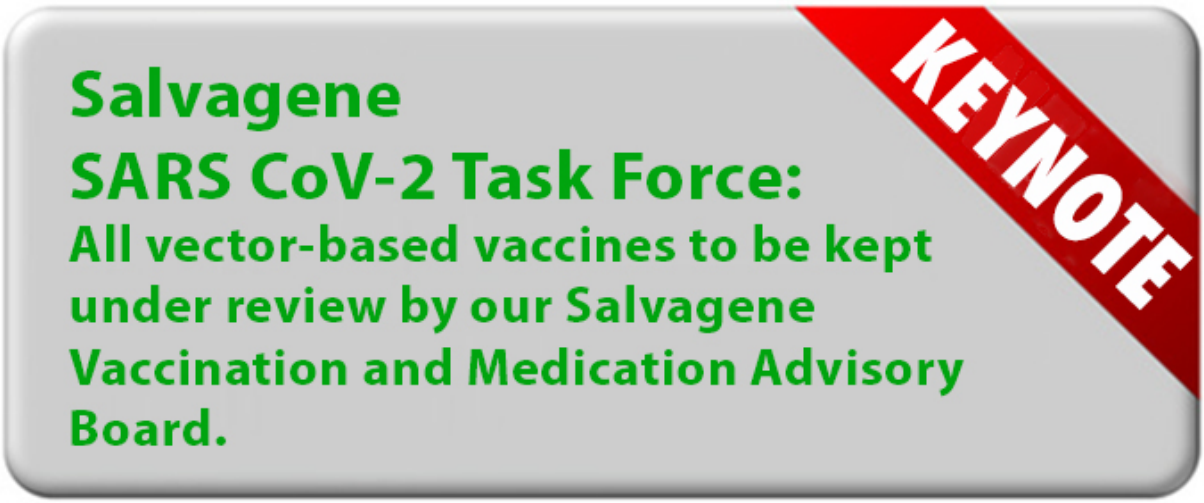
Salvagene GROUP

Business Unit: SARS-CoV-2 Task Force
Keynote: #69

April 2021



Dear Premium Customers,

We are not surprised by the latest developments surrounding the current crop of vaccines and the problems that have arisen, especially with regard to AstraZeneca. Since April 2020, we have repeatedly pointed out shortcomings in the design of the pivotal study, the results of the efficacy study and even fundamental design flaws in the vaccine.

Many governments have concurred with our findings and have reallocated the AstraZeneca vaccine away from certain age groups towards others, contrary to the original specification of the manufacturer. For older people, the vaccine has certain advantages, as reported in detail in our previous Keynote (#68), namely in the production of T-helper cells. For younger people, especially women, there is a significantly higher risk. From the information we have at our disposal now, we must definitively disagree with the assertion: "The administration of the

AstraZeneca vaccine should continue as before, because the advantages outweigh the disadvantages." Although this approach may well be the right one within the overall objective of controlling the pandemic, it is certainly wrong on an individual level.

A distinction must always be made on the basis of age groups and gender-specific groups. Take, for example, females in the 25-40 age bracket who are otherwise healthy and fit – their risk of dying from infection with SARS CoV-2 is lower than from receiving the AstraZeneca jab. Here, the risk/benefit balance weighs against vaccination.

As discussed in Keynote 68, the problem lies in a certain polymorphism of the Factor 5 Leiden gene on the one hand and hormonal contraception on the other, with the combination of progestins and estrogens increasing the risk. What is the underlying problem here, and does it affect all vector-based vaccines?

Essentially, there are three possible causes for this:

1) the spike protein
2) impurities or adjuvants in the vaccine
3) the vector virus itself

In our opinion, the likelihood of the first two being responsible is negligible, leaving the vector virus as the main suspect and potential cause of complications.

Vectors are genetically modified forms of the viruses that trigger the common cold or flu. The AstraZeneca vaccine uses a genetically modified chimpanzee adenovirus that goes by the name of ChAdOx1. By contrast, other vector-based vaccines use a human adenovirus – in the case of Johnson & Johnson, it is human adenovirus 26. The cleverly formulated Sputnik V uses two

different modified human adenoviruses – adenovirus 26 and adenovirus 5 – thereby circumventing vector immunity. Consequently, the efficacy level of Sputnik V is significantly higher than that of Johnson & Johnson.

In principle, we consider Sputnik V to be a highly effective vaccine, but there is still very little clinical data published on it, which makes it difficult to perform a direct comparison with its counterparts developed in the West. We consider the Sputnik V vaccine to be an unquestionably ingenious solution, but unfortunately, it still has the status of a "black box" due to the dearth of information published. For this reason, we cannot recommend this vaccine to our Premium clients at this stage.

So, what exactly is the problem with adenovirus vectors? Back in April 2020, we expressed our concern that adenovirus vectors are known to promote thrombosis, thrombocytopenia and disseminated intravascular coagulopathy, potentially causing multi-organ failure and death, especially after intravenous injection of virus particles. This has been observed repeatedly in pre-clinical studies involving monkeys and rabbits and is something that is already widely understood. Furthermore, when AstraZeneca announced in August 2020 that it was ready to proceed to the approval stage, we pointed out to the EMA that various mechanisms are known whereby adenoviruses cause thrombosis, for example, by stimulating the aggregation of platelets. At the same time, the immune system of the vaccinated individual is producing antibodies against the vector viruses, which can also cause aggregation. A further complicating factor is that adenoviruses bind to vessel walls and trigger inflammation, which can also lead to thrombosis. Around 30 more cases of thrombotic complications have now also been recorded in the UK. To date, the British regulatory authorities and the Medicines and Healthcare products Agency have not published any such reports on BioNTech.

