B, Swanson KA, Mühl J, Chen W, Cai H, Maurus D, Sarkar R, Türeci Ö, Dormitzer PR, Şahin U. Neutralization of SARS-CoV-2 lineage B.1.1.7 pseudovirus by BNT162b2 vaccine-elicited human sera. Science. 2021 Jan 29:eabg6105. doi: 10.1126/science.abg6105. Epub ahead of print. PMID: 33514629.

3 Xuping Xie, Jing Zou, Camila R. Fontes-Garfias, Hongjie Xia, Kena A. Swanson, Mark Cutler, David Cooper, Vineet D. Menachery, Scott Weaver, Philip R. Dormitzer, Pei-Yong Shi. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. doi: https://doi.org/10.1101/2021.01.07.425740

4 Constantinos Kurt Wibmer, Frances Ayres, Tandile Hermanus, Mashudu Madzivhandila, Prudence Kgagudi, Bronwen E. Lambson, Marion Vermeulen, Karin van den Berg, Theresa Rossouw, Michael Boswell, Veronica Ueckermann, Susan Meiring, Anne von Gottberg, Cheryl Cohen, Lynn Morris, Jinal N. Bhiman, Penny L. Moore. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma doi: https://doi.org/10.1101/2021.01.18.427166

5 mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants. Kai Wu, Anne P. Werner, Juan I. Moliva, Matthew Koch, Angela Choi, Guillaume B.E. Stewart-Jones, Hamilton Bennett, Seyhan Boyoglu-Barnum, Wei Shi, View ORCID ProfileBarney S Graham, Andrea Carfi, Kizzmekia S. Corbett, Robert A. Seder, Darin K. Edwards doi: https://doi.org/10.1101/2021.01.25.427948

6 https://clinicaltrials.gov/ct2/show/NCT04505722

2.7 What do the new SARS-CoV-2 variants means for vaccine efficacy?

Keywords-tags: SARS-COV-2 variants, variants, efficacy

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.

Preliminary analyses have shown a potentially slightly reduced vaccine effectiveness of Oxford-AstraZeneca vaccine against the variant of SARS-CoV-2 first detected in the United Kingdom. Preliminary analyses from the South Africa Phase 1/2a trial indicate minimal protection against mild and moderate disease based on a small sample size. This study was not designed to assess efficacy against severe COVID-19. These preliminary findings highlight the urgent need for a coordinated approach for monitoring and evaluation on variants and their impact on vaccine effectiveness.

2.8 Can a patient with suspicion or confirmed COVID-19 infection be vaccinated?

Keywords-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.

2.9 Should contacts of COVID cases be quarantined if they have been vaccinated against COVID before the exposure?

Keywords-tags: COVID contacts, COVID exposure, contraindications, precautions

Individual clinical protection against COVID19 after completing vaccination can be assumed after completion of the vaccination schedule, which may differ depending on the specific vaccine used. In the case of Pfizer/BioNTech (BNT162b2) vaccine, vaccine efficacy is measured from 7 days after the second dose. Before that time and/or in partially vaccinated individuals, we should not assume the person is fully protected, although some degree of protection exists. We can assume that anyone having received 2 doses is protected from 1 week after receiving the second dose, but as with any existing vaccine, vaccination with COVID-19 vaccines may not protect all vaccine recipients.

There is no available data on the role COVID-19 mRNA Vaccine BNT162b2 in terms of prevention of catching the infection and transmitting it, despite being fully vaccinated. For that reason, although we can assume clinical protection for anyone who has been correctly vaccinated, and we might expect a certain reduction in the risk of transmission in a vaccinated person, based on existing knowledge, the rest of currently recommended infection control measures and guidance should be followed in case of exposure, irrespective of the vaccination status.

2.10 Is COVID-19 vaccination safe for those who had COVID-19 disease in the past?

Keywords-tags: safety, COVID disease

People with current acute or prolonged COVID-19 symptoms should defer COVID-19 vaccination until they have recovered or at least four weeks after onset of symptoms or four weeks from the first PCR positive specimen in those who are asymptomatic. This is to avoid wrongly attributing any new symptom or the progression of symptoms to the vaccine.

There is no safety concerns from clinical trials of vaccines which have received WHO Emergency Use Listing approval and stringent regulatory authorities' emergency authorizations so far, after vaccinating hundreds of people with a past history of COVID-19 infection, or with detectable COVID-19 antibodies. People who have had COVID-19 disease (whether confirmed or suspected) can still receive COVID-19 vaccination. However, there is not enough data from the trials to conclude how well the vaccines will work for people who have already had COVID-19. It is not known how long antibodies made in response to natural infection persist and whether immunization could offer more protection. Therefore, if antibodies have already been made to the disease following natural infection, receiving a COVID-19 vaccine would be expected to boost any pre-existing antibodies.

2.11 Is herd protection against COVID-19 possible?

In principle yes, but that will depend on several factors that are not yet known. To safely achieve herd protection immunity against COVID-19, a substantial proportion of a population would need to be vaccinated or get immunized after natural exposure, lowering the chances of the virus to spread in the whole population. The main aim of working towards herd protection is to keep vulnerable groups who cannot get vaccinated or respond to the vaccine (e.g. due to health conditions like allergic reactions to the vaccine, immunodepression) safe and protected from the disease. The percentage of people who need to be immune in order to achieve herd immunity varies with each disease. For example, herd immunity against measles requires about 95% of a population to be vaccinated. The remaining 5% will be protected by the fact that measles will not spread among those who are vaccinated. For polio, the threshold is about 80%.

