Salvagene GROUP

Business Unit: SARS-CoV-2 Task Force
Keynote: #71

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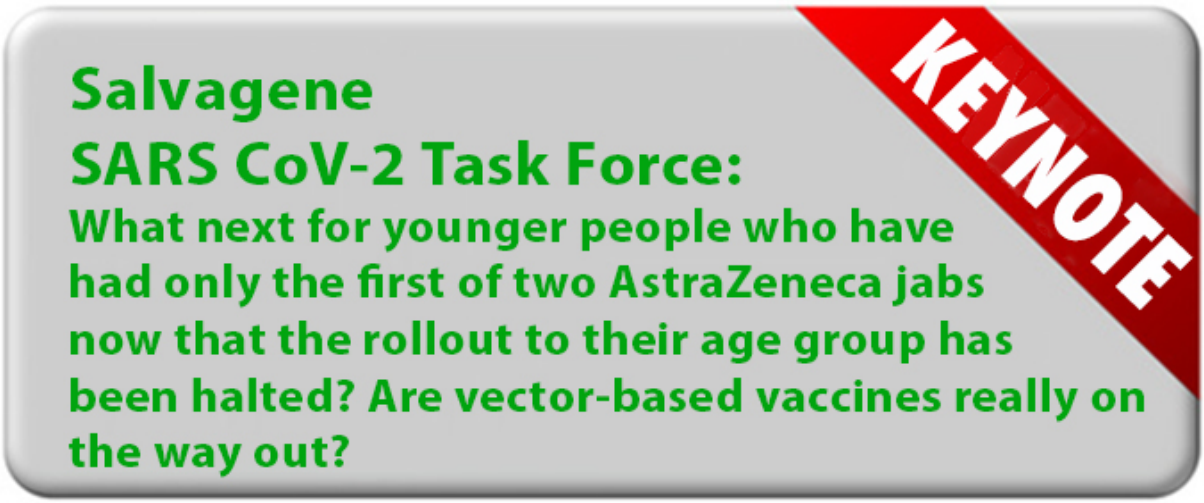

Dear Premium Customers,

As we mentioned in Part 1 of Keynote #70, hundreds of thousands of young men and women have already received their first shot of the AstraZeneca vaccine. How to proceed next is a question that is preoccupying health authorities throughout the EU as well as in other first-world countries such as Australia and Canada.

Most national vaccine commissions have as yet made no official recommendations. According to our information, however, the EU has now decided not to renew its contracts with AstraZeneca and Johnson & Johnson.
The Salvagene SARS-CoV-2 Task Force sees four possible outcomes:

1. The second dose is not administered and vaccination is considered complete on the basis of the first jab alone.

2. A different vector-based vaccine is used for the second jab.

3. Wait until the protein vaccines now in development become available.

4. An mRNA vaccine is administered to complete immunization.

We consider this fourth option to be the best solution, and the Standing Committee on Vaccination (STIKO) at the Robert Koch Institute in Germany concurs.

It should be noted that the principle of "mix-and-match" is already established in other areas and with other viruses, where a different vaccine is administered for the second of two jabs. Take, for example, the Ebola vaccine: the first injection is with adenovirus 26 as a vector into which the gene sequence for an antigen – the Zaire virus – has been cloned. The second dose uses the NVA virus as its vector with multiple antigen sequences. This vaccine is considered to have been a milestone in immunology.

The quest for a vaccine against the Ebola virus went on for many years, but this combination of two vectors seems to work reasonably well. It should be mentioned that Ebola is a very tricky virus, so the success of the twin-vector approach can probably be attributed to the virus coming under attack from two different directions. Both vector vaccines are directed against specific structures of the virus, so the target is the same and the immune system is primed against antigens and vectors alike. At the same time, the vectors not only serve to produce the antigens of the Ebola virus in the cells; they actually reinforce the immune response.

In our opinion, following up on one shot of AstraZeneca with another vector-based vaccine – for example the Johnson & Johnson or even Sputnik V – is not the right short-term solution. As mentioned in our previous keynote, the FDA has currently paused the rollout of the Johnson & Johnson vaccine due to the risk of thrombosis. Meanwhile, the EMA has halted the administration of the AstraZeneca vaccine. Consequently, we are unable at the moment to gauge with any certainty the risk of administering a similar adenovirus vector as a second dose. After restricting AstraZeneca on an age basis, Australia has now cancelled its order for Johnson & Johnson because of its vector-based platform. Ireland also restricts AstraZeneca allocation exclusively to persons aged 60 years and over, and Denmark has become the latest EU country to suspend the use of this particular vaccine on any of its citizens indefinitely.

