

Q&A on the webinar "SARS-CoV-2: Background, Vaccines, and Outlook" on 5/17/2021.

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Vaccines

1. mRNA and vector vaccines

- **What are the advantages or disadvantages of mRNA vaccines?**

The advantages of mRNA vaccines: they are very easy to make, are very effective against coronavirus, are very easy to modify to protect against variants, and are not a replicable virus. The disadvantages: RNA vaccines must be stored cold and injected at least twice, and antibodies are only produced against one protein. We do not yet know how long the protection will last.

- **Do Moderna and BioNTech use the same mRNA sequences?**

Almost, there are only small differences, the sequences are very similar. The technology is the same.

- **The platform of vector vaccines has been around for a long time. The SARS-CoV-2 vaccines are not the first to use viral vectors on a large scale?**

Yes, that is correct, they have already been used against MERS and have also been used on a larger scale against Ebola in DRC/Congo in recent years.

- **Are vector vaccines RNA or DNA viruses (adenoviruses)?**

DNA viruses.

- **How do you ensure that the adenoviruses used in vector vaccines no longer replicate? Would it be dangerous if they could still do so? What would be the consequences if the adenoviruses of a vaccine could replicate uncontrollably?**

Adenovirus-based vector vaccines such as Vaxzevria (AstraZeneca), Covid-19 Vaccine (Janssen) or Sputnik V (Gamaleya) are so-called live vaccines and, by law, their genetic information must be altered so that they can no longer be pathogenic (dangerous). To do this, certain genes of the adenoviruses are removed that are essential for their reproduction. If these genes were not removed, the virus could multiply and cause diseases such as the common cold or diarrhea and infect other people through contact.

- **Should the approval for Sputnik V come: Is there any new data on whether the adenoviruses of the second vaccination were completely inactivated in this vaccine? There were doubts about this from the Brazilian health authorities.**

According to the Brazilian health authority, the adenoviruses of the second vaccination were not completely inactivated in the case of Sputnik V. However, the manufacturers and Russia reject this.

Verification that the changes have been made accordingly is controlled by the health authority in the course of the approval process. In addition, every batch of a vaccine in Europe must be checked and approved by the authorities. This applies to all vaccines marketed in Europe. The risk that these changes in the genetic information were not made in the Russian vaccine is therefore excluded. The vaccine would not be licensed and marketed in Europe.

- **Why do you get a second dose with vector vaccines?**

Many vaccines, such as vector vaccines, but also mRNA or inactivated vaccines, require two doses to develop a sufficiently high and, above all, stable antibody titer.

Which dose level and which interval of doses provides optimal vaccine protection is determined in clinical trials.

2. Live and dead vaccines/ inactivated vaccines

- Why are inactivated vaccines not increasingly used? According to statistics, these protect against ALL variants of SARS-CoV-2?

Inactivated vaccines use good and established technologies, and many inactivated vaccines against SARS-CoV-2 are also being developed. In Asia, inactivated vaccines are mainly available. In Europe, two candidates are currently in the approval process (Novavax and Sinovac).

- When can inactivated vaccines and when can live vaccines be expected in Austria? And how easily can these vaccines be adapted to mutations?

The first inactivated virus vaccines will be licensed in June/July 2021. Whether live vaccines will also come in the foreseeable future is difficult to say. Currently, there is only one manufacturer in India.

3. Approval

- Why do vaccines usually take ten to fifteen years to develop and obtain regulatory approval?

There are many reasons for this: Basic research takes time, and studies are conducted to determine the ideal "candidate" for development. This can take several years. Then the preclinical studies are completed step by step, followed by the clinical trials. The approval process itself also takes another 18 months on average.

On average, a clinical trial takes about two years from preparation to completion, and the approval process for vaccines takes about 6 - 12 months. If new data are generated, one always determines the profitability, and much more. These and even more factors influence the duration of development.