The proportion of the population that must be vaccinated against COVID-19 to achieve herd immunity is not known yet. It depends on several factors, including the capability of the virus to transmit, the so-called reproducibility index, which is estimated to be between 2 and 4 for SARS-COV-2. This means that 1 infected person will pass the disease on to an average of 2-4 susceptible people. The vaccine's capability to reduce transmission of the virus is also essential, and we don't know yet to what degree available COVID-19 vaccines will impact transmission. Currently It is estimated that 70-80% of the population should be immunized to achieve herd protection against COVID-19. This is an important area of research and this estimate will likely vary according to the virus, the community, the vaccine, the populations prioritized for vaccination, and other factors. We are still learning about immunity to COVID-19. Most people who are infected with COVID-19 develop an immune response within the first few weeks, but we don't know how strong or lasting that immune response is, nor how it affects SARSCoV-2 transmission.

Achieving herd protection with safe and effective vaccines makes diseases rarer and saves lives. But the primary purpose of the COVID-19 vaccination programme is not to achieve herd immunity. WHO has prioritized vaccinating risk groups first, with the aim of achieving a rapid reduction in hospitalizations and COVID-19 fatalities in nursing homes, long-term care facilities and among others at higher risk of severe illness from COVID-19.

2.12 What is the latest evidence on vaccine effectiveness against the new variants of the virus?

Multiple SARS-CoV-2 variants are circulating globally. Several new variants emerged in the fall of 2020, most notably:

- In the United Kingdom (UK), known as B.1.1.7
- In South Africa known as 20H/501Y.V2 or B.1.351
- In Brazil, known as P.1.

Recently published and pre-print studies show that antibodies generated after vaccination with Moderna vaccine generally produce neutralizing antibodies against the B.1.1.7[7] variant, but show a reduction in this capacity compared to that observed against the original strain first identified in Wuhan, China[8]. Studies carried out with the Comirnaty® vaccine (BNT162b2)[9,10,11] show that the serum of vaccinated people neutralizes strains with the N501Y mutation, present in the B.1.1.7 and B.1.351 variants[3,4] and that the neutralizing antibody titer against this variant is lower and similar to that of convalescent patients[3].

In addition, and importantly, data obtained from the large-scale use of these vaccines through vaccination programmes show that, in Israel, with the use of Comirnaty® vaccine, with high circulation of variant B.1.1.7 (81.5% of circulating strains), the vaccine shows: 89.4% effectiveness against SARS-CoV-2 infection, 93.7% effectiveness against symptomatic COVID-19, 93.3% effectiveness against hospitalizations, 93.9% effectiveness against hospitalizations in critical care and 92.9% effectiveness against deaths, 7 days after the second dose[12] Another study[13] showed that the B.1-351 variant first identified in South Africa, negatively impacts the neutralizing antibody titer induced by mRNA vaccines (such as Comirnaty® and Moderna vaccines) more than other variants, but we don't have yet clinical efficacy data against this variant. Another trial conducted in South Africa[14] showed that the Oxford-Astra Zeneca vaccine lacked efficacy to prevent mild disease caused by the B.1-351 variant, but the study was not powered to analyze efficacy against severe disease.

Trials of the Novavax, Janssen (Johnson & Johnson), and AstraZeneca vaccines in South Africa, where the B.1.351 variant represents virtually all of the circulating SARS-CoV-2, have found that although their vaccines had lower efficacy rates in South Africa than in trials in other countries, vaccinated participants who received the vaccine were still less likely to require hospitalization for COVID-19 than those who received placebo.

Four key concerns stemming from the emergence of the new variants are their effects on viral transmissibility, disease severity, reinfection rates (i.e., escape from natural immunity), and vaccine effectiveness (i.e., escape from vaccine-induced immunity).

The 501Y.V2 variant has been estimated to be 50% more transmissible[15] than preexisting variants in South

7 Wu K, Werner AP, Moliva JI, Koch M, Choi A, et al. mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants. bioRxiv 2021.01.25.427948; doi: https://doi.org/10.1101/2021.01.25.427948.

8 Edara VV, Floyd K, Lai L, Gardner M, Hudson W, et al. Infection and mRNA-1273 vaccine antibodies neutralize SARS-CoV-2 UK variant. medRxiv preprint 2021; doi: https://doi.org/10.1101/2021.02.02.21250799.

9 Collier DA, Meng B, Ferreira IATM, Datir R, The CITIID-NIHR BioResource COVID-19 Collaboration, et al. Impact of SARS-CoV-2 B.1.1.7 Spike variant on neutralisation potency of sera from individuals vaccinated with Pfizer vaccine BNT162b2. medRxiv 2021.01.19.21249840; doi: https://doi.org/10.1101/2021.01.19.21249840

10 Xie X, Zou J, Fontes-Garfias CR, Xia H, Swanson KA, et al. Neutralization of N501Y mutant SARS-CoV-2 by BNT162b2 vaccine-elicited sera. bioRxiv 2021.01.07.425740; doi: https://doi.org/10.1101/2021.01.07.425740

11 Muik A, Wallisch AK, Sänger B, Swanson KA, Mühl J, et al. Neutralization of SARS-CoV-2 lineage B.1.1.7 pseudovirus by BNT162b2 vaccine-elicited human sera. bioRxiv 2021.01.18.426984; doi: https://doi.org/10.1101/2021.01.18.426984.

12 Haas E, Angulo F, McLaughlin J et al. BNT162b2 effectiveness against SARS-CoV-2 infections and COVID-19, Israel

13 Emary K, Golubchik T, Aley P et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 VOC 202012/01 (B.1.1.7). Available at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3779160

14 Madhi Sh, Baillie V, Cutland C. Safety and efficacy of the ChAdOx1 nCoV-19 (AZD1222) Covid-19 vaccine against the B.1.351 variant in South Africa. Available at: https://doi.org/10.1101/2021.02.10.2125

15 Pearson CAB, Russell TW, Davies N, et al. Estimates of severity and transmissibility of novel SARS-CoV-2 variant 501Y.V2 in South Africa. London: CMMID Repository, 2021 (https://cmmid.github.io/topics/covid19/sa-novel-variant.html).