As already explained in previous Keynotes, Sputnik V uses two different adenoviruses as its vectors. However, we are far from satisfied with the study data so far made available. The vaccine was developed by the state-run Gamaleya Research Institute in Russia. Our key reservation – and one that was skirted over in the Lancet medical journal – is that the tests to check reactions to the vaccine were also devised by the same institute. This is contrary to general scientific practice in which a range of different tests are carried out, each of which has been developed independently of the others. For this reason – and especially with the pressure to introduce Sputnik V in Europe gaining momentum – we reiterate our cautious stance.

The next option on the table is to examine the feasibility of administering an mRNA vaccine as the second dose. It has to be said that not a single study of this strategy has been completed anywhere in the world so far. The WHO has also not yet made any recommendation with regard to cross-vaccination. By far the most advanced study is taking place in the UK where Com-CoV has been set up to investigate different combinations of vaccines. In some

cases, AstraZeneca is administered as the first jab, and in others as the second. The UK team are also varying the interval between first and second doses. So far, the second vaccine has been exclusively BioNTech, but now Moderna and Novavax are being added to the mix. For these trials, a relatively large number of volunteers first had to be recruited. Unfortunately, there are no published results from the trials as yet. Therefore, the option of waiting for these study results is not an option for the group who have had only a first dose. The option of administering an mRNA-based vaccine as the second shot would seem to be the one incurring the lowest risk.

It is not yet clear why the AstraZeneca vaccine increases the risk of cerebral venous sinus thrombosis (CVST). The mRNA vaccines are "purer" than vector vaccines in that they contain only a lipid envelope and the blueprint for the spike protein of the SARS CoV-2 coronavirus. This is the big advantage of mRNA vaccines – they consist of so few components that their effect can be readily controlled.

The next option is to administer a protein vaccine second time around. To date, none of the protein vaccines has passed the approval stage anywhere in the western world. The project that has advanced furthest is Novavax. Theoretically speaking, this vaccine contains only the protein of the virus and no other components, so along with the mRNA vaccines, it can be classified as relatively "pure". The drawback here is that the spike protein may be intercepted by antibodies, making the vaccine less effective. And this is the problem with protein vaccines in general. From what we currently know about Novavax, its efficacy is relatively weak compared to mRNA vaccines. The Chinese vaccines are also partly protein-based, and it is precisely for this reason that China has admitted – albeit unofficially – that their vaccines have the same problem of significantly lower effectiveness. This has even been acknowledged by the director of the Gao Fu Center for Disease Control and Prevention. China has now embarked on trials similar to those being conducted at Oxford, in which the vaccines are combined.

In Spain and the UK, a debate has begun about whether young people should forego a second vaccination after having already received one dose of AstraZeneca. We have always been opposed to any such strategy, because a second vaccination dose is essential. The studies show that the immune response is strong just a few weeks after vaccination, but they do not offer any conclusions on how long this immune response lasts. The first vaccine dose does indeed activate antibodies and immune cells, but it is only with the second dose that antibody response is optimized and the memory cells are activated, especially the T-memory cells which we measure regularly as part of our Covid 19 Immunization Program. We stress the importance of these T-memory cells being trained up, and it is the second dose that builds up immune memory. Consequently, we do not think it is a good idea to simply skip the second jab. The immune system is highly complex, with many different processes operating in a regulated sequence over a set length of time. For this reason, the vaccine manufacturers always stipulate an optimal time interval between first and second doses, and this should be adhered to. If the second vaccination is postponed for too long, the body's memory of the first dose may already have faded to such an extent that the desired effect is no longer achieved.

And on the subject of mix-and-match vaccinations, we should also mention the negative experiences of our colleagues in the fight against the HIV virus. To date, there is no effective vaccine against HIV. The AIDS virus is too elusive, because it attacks the immune cells themselves and mutates extremely quickly. Fortunately, it appears that the SARS-CoV-2 mutations so far discovered resemble each other closely, and the virus does not seem to have as many options for sharpening up its act as its HIV counterpart. Of course, the situation may change for the worse at any time. SARS-CoV-2 has already generated very many mutations. With the variants coming in from South Africa and Brazil, we may be facing an inundation of escape mutations, which might make mixing vaccines the more effective strategy.