- Many continue to criticize the rapid progress towards vaccination against SARS-CoV-2, arguing that approval for a vaccine should take longer (timeline 10 to 15 years). What can you say in response?

It was allowed in the case of SARS-CoV-2 to combine individual study phases. In addition, preclinical studies, which previously had to be conducted before clinical studies, were allowed to be done in parallel with clinical studies. This is referred to as "telescoping development." Furthermore, bureaucratic hurdles were reduced by the authorities - e.g., review periods were shortened or step-by-step submission of documents was made possible. Ultimately, however, the same data had to be submitted for the Corona vaccines that are generally required for the development and approval of vaccines. There are no restrictions here.

- What was the reason that mRNA vaccines were not approved for all these years and suddenly became (emergency) approved in the wake of SARS-CoV-2?

It took years of development to discover that mRNA vaccines must be packaged in lipid nanoparticles (LNP) to reach cells. Moreover, both Moderna and BioNTech lacked the financial resources for rapid development.

- [Research and development in mRNA technology has been going on for about 20 years now. Why was this technology not used or approved for vaccinations earlier?](#)
- It was not until 2005 that it became possible to use this technique at all. mRNA vaccines against HIV and influenza were tested in clinical trials, but did not work. HIV and influenza are difficult in terms of their characteristics, and no technique has worked for HIV. Antibodies produced in the course of corona vaccination against the spike protein of SARS-CoV-2 inactivate the virus. This fact made it even conceivable that synthesis of this protein from mRNA could provide protection. However, this was not clear before, and one can speak of a huge luck that the technique worked so well.

4. [Mixing vaccines](#)

- [Are there data on mixing vaccines - i.e., switching from mRNA to vector vaccine after the first partial vaccination or vice versa?](#)

Yes, there are now data from the UK and Spain, where subjects received the first partial vaccination with Vaxzevria (AstraZeneca) and a second partial vaccination with Comirnaty (BioNTech/Pfizer) after about 29 days. In the Spanish study (CombiVacs), neutralizing titers were significant after the second immunization, and sufficient neutralizing antibodies were present. However, in this study, there was no direct comparison of a second partial immunization with Vaxzevria or Comirnaty without vaccine switching. There was also no data on the cellular immune response that would have provided information on cytotoxic T cells and memory cells (B cells). Thus, how long the vaccine protection will be maintained is uncertain.

- [Is it advisable to change vaccines and switch from a vector vaccine to an mRNA vaccine, for example?](#)

Unfortunately, this is not yet known; there are not yet sufficient data on this - see previous question. Therefore, according to current data, the first two partial vaccinations should be carried out with the same vaccine.

- [After a full immunization with AstraZeneca \(after two partial vaccinations\), can a third vaccination be given with an mRNA vaccine? When does this make sense?](#)

Yes, this is safe and can be useful when new virus variants emerge. At present, the virus variants circulating in Europe are those against which AstraZeneca's vaccine offers reasonable protection. However, if one of those variants (e.g., the South African one) spreads, of which we know that the vaccine protection of Vaxzevria (AstraZeneca) is significantly reduced, it makes sense to be vaccinated again with an mRNA vaccine. It is still uncertain whether a single immunization will then be sufficient here or whether two partial vaccinations will again be required.

5. Comparison with other diseases and vaccines

- What makes the Corona vaccines different from other vaccines against TBE, influenza or pneumococcus, so that you have to sign a statement regarding possible side effects before receiving the vaccine?

Each vaccine is individual and tailored to the virus. However, the technologies are usually used for several types of viruses. You sign the declaration to confirm that you have been sufficiently informed about the vaccination and its side effects (it is a kind of disclaimer).

- Why does a flu wave die down on its own, but COVID doesn't?