Africa, and B.1.1.7 to be between 43% and 82% more transmissible[16] than preexisting variants in the United Kingdom.

A preliminary analysis by the National Institute of Communicable Diseases showed that the 501Y.V2 variant was associated with in-hospital mortality that was 20% higher in the second wave in South Africa than in the first wave[17] . Evidence from the United Kingdom indicates that the B.1.1.7 variant may be associated with a higher risk of death than preexisting variants in the United Kingdom[18] .

In summary, to date, laboratory data and evidenced generated by vaccination programmes suggest that current vaccines induce antibody responses that maintain their neutralizing capacity against new variants. SARS-Cov-2 surveillance and genomic sequencing of isolates is essential so that, if necessary, the antigenic composition of current vaccines can be modified.

Regulatory agencies, including the European Medicines Agency (EMA), are developing guidelines for vaccine manufacturers on the regulatory requirements they will need to comply with in order to receive authorization for vaccines against these new variants.

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

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.

2.14 Will annual vaccination be necessary?

Since the first people in the COVID-19 vaccine clinical trials were vaccinated at the end of July 2020 and the first vaccines were approved in December 2020, we only have information about protection against disease for a few months after vaccination. The phase 3 trials have not finished yet for all vaccines and trial participants will continue to be monitored, so we will learn more, but we do not yet know whether booster doses will be needed. Based on the elements of the immune response activated after vaccination with either the mRNA or adenovirus vaccines, it is likely that immunity will be long-lived. Furthermore, the increasing

16 Davies NG, Abbott S, Barnard RC, Jarvis CI, Kucharski AJ, Munday JD, Pearson CAB, Russell TW, Tully DC, Washburne AD, Wenseleers T, Gimma A, Waites W, Wong KLM, van Zandvoort K, Silverman JD; CMMID COVID-19 Working Group; COVID-19 Genomics UK (COG-UK) Consortium, Diaz-Ordaz K, Keogh R, Eggo RM, Funk S, Jit M, Atkins KE, Edmunds WJ. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. Science. 2021 Apr 9;372(6538):eabg3055. doi: 10.1126/science.abg3055. Epub 2021 Mar 3. PMID: 33658326.

17 Abdool Karim SS, de Oliveira T. New SARS-CoV-2 Variants - Clinical, Public Health, and Vaccine Implications. N Engl J Med. 2021 Mar 24:NEJMc2100362. doi: 10.1056/NEJMc2100362. Epub ahead of print. PMID: 33761203; PMCID: PMC8008749.

18 Horby P, Huntley C, Davies N, et al. NERVTAG paper on COVID-19 variant of concern B.1.1.7. London: Department of Health and Social Care, Scientific Advisory Group for Emergencies, January 2021 (https://www.gov.uk/government/publications/nervtag-paper-on-covid-19-variant-of-concern-b117).

presence of variants might affect whether or how often additional doses would be needed. Scientists are continuing to monitor variants and the ability of currently available vaccines to protect against them.

2.15 Is it true that a new variant of the virus causes more severe disease?

Since many variants are emerging continuously everywhere, it is not possible to measure how transmissible or more severe a given variant is with respect to others that have already circulated worldwide or that are circulating today. On the other hand, of the thousands of variants that are emerging on the SARS-CoV-2 genomes, it is reasonable to expect that some variants can eventually achieve biological advantages and be more transmissible, clinically aggressive or resistant to treatments or vaccines. Moreover, explanations other than genetic advantages, such as the randomness associated with the model of infection (e.g. super-spreaders hosts or events) and social behaviour, can also explain the predominance of a particular strain.

While mutations of SARS-CoV-2 are expected, it is important to continue to monitor the public health implications of new virus variants. WHO routinely assesses if variants of SARS-CoV-2 result in changes in transmissibility, clinical presentation and severity, or if they impact on countermeasures, including diagnostics, therapeutics and vaccines. Meanwhile, current disease control measures recommended by WHO continue to be effective and should be adapted in response to increasing disease incidence, whether associated with a new variant or not.

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

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?

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.

2.18 Does vaccination protect against transmission? If not, how will we ever get back to normal life?

Although we can assume clinical protection for any subject who has been correctly vaccinated, and a certain degree of reduction in the risk of transmission in the vaccinated subject could be expected with the existing knowledge, the rest of the infection control measures should currently be followed, regardless of vaccination status until we have clear evidence of the impact of vaccines against transmission.

Interestingly, we are starting to receive some real-world data pointing out that these vaccines may impact also transmission and not only protect against clinical disease. For example, data from Israel[19,20], showing that the viral load is reduced 4-fold for infections occurring 12-28 days after the first dose of Comirnaty® BNT162b2 mRNA vaccine, hint to lower infectiousness, further contributing to vaccine impact on virus spread.

2.19 If a person tests PCR confirmed positive for COVID-19 shortly (within two weeks) after being vaccinated with the first dose of vaccine, should she/he receive additional doses and how many: one or two?

If a person is infected with COVID-19 after having received the 1st dose of a COVID-19 vaccine, he/she should complete the schedule and receive the 2nd dose once he /she has fully recovered and has completed the isolation period, ensuring the recommended interval between doses has elapsed. In the case of the Janssen vaccine, which only requires one dose, if the person is infected with COVID-19 after having received this dose, no additional doses should be administered.

A person infected with COVID-19 following vaccination:

- Should still get the second dose.
- Need not get another dose if the first was Jannsen (J&J) vaccine.

2.20 What about those who test PCR confirmed positive for COVID-19 shortly (within two weeks) after the second dose, should they receive additional doses?

In the case of infection with COVID-19 within a few days after receiving the 2nd dose of a COVID-19 vaccine, no additional doses are indicated. A few days after receiving this dose, it is considered that the person has not yet generated sufficient protection or may have already been infected before receiving the second vaccine. If infection occurs more than 14 days after complete vaccination, the possibility of vaccine failure should be assessed, especially in the case of severe COVID-19 infection.