To put it bluntly, the finger of suspicion is increasingly being pointed at the ChAdOx1 vector virus. Why is this? Back in April

2020, when Oxford University published initial details of their vaccine project, we were very surprised to learn that they had opted for a chimpanzee virus. We took the view that this offered no real advantage and cast some doubt on the experience of the research team in vaccine development. Because of the differences in the RGD loops (surface molecules on the viruses that mediate docking to the cell) between the ChAdOx1 and human adenoviruses, the risk profile of the AstraZeneca vaccine differs in this respect from vaccines that use human adenoviruses.

The chimpanzee virus could therefore be the critical flaw in the make-up of the AstraZeneca vaccine. All other manufacturers use human vector viruses. Whether this is really the cause remains an open question. And on this basis, we cannot recommend the Johnson & Johnson vaccine or indeed any of the other vector-based vaccines at this time. In addition, the Johnson & Johnson vaccine has only recently been licensed. Consequently, little or no data on side-effects has so far become available. These conclusions are especially relevant for our American clients, but also for our European clients, as approval is expected there soon. In any case, it is clear that the mRNA-based vaccines are superior to the vector-based vaccines.

The same reservations apply for our European clients, who will soon be confronted with the dilemma of locally produced Sputnik V vaccine within the EU and its expected approval by the EMA in the next few weeks. Until it is clear whether the problem causing the development of thrombosis is a combination of the mechanism described above with the specific profile of young women who have the relevant polymorphism on the Factor 5 Leiden gene and have been on the estrogen-progestin contraceptive pill for some time, we are not making any recommendation in favor of vector-based vaccines for this particular risk group (female and young) for the time being. The EMA has now officially confirmed a link between AstraZeneca and sinus vein thrombosis. Although they accept this risk as a possible side-effect, they have not changed the unrestricted approval status of the AstraZeneca vaccine. We might be able to understand this decision if only one vaccine were

available, but there are alternatives that do not require the recipient to take this risk.

Despite the reservations expressed above, we remain open to vector-based vaccines, including AstraZeneca, for use in older males because of the benefit they confer in terms of producing new T-helper cells, as mentioned above. Production of these cells is generally less active in older people because their T-helper cell profile has evolved over a lifetime and delivers a less precise response to a potential infection. This is where AstraZeneca offers a bonus for elderly recipients.

A new challenge arises with people who have already received their first shot of AstraZeneca. The question is how to proceed with administering the second dose, as different countries adop different approaches. There is actually only one defensible compromise: at the moment, it looks as if many European governments, as well as those in Australia and Canada, are leaving it up to the individual who has had the first dose of AstraZeneca vaccine to decide whether to have the second. The vaccinated person then takes the liability on him or herself. There is a guideline from AstraZeneca on this. For the risk group comprising young women who are taking hormonal contraception or are genetically vulnerable, we consider it unsuitable. The Standing Vaccine Commission (STIKO) in Germany goes so far as to recommend an mRNA-based vaccine as second dose, but we have strong reservations about this solution. It sounds good in theory, as the antibodies would be produced in a broader configuration, but there has not been a single study anywhere in the world on the implications, so we would therefore not recommend this course of action. Changing the name of the product, as is now being considered in the UK, does not solve the existing problem either, of course.

Fortunately, not a single one of our Premium clients has so far had an AstraZeneca vaccination. If a client had done so, it would make sense to measure certain factors, especially blood clotting, to see

what the consequences of the first jab were, to assess the risk profile and to do an antibody count (especially types 1-3), with the aim of establishing whether the immunity level is adequate. This would buy time until the first studies on mixed vaccinations become available.

Premium clients who have a case of this kind among their circle of acquaintances are welcome to get in touch with their Salvagene consultant and to provide us with contact details. We will be happy to advise on what kind of tests are appropriate in the individual case.

In combating the pandemic, it is crucial to address immunity in children and adolescents, as they are coming more and more into focus as carriers and are also manifesting increased complications and illness. Although Johnson & Johnson has already done a lot of preliminary work, especially in the USA, and has delivered essentially positive results, we cannot make a recommendation here either until the vector-based issue is completely clarified. We continue to favor the BioNTech vaccine for our Premium clients and their children, even ahead of the more recent Moderna. Quite simply, the BioNTech product has more data on its effectiveness in adolescents. We are nonetheless not quite as gung-ho as our colleague Akiko Iwasaki at Yale University. From a scientific point of view, Israel is the benchmark country, so we expect to have a lot more data when their rollout of BioNTech among the under-16s begins in May.

We are much more cautious about the announcement made by Pfizer and BioNTech and about the corresponding study on the effectiveness of their vaccine against the South African variant. This study involved a few hundred volunteers over a period of six months. For most of this time, the South African variant did not exist at all, so we are not able to say with any certainty how effective Pfizer is against the South African virus variant.

The conclusion we reach from all of the above, especially for our American clients, is that, even if the CDC says that vaccinated persons can travel again and restrictions on foreign travel are eased, the level of protection offered by vaccines against mutants still remains very limited. Another new mutation has emerged in Brazil and is spreading through South America at a phenomenal speed. Meanwhile, a new variant has appeared in Africa (Tanzania and Angola) with over 120 mutations. We therefore continue to recommend that Premium clients who have been vaccinated should travel as little as possible.

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