Flu waves subside when the air becomes drier and warmer or people are outside more. Many people also have some protection against influenza, which is not present in the coronavirus. Furthermore, the coronavirus is more infectious and stable than the influenza virus that causes flu. However, in Austria now, in May, we are also seeing a reduction in corona cases, similar to what we saw in the summer of 2020, but we don't quite know why that is.

Vaccination and antibodies

1. Vaccination for children

- What is the current status of vaccines for children?

Approval of BioNTech/Pfizer's mRNA vaccine for adolescents 12 years and older was recently granted in Europe. Next, one study each for children 5-12 years of age and one for neonates and children under five years of age will be conducted in a phased manner. An extension of approval for children up to 12 years of age is expected in the fall of 2021, followed by the very young. For AstraZeneca's vaccine, it seems to take a while longer; currently, no studies have been reported - except for one in China. With the vaccine from Janssen ("Johnson&Johnson"), a clinical study is currently being conducted in adults and adolescents aged 12 years and older, which is currently on pause. Data on this are expected in the coming months.

- Are there any special criteria/ peculiarities in the approval system for the development of vaccines for children?

Yes, studies in children may only be conducted after close consultation with the authorities, as they represent a particularly vulnerable group. Before this is permitted, data on safety and efficacy in adults must be available. Subsequently, studies in children can be started step by step, starting with the older ones.

2. Adaptation of vaccines for women

- Why can't women also be used in clinical phase 1? They aren't all pregnant. The argument is often that too little research is being done on vaccines for women. It has also been suggested that the dosage of vaccines for women is too high.

At this point, unfortunately, there are too few data on whether the vaccine is toxic to reproductive organs or how the vaccine might affect unborn children (a participant in the study could become pregnant). Therefore, regulatory agencies rarely agree to

include women of childbearing age in the early clinical phases (except for drugs for rare or life-threatening diseases).

- Are gender considerations taken into account when dosing the vaccine?

No, not at this time. Dosing and evaluation for safety, immunogenicity and efficacy will be staggered by age.

3. Vaccination after covid disease has occurred.

- Is there a recommendation for vaccination after a Covid 19 infection or in general after an infection with the coronavirus? If so, from when and why? Does one not already have protection against infection?

This depends mainly on the antibody titer. If this is very high after the infection (depending on the analysis method), the titer should be determined again after about six months. In this way it can be determined whether sufficient antibodies are present or whether a vaccination would be necessary.

In general, a value of 15 BAU/ml (neutralizing antibodies determined by ELISA) or higher results in a positive predictive value for the presence of neutralizing antibodies of 99.10 %. From this value onwards, the result is considered to be evidence of neutralizing antibodies with a validity period of three months (in accordance with Covid-19 Opening Regulation §1, Para. 2, No. 7). If a new virus variant occurs, against which the neutralizing effect of the antibodies of the "old" variant is significantly lower, vaccination with an updated vaccine would be necessary.

- Is one dose of BioNTech/Pfizer enough if you have had covid before and have antibodies?

This is not excluded and depends mainly on the antibody titer after infection and how high it is then after the first immunization. Even in the case of viral infection without symptoms, the first vaccination dose usually acts as a boost.

4. Antibody titer after vaccination

- What is the guideline value for antibodies as fully immunized, are there any guideline values here in terms of a "sensible" titer? Are there differences in the vaccines, what is a good value with which vaccine?

How high the antibody titer must be in order to assume vaccination protection is currently not known. For other vaccines, it has been determined that a fourfold increase compared to the titer before immunization is sufficient for vaccination protection; currently, this titer is also used. Unfortunately, there is no general guideline value for a titer, since the values vary due to the different analysis methods.

- Is the antibody titer (SARS-CoV-2-S-AK, > 5000 BAU/ml) a good indication of immune protection?

The value given here describes the calculated level of binding antibodies (the unit BAU stands for "Binding antibody units" and is a WHO standard). This is based on a

so-called ELISA method, which is used to detect neutralizing antibodies. A value of 15 BAU/ml or more results in a positive predictive value for the presence of neutralizing antibodies of 99.10 %. From this value on, the result is considered as proof of neutralizing antibodies and immune protection with a validity period of three months (according to Covid-19 opening regulation §1, Abs 2, Ziffer 7).