A person infected with COVID-19 following 2 doses of a COVID-19 vaccine:

- Need not receive an additional dose.

2.21 Will recipients of a COVID-19 vaccine test PCR positive after the vaccination? And what about the antibody tests?

Prior receipt of the vaccine will not affect the results of SARS-CoV-2 nucleic acid amplification or antigen tests for diagnosis of acute/current SARS-CoV-2 infection. False positives due to vaccination in PCR of nasopharyngeal swabs are not possible. The available vaccines involve the administration of either a fragment of mRNA encoding the S protein (Pfizer or Moderna vaccines), genes inserted into the viral vector that will produce the S protein (AstraZeneca or Janssen vaccines) or the whole virus inactivated (Sinopharm).

19 E. Petter et al. Initial real world evidence for lower viral load of individuals who have been vaccinated by BNT162b2. medRxiv.org. doi: 10.1101/2021.02.08.21251329.

20 M. Levine-Tiefenbrun et al. Decreased SARS-CoV-2 viral load following vaccination. medRxiv.org. doi: 10.1101/2021.02.06.21251283.

Neither the mRNA nor the genes inserted into the viral vector reach the respiratory tract, so they cannot be detected in the nasopharyngeal mucosa. In addition, RT-PCR techniques are designed to amplify other sequences of the virus and the result is only positive when amplification of several genes takes place.

However, it is important to note that currently available antibody tests for SARS-CoV-2 assess levels of IgM and/or IgG to the spike or the nucleocapsid protein. The mRNA and vector vaccines induce antibodies against the spike protein. The Sinopharm vaccine contains inactivated SARS-CoV-2 virus, which elicits an immunological response to both the spike and nucleocapsid proteins; thus, a positive result in a test for spike protein IgM or IgG or a test that specifically evaluates IgM or IgG to the nucleocapsid protein could indicate either prior infection or prior vaccination. Antibody testing is not currently recommended to assess immunity to COVID-19 following vaccination with any of the COVID-19 vaccines.

- Vaccination does not influence PCR or antigen test results for COVID-19 infection.
- Antibody testing following vaccination is not recommended.

3. Vaccine efficacy and duration of protection

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

TAGS: long-term protection, vaccine protection, duration, persistence

The recommended schedule is two doses separated by a period of at least 21 days in the case of Pfizer/BioNTech's, 28 days in the case of Moderna's vaccine and 8-12 weeks in the case of AstraZeneca vaccine; 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.

3.2 Several vaccines in use give efficacy figures above 90% based on clinical trials. Will they achieve this in practice?

Keywords-tags: efficacy, clinical trials

In its target profile for COVID-19 vaccines, WHO set the minimal standards, including for efficacy, that must be demonstrated in clinical trials for candidate vaccines to be considered for WHO approval. There is no maximum level of efficacy identified.

The clinical data for efficacy of COVID-19 vaccines, which received WHO Emergency Use Listing approval

and stringent regulatory authorities' emergency authorizations so far are indeed promising. Efficacy will continue to be monitored as the vaccines are rolled out to the public. The compiled data will inform whether the rates observed in clinical trials will be consistent over a much larger population.

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

Keywords-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?

- Keywords-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 titters after vaccination, should he/she be vaccinated again with another vaccine? Is it safe? What should be an interval between two vaccinations?

Keywords-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?

Keywords-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 Pfizer/BioNTech (BNT162b2), Moderna and AstraZeneca vaccines, we can assume that anyone having received 2 doses is protected from 1-2 weeks after receiving the second dose. 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?

Two doses of the vaccine 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.

4. Co-administration, dose-interval and interchangeability

4.1 What do we know about co-administration with other vaccines (for example flu and COVID-19)

Keywords-tags: co-administration, co-vaccination

- Data on co-administration with other vaccines are not yet available.
- WHO recommends that immunogenicity and safety studies be conducted of co-administration with other vaccines, including influenza and pneumococcal vaccines, to adults and older persons.
- When sufficient data are available WHO will review the information and make a recommendation in this regard.
- Until such data are available, there will be a prescribed minimum interval of 2 weeks between administration of a COVID-19 vaccine and any other vaccine against other conditions.

4.2 Can a person receive different vaccines for the first and second doses? Is this safe and efficacious?

Keywords-tags: interchangeability

There is no evidence as to the interchangeability of the different COVID-19 vaccines although studies are underway. Therefore, every effort should be made to determine which vaccine the individual received and to complete the vaccination schedule with the same vaccine. However, if different COVID-19 vaccine products are inadvertently administered in the two doses, no additional doses of either vaccine are recommended at this time. Recommendations may be updated as further information becomes available on interchangeability.

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

Keywords 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 6 weeks in exceptional circumstances in which countries are facing vaccine supply constraints combined with a high disease burden. For 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.

4.4 Which is the rationale of the 1 dose schedule for Pfizer/BioNTech (BNT162b2) vaccine proposed by UK authorities?

Keywords Tags: 1 dose schedule, reduced schedule, vaccine intervals

Vaccines are typically given in more than one dose to increase quantity, quality and longevity of antibody responses. Concretely, the vaccine booster doses allow stimulation of robust long-lasting immunity with high affinity and highly neutralizing antibodies, as compared to the B cell responses induced by first dose only. Considering the epidemiological situation and that the vaccine roll-out is slower than expected the UK authorities have decided to delay the administration of the second dose up to 12 weeks to increase the immediate vaccine coverage. One single dose might be protective enough according to the existing data although the concrete duration of this protection, and the efficacy provided against severe COVID-19 of just one dose is not clear yet.

4.5 Is it dangerous to get more than one vaccine, or does it increase protection?

Several vaccines have demonstrated efficacy against SARS-CoV-2 mediated disease, yet there is limited data on the immune response induced by heterologous vaccination regimens using alternate vaccine modalities. Most coronavirus vaccines are given as two injections: an initial 'prime' dose followed by a 'boost' to stimulate the immune system's memory cells and amplify the immune response. Optimal protection against COVID-19 is estimated to be effective after the prescribed number of days following the last recommended dose.