Our Task Force continues to research into escape variants which constitute the biggest threat posed by mutation. As a company operating in the health sector, we are at home in the field of genetics and mutations, so we find ourselves working in our specialist field. Escape variants arise when the virus spreads in a population that lacks complete immune protection. This is the case, for example, when immunity gradually declines after vaccination or a survived infection. In a population with some degree of immunity, such as in Israel, the UK and the USA, an escape variant would have an advantage over the original virus where both have a similar capacity for transmission. In such a scenario, an escape variant would become the dominant form relatively quickly. In countries where immunity is low, such as most EU countries, an escape variant would be in direct competition with the dominant variants, which in turn would still find a sufficient number of susceptible hosts. In this case, an escape variant would only gain a foothold if it were also more transmissible. From this, we have to assume that future escape variants will generally emerge in countries with high vaccination rates. Essentially, we can expect the entire pandemic to develop further and with uneven distribution. The fact that poorer countries account for only 0.2% of vaccines administered in the world underlines the challenge of getting a grip on the global pandemic.

As we predicted at the start of this year, the course that the pandemic ultimately takes will be decided mainly by escape mutations. Fortunately, there are a number of countries – most notably the UK – that have an exemplary record in gene sequencing and in sharing their findings. Platforms for monitoring coronavirus mutations are also being built up very strongly in other countries. We think that this is the decisive moment for sharing expertise and for mapping the spread of mutations in the different regions of the world.

The mRNA vaccines are relatively easy to adapt. If a so-called "wild-type virus" were to emerge between first and second vaccination, it would make sense for the second dose to be a

version that has been updated for the variant now in circulation. This is where BioNTech and Moderna in particular are working at full speed. However, they are also permanently in reactive mode, waiting for the next mutation to happen before they can take corrective action.

When it comes to adapting the vaccines, the question of approval inevitably arises. In theory, the process ought to be re-opened, and the extra work involved for manufacturers should not be underestimated either. For example, we are in direct contact with CureVac whose vaccine is produced by Bayer, and we can readily appreciate the practical difficulties in the production of an mRNA-based vaccine that has to be adapted at short notice.

We have indicated several times that the situation is becoming more and more complex, and we are not entirely convinced by the way the global vaccination program has been handled so far, not least in organizational terms, because too many individual factors have to be taken into consideration in developing the optimal vaccination strategy for the individual. General guidelines for vaccination are implemented by anonymous test centers, which we do not consider optimal in view of the increase in mutations. We also do not consider allowing the public the choice of a specific vaccine to be the best solution, because the technical considerations are far too complex for a lay person to understand. In our opinion, this task should be placed in the hands of general practitioners following suitable training. After all, the family doctor is still best placed to assess a patient’s health and constitution, including their medical history, and then to make an individual recommendation.

Salvagene Premium clients have the great advantage that our Advisory Board has been working on this for months and that we keep them continuously informed on an up-to-date and individual basis.

Finally, despite the great progress made, especially in the USA, we would like to point out that people are still at risk of infection despite having been vaccinated. Vaccines do not offer complete protection against infection, and certainly not against symptom-free infection. This may manifest itself as a cough and a raised temperature. We urge vaccinated individuals not to regard themselves as exempt from testing and thereby allow the virus to covertly develop immunity to the vaccine and subsequently spread among others who have been vaccinated. This general principle applies to all: vaccination is not the end of the story. We will discuss the subject of immunity and infectiousness of vaccinated people in a separate article.

Before we round off this present report, however, we would like to remind you of the findings of our colleagues in aerosol research. The overwhelming majority of all infections take place in unventilated rooms, and this especially applies to the newer mutations with their significantly higher viral load. With summer just around the corner, we explicitly warn against spending too much time in enclosed spaces that rely on air-conditioning.

SALVAGENE HQ
Université Paris Sorbonne
125 Rue Saint-Jacques, 75005 Paris

SALVAGENE UK
52 Grosvenor Gardens • SW1W 0AU London UF
Tel: 0044 20 3287 0644

SALVAGENE USA
101 Avenue of the Americas, 8th floor • 10013 New York
Tel: +1 646 583 0370

info@salvagene.com • www.salvagene.com