- **Why do some people not form antibodies even a few weeks after vaccination? Can there still be protection?**

Some people do not respond to certain antigens and do not get protection from vaccination, even after repeated vaccination. In the case of SARS-CoV-2, it is not yet known exactly what is needed for reliable protection. But without antibodies, proper protection is unlikely.

- **On what factors does it depend whether someone forms many or few antibodies as a result of the respective vaccination?**

It depends mostly on how the immune system is structured or how the body recognizes antigens (foreign bodies). This is the case with any pathogen - for example, some people form antibodies against the hepatitis B virus very quickly, and some need to be vaccinated up to four times for this. Age also plays a role.

- **Is it useful to have the immune status determined by an antibody test after a vaccination or a Corona infection?**

Conditionally. You can see with the test whether you have antibodies or not. If you don't have any, then there is probably no protection. In this case, one should - after a Corona infection for the first time or after previous vaccination again - be vaccinated with another vaccine.

If antibodies are detected with the test, it is currently not clear whether one is protected or not. Because currently it is not known how many antibodies are needed to be protected, and it will take time to know.

5. Duration of protection by antibodies

- **How long does antibody protection last after vaccination?**

Currently, there are data that neutralizing antibody titers remain stable for at least about 9-10 months. A drop is generally not critical, what is important is the threshold value from which one can assume vaccination protection. This must not be fallen below. However, sufficient data are still lacking to be able to say which antibody titer correlates with vaccination protection.

- **Why do you have antibodies for only about 6 months after infection, but longer after vaccination?**

It is not yet known how long antibody titers last after vaccination, and data are still lacking on the titer up to which vaccine protection is maintained. At least it is currently known that a protective titer lasts up to about nine months (data from clinical studies). Where the threshold value is, which says from which titer one is no longer protected, is still unknown. In general, however, it is not unusual for the titer to drop after a vaccination or infection and no longer be detectable. This is because, in addition to the antibodies, the cellular immune response provides information

about whether a memory of the immune system has been built up, so that specific antibodies can be rapidly produced again in the event of a re-infection.

6. Other strategies for vaccination

- In vaccines, the antibody response against the spike protein is considered an important parameter. However, it seems that the proportion of antibodies against the nucleocapsid protein of the virus is higher after a passed corona infection. Why then do the vaccines not focus on the nucleocapsid protein?

The main immune response in SARS-CoV-2 is directed against the receptor binding domain of the viral spike protein. It is assumed that at least a fourfold increase in antibody titer is required to be protected against infection. Unfortunately, the titers against the nucleocapsid do not correlate with vaccination protection, as has been observed from infection studies.

- Isn't it possible to "glue" the spikes/receptors so that the virus can no longer attach to a cell?

This would be theoretically possible, but one would need a lot of time to produce something like this. This method would also only work at the very beginning of the infection or prophylactically, because otherwise there would be too much virus for the "glue" in the body.

- Why can't we focus more on therapies instead of vaccines and inject the genetic code of specific SARS-CoV2- antibodies with target B/T cells?

It is possible to inject the antibodies yourself, but this is very expensive and very prone to resistance. Moreover, against viruses, prevention is much better than therapy.

In the case of infection with the coronavirus, antibodies are produced against the virus as part of the body's own immune defense. If one would like to additionally introduce the information for antibodies via vectors or similar, sequences of different antibodies would have to be used to obtain protection. With a vaccine it is sufficient to inject it two or three times, with an antibody vector one would have to inject again and again or do a kind of gene therapy so that the antibodies are permanently produced. So this method would be very laborious and very expensive, and besides, it would not be clear whether it would work at all.