There is currently no evidence as to the interchangeability of the different COVID-19 vaccines although studies are underway. In fact, there is a trial run by investigators at the University of Oxford, which will test participants' immune responses to receiving one shot of the AstraZeneca vaccine and one shot of the Pfizer vaccine- an heterologous prime-boost combination; with additional possible COVID-19 vaccines to be included in the future.

The ability to mix and match vaccines could make vaccination programmes more flexible: it would speed up the process and reduce the impact of any supply-chain disruptions. But in the meantime, every effort should be made to determine which vaccine the individual received and to complete the vaccination schedule with the same vaccine. However, if different COVID-19 vaccine products are inadvertently administered in the two doses, no additional doses of either vaccine are recommended at this time. Recommendations may be updated as further information becomes available on interchangeability.

5. Safety

5.1 How will we know if COVID-19 vaccines are safe?

Keywords-tags: safety, vaccine development, quality, regulatory agencies, pharmacovigilance

- In the past, vaccines have been developed through a series of steps that can take many years. Now, given the urgent need for a COVID-19 vaccine, unprecedented financial investments and scientific collaborations are changing how vaccines are developed. These changes to accelerate progress do not make the system any less rigorous.
- Like all vaccines, COVID-19 vaccines should go through a rigorous, multi-stage testing process, including large (phase III) trials that involve tens of thousands of people. These trials, which include people at high risk for COVID-19, are specifically designed to identify and asses any common side effects or other safety concerns. What is different this time is that some of the steps in the research and development process are happening in parallel, while still maintaining strict clinical and safety standards.

- As with all vaccines developed in the past, if a clinical trial shows that a COVID-19 vaccine is safe and effective, a series of independent reviews of the efficacy and safety evidence is required. After a COVID-19 vaccine is introduced, WHO will support work with vaccine manufacturers, health officials in each country, and other partners to monitor for any safety concerns on an ongoing basis.

5.2 How are we going to monitor vaccine safety?

Keywords-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 system 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.

5.3 Do COVID-19 mRNA vaccines cause Bell's paralysis?

Keywords-tags: Bell paralysis, AEFIs, adverse events, safety

Bell paralysis is an acute and temporary peripheral facial nerve paralysis of idiopathic nature. Four cases of Bell paralysis have been reported among the 38,000 participants in the Pfizer/BioNTech (BNT162b2) phase 3 trial, all of them in the BNT162b2 vaccine arm of the trial. In the phase 3 trial of Moderna's mRNA-1273 vaccine, another 4 cases of Bell paralysis were found among the 22,000 participants, 3 cases in the vaccine arm and 1 case in the placebo arm. Regulatory agencies (in the United States and the United Kingdom) have found no clear basis upon which to conclude a causal relationship at this time between Bell paralysis and COVID-19 mRNA vaccines, considering that the number of Bell's palsy cases seen in both COVID-19 mRNA vaccines trials was consistent with the expected background rate in the general population. This, as any other potential safety signal, has been recommended to be closely watched, but does not currently have any impact on vaccine indications or practical use.

5.4 If a case of Bell's palsy occurred after the 1st vaccination - do you recommend to administer second dose?

Keywords-tags: Bell paralysis, AEFIs, adverse events, safety

Yes. Cases of Bell's palsy were reported following vaccination in participants in the Pfizer-BioNTech and Moderna clinical trials. However, there is currently no conclusive evidence that these cases were causally related to vaccination. Post-authorization safety surveillance will be important to assess any possible causal

association. In the absence of such evidence, persons with a history of Bell's palsy may receive BNT162b2 or 1273mRNA vaccine unless they have a contraindication to vaccination.

5.5 Could there be as yet unidentified side effects of the vaccines?

Keywords-tags: AEFIs, adverse events, safety

After the successful completion of phase III trials and after the product is licensed, phase IV studies, also called post-marketing surveillance studies, are used to continue monitoring the safety and effectiveness of the vaccine once applied to the population. Phase IV constitutes the expansion of knowledge about the efficacy of the vaccine once it has been approved for commercialization and begins to be applied systematically in the population. In addition to the adverse reactions that could occur with its use and that had not been detected in the previous phases, the effectiveness is also evaluated through continuous epidemiological surveillance.

Some previously unidentified side effects could be detected when the number of vaccinees and the heterogenicity of the population is increased, however, these should be very rare and safety monitoring programmes are in place to monitor and evaluate them.

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

Keywords-tags: AEFIs, adverse events, safety

Reactogenicity and adverse events were generally milder and less frequent in participants in the older group (≥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). The vaccine's adverse events profile did not suggest any specific safety concerns. The median onset of systemic adverse events was 1-2 days after either dose for a median duration of 1 day. Severe adverse reactions occurred in 0.0% - 4.6% of participants. The incidence of serious adverse events, deaths, and discontinuations due to AEs were low and comparable for both the vaccine and placebo groups. There were no specific safety concerns identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection.

5.7 Is there a higher incidence of adverse effects in people with a history of infection?

Keywords-tags: adverse events, AEFIs, safety, previous COVID infection

- The Moderna and AstraZeneca vaccine trials did not recruit a sufficient number of persons with a previous SARS-CoV-2 infection to report on whether adverse effects were different to those reported without prior infection. However, the available data do not show a safety signal.
- Vaccination may be offered regardless of a person's history of symptomatic or asymptomatic SARS-CoV-2 infection. There are not sufficient data to recommend the interval between a documented SARs-CoV-2 infection and vaccination. The added protection of vaccinating previously infected individuals is yet to be established. Currently available data indicate that symptomatic reinfection within 6 months after an initial infection is rare. Thus, persons with PCR-confirmed SARS-CoV-2 infection in the preceding 6 months may delay vaccination until near the end of this period. When more data on duration of immunity after natural infection become available, the length of this time period may be revised.
- WHO does not recommend pre-vaccination screening for prior infection.