- How high is the risk that vaccination will lead to even more dangerous mutations in the pandemic? Some epidemiologists claim that this is a risky game.

We have a pandemic and are obliged to use all our knowledge and available technology to protect people and prevent deaths. The currently available vaccines protect against all variants known so far. Variants can only emerge as the virus replicates. Therefore, vaccines will reduce replication and help fewer variants emerge rather than cause new, pathogenic variants to emerge. Variants emerge in people who are not vaccinated. So far, no vaccine has caused a virus to become more dangerous.

COVID-19 disease

- Can we already say with certainty what influences the different courses of the disease?

No, you can't. Important parameters are age, gender, immune status, weight (or overweight), and type 2 diabetes mellitus. But why young, healthy people develop severe corona is still unclear.

- Do gender/hormone concentrations play a role in COVID?

Which criteria have an influence on an infection with the coronavirus and a disease is not yet completely clarified. What is certain is that COVID-19 leads to death more frequently in men than in women. According to international studies, men worldwide are almost three times more likely to require intensive care treatment and are about 1.4 to 1.7 times more likely to die from COVID-19 than women (depending on the study). On the other hand, the female immune system appears to be better equipped to fight SARS-CoV-2. For example, the innate immune response to viral infections begins to decline massively in men at about age 60, whereas this decline does not begin in women until about six years later. Immune defenses, such as those provided by T cells, in the early stages of corona infection are also more robust, even in older women. The female sex hormone estrogen appears to play a protective role by suppressing receptors that SARS-CoV-2 uses to invade cells. In addition, the X chromosome contains many genes that regulate the immune response and play a particularly important role in the early phase of infection.

- What is the impact of existing chronic inflammation in COVID infections?

There is currently only limited scientific data on this. In rheumatoid arthritis (RA), inflammatory bowel disease (IBD), psoriasis or other autoimmune diseases that cause inflammation, drugs are needed to reduce the body's overreaction. This can affect the ability to fight infections, including SARS-CoV-2. It can also affect the formation of antibodies after vaccination. However, a small clinical study of about 60 participants with chronic inflammation showed that there was no significant difference in them in terms of side effects or antibody formation after vaccination with BioNTech/Pfizer's mRNA vaccine.

- As with HIV, are there known people with certain genetic conditions who cannot contract COVID-19?

No, not yet.

- Can vaccination against Sars-Cov-2 aggravate still existing post-Covid symptoms (general fatigue, decreased sense of smell and taste, or eye problems after conjunctivitis and keratitis)?

Vaccination cannot affect these symptoms, they occur due to the SARS Cov-2 infection, it takes the whole virus.

- Are there any known serious long-term effects that are effective for more than one year?

In this context, the World Health Organization (WHO) mentions persistent symptoms and possible late effects that patients report weeks later after an acute COVID-19 infection (Long COVID). Symptoms include fatigue syndrome, reduced exercise

tolerance in combination with persistent shortness of breath, palpitations, dizziness, loss of smell and/or taste, listlessness, persistent diarrhea, etc. Since SARS-Cov-2 is a virus that causes respiratory symptoms and can lead, among other things, to fibrosis of the lungs, it is not yet possible to assess whether long-term damage may occur as a further consequence.

- **Are there severe courses of COVID-19 in children?**

In children, severe courses of COVID-19 are rare, but they do occur. Current evidence suggests that children with certain underlying diseases and infants (< 1 year) may be at increased risk for severe disease.

Similar to adults, children with severe COVID-19 may develop respiratory failure, myocarditis, shock, acute renal failure, coagulopathy, and multiple organ systemic failure. Some children with COVID-19 have developed other serious problems such as intussusception (intussusception of the intestine) or diabetic ketoacidosis. In rare cases, "Multisystem Inflammatory Syndrome in Children (MIS-C)" has been reported.