5.8 Can COVID-19 vaccination affect fertility?

Keywords-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 suspended the use of the Oxford Astra-Zeneca vaccine or specific vaccine batches?

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 has led to the opening of an investigation and a precautionary suspension of the use in a few countries of the vaccine batch distributed to European Union countries.

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.

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 specify 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 GAVCS 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?

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?

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.

5.12 Is it dangerous for children to be vaccinated if they were not included in clinical trials?

It should not be assumed a new vaccine tested in adults will generate the same immune response in children without also testing it in children. Also, different vaccine schedules are sometimes needed to achieve a similar response in children as in adults. Children should not be vaccinated until we have proper safety and immunogenicity data.

The results of phase 1, 2 and 3 trials of several vaccines administered to thousands of adults together with the real life experience with more than 350 million of doses administered worldwide demonstrate these vaccines are safe and well-tolerated in adults. This suggests these same vaccines can begin to be safely tested in children in the near future, in fact, pediatric clinical trials are scheduled to begin this Spring for various COVID-19 currently licensed vaccines.

5.13 Why were children not included in clinical trials?

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 learnt 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?

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[21].

6. Precautions and contraindications

6.1 What about allergic reactions and contraindications with COVID-19 vaccines?

TAGS: allergic reactions, allergy, contraindications, precautions, vaccine adverse effects

Vaccines, like any other pharmaceutical product, may cause allergic reactions, from mild to severe, in people with very high sensitivity to the active substance or to any of the ingredients contained in the vaccine. The safety data based on clinical trials has not shown any increased risk of allergic reaction, although given the limited number of vaccines administered so far, very rare) allergic reactions (which means fewer than 1 per 10,000 people vaccinated) may still occur.

As a general rule with all injectable vaccines, appropriate medical treatment and supervision should always be readily available, and a post-vaccination observation period of at least 15-20 minutes should be guaranteed. The persons with a history of an immediate allergic reaction of any severity to a vaccine or injectable therapy and persons with a history of anaphylaxis due to any cause should be observed for 30 minutes after vaccination.

- COVID-19 vaccines may cause an allergic reaction, like any other vaccine or drug.
- Recipients should be observed for 15-30 minutes following vaccination.

6.2 Can people with allergies be vaccinated with mRNA vaccines?

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.

21 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)

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 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?

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 vaccination, all vaccinees should be observed for at least 15 minutes after vaccination.

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

6.4 Can immunocompromised people be vaccinated?

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 Can children be vaccinated and what is the maximum age for vaccination?

TAGS: children, pediatric population, contraindication, precaution, age, vaccine, Comirnaty, mRNA vaccines, vector vaccines, AstraZeneca vaccine, Janssen vaccine, elderly, frail population

At this point in time, vaccines that have been authorized by WHO and/or other stringent regulatory authorities are to be used only for people from age 16 or 18, depending on the vaccine.

However, the vaccine developers have already put in place protocols for testing the vaccines in younger age groups. The results are not yet available on any of these yet.

Once the results are evaluated for safety and efficacy, WHO will be able to provide specific recommendations for particular vaccine products and younger age groups.

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.
- 16 or 18 is the mínimum age recommended by COVID-19 vaccine producers.
- No maximum age has been recommended by producers.

6.6 Can approved COVID vaccines be administered to people with coagulant disorders or chronic treatment with anticoagulants?

TAGS: coagulant disorders, chronic treatment, anticoagulants, precautions, safety, mRNA vaccines, Comirnaty, mRNA1273, Moderna, Pfizer-BioNTech, vector vaccines, AstraZeneca vaccine, Janssen vaccine,

- In people with coagulation disorders, except for a specific medical criterion, small-volume intramuscular injections, such as this one, can be applied with reasonable security. The use of a 0.5 or 0.6mm (25 g or 23 g) fine needle and after vaccination, maintaining pressure at the injection site (without scrubbing) for 2 minutes, is recommended. In any case, the person vaccinated must be informed about the possibility of an hematoma at the injection site.
- People on chronic treatment with anticoagulants, which are under control and have a stable INR, can receive intramuscular vaccination without any problem.

6.7 Can pregnant women be vaccinated?

TAGS: pregnancy, contraindications, precautions, safety, mRNA vaccines, Comirnaty, mRNA1273, Moderna, Pfizer-BioNTech, vector vaccines, AstraZeneca vaccine, Janssen vaccine,

Although there have been no safety issues in COVID-19 vaccination of pregnant women, there is not enough evidence to recommend its use during pregnancy.

In very particular situations where pregnant women are part of a group in which vaccination is recommended for their high exposure or high risk of complications of COVID-19 (health workers at high risk of exposure, advanced age, obesity, hypertension or pre-existing diabetes, or others), vaccination may be offered according to a benefit/risk assessment facilitating the necessary information and with the relevant informed consent, for the pregnant woman herself to decide whether to accept the vaccination.

It is not necessary to perform a pregnancy test before vaccination. However, if an inadvertent pregnancy occurs between the two vaccination doses, the second dose should be administered after delivery and your reference healthcare professional must be informed.

6.8 Can breastfeeding women be vaccinated?

TAGS: breastfeeding, contraindications, precautions, safety, mRNA vaccines, Comirnaty, mRNA1273, Moderna, Pfizer-BioNTech, vector vaccines, AstraZeneca vaccine, Janssen vaccine

It is not known whether mRNA or vector 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 if a lactating woman is part of a group recommended for vaccination (e.g. health workers).

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

Keywords-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?

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[22,23,24]; 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?

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.

22 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

23 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

24 Merrill JT, Erkan D, Winakur J, James JA. Emerging evidence of a COVID-19 thrombotic syndrome has treatment implications. Nat Rev Rheumatol2020;16:581-9. doi:10.1038/s41584-020-0474-5. https://www.nature.com/articles/s41584-020-0474-5

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.

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

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 and allocation and deployment

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

TAGS: vaccines, priorization, 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?

Not everyone can be vaccinated at once. Recommendations for how to allocate these 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.

7.3 What if a second dose of Astra Zeneca is not available because the programme has been suspended or there is insufficient supply?

It is recommended that all vaccinated individuals receive two doses. If administration of the second dose is inadvertently delayed beyond 12 weeks, it should be given at the earliest possible opportunity. There is no evidence as to the interchangeability of the different COVID-19 vaccines although studies are underway. Therefore, every effort should be made to complete the vaccination schedule with the same vaccine. Recommendations may be updated as further information becomes available on interchangeability.

8. Regulatory approvals

8.1 What does emergency use authorization mean?

TAGS: Regulatory agency, 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 vaccines for emergency use: Pfizer/BioNTech (BNT162b2), Oxford/Astra Zeneca and Janssen (Johnson & Johnson) vaccines. 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 is:

- 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

8.2 Why is WHO slower in authorizing emergency use of vaccines than the US, UK and the EMA?

TAGS: regulatory agency, EMA, WHO, emergency use

WHO assesses candidate vaccines upon request by the manufacturer. At least ten companies have either expressed an interest or submitted initial dossiers.

In the current emergency context, WHO is conducting a rolling review of several candidate vaccines, which means the data are reviewed at various stages as they become available rather than waiting until all data have been collected and submitted following completion of stage 3 clinical trials.

WHO has granted emergency use listing (EUL) for the Pfizer/BioNTech (BNT162b2) and Oxford/Astra Zeneca AZD1222 vaccines. WHO works quite closely with the European Medicines Agency and other national regulatory agencies and its committees are expected to issue an opinion on more vaccines soon.

9. COMIRNATY® - Pfizer-BioNTech vaccine

9.1 How does Comirnaty vaccine work? (SEE QUESTION 1.3)

9.2 What adverse reactions are associated with Pfizer/BioNTech's Comirnaty vaccine?

TAGS: safety, adverse reactions, mRNA vaccines, Comirnaty, Pfizer-BioNTech

Pfizer/BioNTech's Comirnaty vaccine safety assessment was performed during a phase 3 study with more than 44,000 participants (16 years of age or older), of which more than 21,700 received a vaccine (the others received a placebo) and more than 19,000 were followed up during 2 months after receiving the 2nd dose.

The most frequent adverse reactions were: pain at the site of injection (>80%), fatigue or a feeling of tiredness (>60%), headache (>50%), myalgias and cold cramps (>30%), arthralgias (>20%), fever, and inflammation at the site of injection (>10%); being mostly of mild or moderate intensity and disappearing in a few days after vaccination.

These reactions were more frequent after the second dose and this decreased with age.

Symptomatic treatment can be used, with analgesics and/or antipyretics (such as paracetamol) to treat these effects, although prophylactic use before vaccination is not currently recommended.

Most common adverse reactions

- Are mild or moderate
- Disappear within a few days
- Are more frequent after second dose

10. mRNA 1273 – Moderna vaccine

10.1 How does Moderna vaccine work? (SEE QUESTION 1.3)

10.2 What adverse reactions are associated with Moderna's mRNA-1273 vaccine?

TAGS: safety, adverse reactions, immunogenicity, efficacy, mRNA vaccines, mRNA1273, Moderna

Moderna's mRNA-1273 vaccine safety and immunogenicity assessment were evaluated in clinical trials that included 30,400 volunteers of different ages, races and ethnicities. 82% were at risk of occupational exposure and 22.3% had at least one high-risk factor.

Efficacy observed 14 days after administration of the second dose suggested that it can prevent illness in 94.1% of the adults vaccinated and 86.4% of the over 65 years of age adults with or without comorbidities. Efficacy observed in people with any comorbidity and any age group was 90.9%.

Most of the adverse effects detected were mild or moderate, disappeared a few days after receiving the vaccine and were not different to others described for the most common vaccines (including severe allergic reactions). The most frequently reported in clinical trials was pain at the site of injection, which may appear on the first 7 days postvaccination and resolve in a few days. Other adverse effects reported in the first 7 days after administration of the first and second dose were: sweating, erythema and increased sensibility on the vaccinated arm, fatigue, headache, muscular pain, cramps, joint pain, fever, nausea and vomiting.

Most common adverse reactions

- Are mild or moderate
- Disappear within a few days

11. Vaxzevria – Oxford-Astra Zeneca vaccine

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

TAGS: COVID-19 vaccines, vector vaccines, Oxford-AstraZeneca, ChAd-Ox-1

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 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

11.2 Why were older adults not sufficiently included in the Astra Zeneca clinical trials?

Older adults were included in the AstraZeneca clinical trials, but not in the same proportion as in the other younger age groups to draw statistically meaningful conclusions by the time the submission package was sent for the regulatory agencies. However, the Strategic Advisory Group of Experts on Immunization (SAGE), an advisory group to the WHO, recommends the AstraZeneca vaccine for adults 65 years old and older, based on their review of a more limited set of data in conjunction with the specific immunogenicity data in this age group and together with data from all age groups, showing the vaccine may be effective at preventing

the severe disease from COVID-19, as well as hospitalizations and death. Similarly, the European Medical Agency EMA has established no upper age limit. In addition to recommending the vaccine for older adults, SAGE supports administering both doses, 8 to 12 weeks apart, noting that the vaccine is more effective when there's a longer gap between doses.

Importantly, the real life data coming from UK or Scotland[25], shows a great effectiveness in this age group, above 80%, similar to that of Pfizer's mRNA vaccine.