Side effects of vaccination

1. Thromboses

- **With which vaccine do thromboses or resulting embolisms occur most frequently? And when - immediately after vaccination or with a time delay?**

Thrombosis and thrombocytopenia occurred predominantly with the adenovirus-based vector vaccines, i.e., Vaxzevria (AstraZeneca) and Covid-19 Vaccine (Janssen). Symptoms occur within three weeks of vaccination.

- **Is the likelihood of developing sinus vein thrombosis (SVT) after the second vector vaccination less than after the first?**

Based on the currently published data, the probability of SVT after the second partial vaccination seems to be about the same as with the first partial vaccination. However, the data on this is still very thin.

- **Wouldn't it be better to use an mRNA vaccine for the second vaccination after a first vaccination with AstraZeneca? Aren't there studies that indicate that the protection is even better in that case?**

There is currently no recommendation to perform the second partial vaccination with a different type of vaccine. Although there are already initial data on safety and non-specific immune response, at what interval and with what dose the immunization should be carried out. Whether a cellular immune response is also formed, how long the vaccination protection lasts and the direct comparison with homologous immunization - i.e. both times with the same vaccine - are still missing.

- **Do we know why mainly young women are affected by thrombosis after vaccination with AstraZeneca and not older women?**

No, unfortunately not. In 40% of all thromboses, the causes are unknown. This may be due to hormonal or genetic reasons. Currently, we know the underlying mechanism, but unfortunately not all causes.

2. Other side effects

- Can we be sure that autoimmune diseases or other vaccine damage will not occur years after vaccination?

For the most part, yes, vaccine reactions usually occur within the first three months, if any. So far, there has been no evidence that the vaccines could trigger autoimmune responses.

- Do the vaccines have any effects on unborn children? Can the vaccines cause malformations/miscarriages?

Several preclinical and clinical studies are still ongoing in this regard. Both BioNTech/Pfizer (mRNA) and Janssen (vector vaccine) are currently conducting studies on risks in pregnant women. Currently, there are no data to suggest an increased risk to pregnant women or their unborn child.

Facts vs common myths

- How high is the risk that in the case of vaccinations with mRNA, there could be undesirable changes in the DNA (genetic information) due to the process of reverse transcription - possibly via retroviruses? And that these only occur after a longer period of time or in the children of vaccinated parents?

This risk is extremely low because the coronavirus is not a retrovirus and because there is hardly any reverse transcriptase in human cells. And for children of vaccinated parents to inherit such a change at all, the potential foreign DNA would also have to enter the germline cells, also extremely unlikely.

- How can we ensure that the DNA of vector vaccines is not integrated into the human genome?

We know that adenoviruses integrate with very low probability. Furthermore, many tests have been done in the last 30 years showing that the vectors do not integrate.

- Can SARS-CoV-2 become incorporated into body cells when infected, then become undetectable with tests and later "break out" again?

There are the long-term covid infections, where the virus stays longer but is still detectable. Since coronaviruses are not retroviruses, integration is unlikely or can be ruled out almost 100%.

- Why didn't the virus come out of a biotechnology lab? What do you hold against someone who holds this opinion?

There are many arguments against breaking out of a lab. Four of the most important are: 1) The differences (about 1200 bases) between SARS-CoV-2 and the next known viruses are very high, i.e., you have never seen a virus like SARS-CoV-2. 2. one does not see any characteristics that would have resulted from manipulation. 3. coronaviruses are recombination artists, and there are so many variants of coronaviruses in diverse animals that emergence in nature would be plausible. 4. SARS-CoV-1 also arose naturally in 2003, but we still do not know where.

- How can the low incidence of blood group 0 be explained?

This correlation was observed at the beginning of the pandemic, but with the data now available, it is clear that there is no link between COVID-19 incidence and blood type.

- Will we be able to completely eradicate SARS-CoV-2?
Possibly, but probably not in the next five to ten years.

A big thanks to Christina Nicolodi and Tim Skern for answering the many questions!