11.3 Is the Astra Zeneca vaccine (Vaxzevria) safe and efficacious to use in people 65 years and older?

The AstraZeneca US Phase III trial of Vaxcevria[26] has demonstrated favorable reactogenicity and overall safety profile. The vaccine was well tolerated, and the independent data safety monitoring board (DSMB) identified no safety concerns related to the vaccine. The DSMB conducted a specific review of thrombotic events, as well as cerebral venous sinus thrombosis (CVST) with the assistance of an independent neurologist. The DSMB found no increased risk of thrombosis or events characterised by thrombosis among the 21,583 participants receiving at least one dose of the vaccine. The specific search for CVST found no events in this trial.

The Strategic Advisory Group of Experts on Immunization (SAGE), an advisory group to the WHO, recommends the AstraZeneca vaccine for all adults at the age of 18 years and above, including people at the age of 65 years and older. Similarly, the European Medicines Agency (EMA) has established no upper age limit.

Furthermore, the real-life data of the use of the vaccine at great scale coming from the United Kingdom show similar high effectiveness to prevent moderate to severe disease independent of the age, and similar to Pfizer-BioNTech vaccine. Concretely, data from Scotland[27] showed an effectiveness in preventing hospitalization of 94% (95% CI 73-99) (with similar rates when the data is restricted to the population aged 80 and over (81%; 95% CI 65-90, at 28-34 days after vaccination)) and data from the United Kingdom as a whole[28] showed an effectiveness of 80.4% (95% CI: 36.4-94.5) for AZ vaccine, with the median age being 88 years; while the effectiveness of the Pfizer vaccine was 71.4% (95% CI: 46.5-90.6), median age 87 years.

11.4 Is Vaxzevria, the Oxford-Astra Zeneca vaccine safe?

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 Oxford-Astra Zeneca 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

25 Hyams C, Marlow R, Maseko Z, King J, Ward L, Fox K, et al. Assessing the Effectiveness of BNT162b2 and ChAdOx1nCoV-19 COVID-19 Vaccination in Prevention of Hospitalisations in Elderly and Frail Adults: A Single Centre Test Negative Case-Control Study. Available at SSRN: https://ssrn.com/abstract=3796835 or http://dx.doi.org/10.2139/ssrn.3796835

26 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.

27 Vasileiou E, Simpson CR, Robertson C, Shi T, Kerr S, et al. Effectiveness of First Dose of COVID-19 Vaccines Against Hospital Admissions in Scotland: National Prospective Cohort Study of 5.4 Million People. Available at SSRN: https://ssrn.com/abstract=3789264

28 Hyams C, Marlow R, Maseko Z, King J, Ward L, Fox K, et al. Assessing the Effectiveness of BNT162b2 and ChAdOx1nCoV-19 COVID-19 Vaccination in Prevention of Hospitalisations in Elderly and Frail Adults: A Single Centre Test Negative Case-Control Study. Available at SSRN: https://ssrn.com/abstract=3796835 or http://dx.doi.org/10.2139/ssrn.3796835

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 specify 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[29].

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 Astra Zeneca (Vaxzevria) vaccination campaigns despite WHO, EMA and other regulatory authorities recommending its continued use following investigations of potential side effects?

The action taken by some countries to temporarily pause or restrict to certain age groups the use of the 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 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[30] confirms 76% (CI: 68% to 82%) vaccine efficacy against symptomatic COVID-19 and 100% efficacy against severe or critical disease and hospitalization.

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 Astra Zeneca (Vaxzevria) vaccination?

No underlying conditions in the individuals who suffered from Thrombosis with Thrombocytopenia Syndrome (TTS) after Astra Zeneca vaccination were found, and no underlying conditions contraindicate or pose a special precaution to Astra Zeneca vaccination to date. Rare clotting problems like cerebral venous thrombosis are more common among pregnant or postpartum women. Other risk factors for such

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

30 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.

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?

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?

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.

11.9 Can pregnant women receive COVID-19 vaccine AstraZeneca (Vaxzevria)?

Vaccination for pregnant women is not recommended due to the lack of specific data. Pregnant women should only receive vaccination if the benefit of vaccination outweighs the potential vaccine risks. Pregnant woman should consult with their health provider before being vaccinated against COVID-19. This is also the case for vaccination with the AstraZeneca vaccine. There is no indication for doing a pregnancy test before vaccination. In case of inadvertent vaccination during pregnancy, interruption of gestation is not indicated.

11.10 If Astra Zeneca (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?

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)?

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[31]. It is rare, occurring in anywhere from 1 in every 125,000 to 1 in 1 million people[32,33] ; 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[24,25].

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 thrombocytopenia) [26]. 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 – Johnson & Johnson vaccine

12.1 How does the Janssen COVID-19 vaccine work?

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.COV2-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:

31 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

32 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

33 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

- 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?

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?

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?

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 Can pregnant or breastfeeding women receive the Janssen COVID-19 vaccine?

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.

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

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 B1.351 (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.

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

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 B1.351 (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.

13. Who specific Q&A

13.1 What is WHO's position on vaccine certificates for travel?

TAGS: COVID-19 vaccines, biological certification, vaccine certification, vaccine passport

Proof of receipt of vaccination by any recipient, either paper-based card or digital certificate, is important for every vaccine. This is critical for monitoring of vaccination coverage, understanding of the vaccination effectiveness, improving the vaccination programme's efficiency, services and outcomes.

At present, WHO does not support the introduction of requirements for proof of vaccination against COVID-19 for international travel as a condition for departure or entry, given that there are still critical unknowns regarding the efficacy of vaccination in reducing transmission. In addition, considering that there is limited availability of vaccines, preferential vaccination of travellers could result in inadequate supplies of vaccines for priority populations considered at high risk of severe COVID-19 disease. WHO also recommends that people who are vaccinated should not be exempt from complying with other travel risk-reduction measures.

Vaccine certificates for travel:

- Are premature because we still don't know much about the virus, the vaccines and vaccine supply.
- May result in inadequate supplies of vaccines for priority populations.