Salvagene GROUP

Business Unit: SARS-CoV-2 Task Force
Keynote: #65

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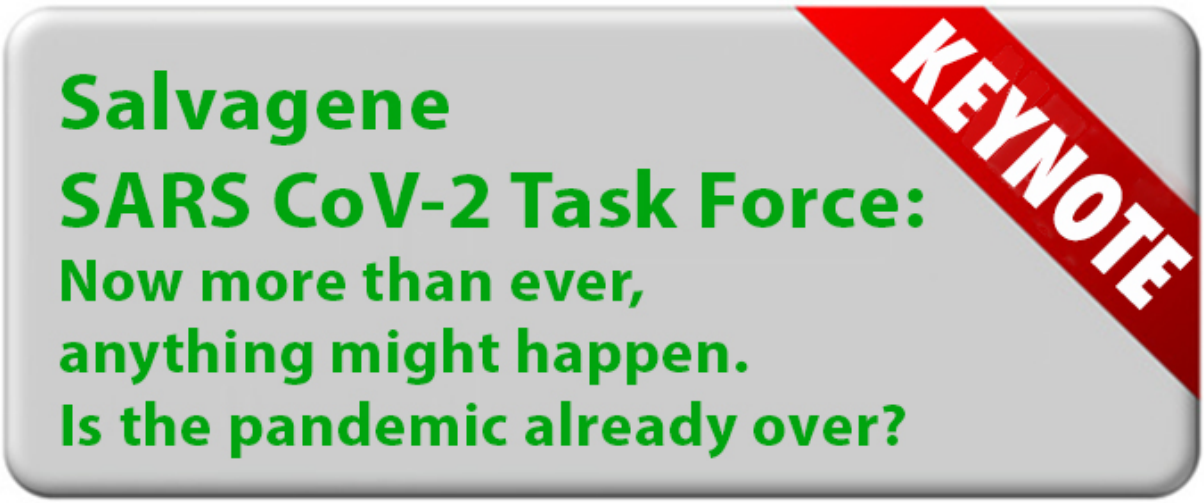

Dear Premium Customers,

Politicians and vaccine manufacturers are sounding upbeat, predicting that the pandemic will be over by summer at the latest.

The incidence of infection varies greatly around the world. Some countries have very low vaccination rates and yet cases of infection are still falling, in contrast to other countries where the speed of vaccination rollout is high but they have little to show for it. For example, some parts of the USA have partially lifted their lockdowns and case numbers are falling, while other states with even stricter lockdowns have been unable to make any headway in reducing infection levels. This may be due in part to the new and unfamiliar variants that have emerged in New York and California. The two factors driving these massive variations are the changing seasons and the appearance of mutant forms. It is reasonable to assume that, in the northern hemisphere and regions closer to the equator, the natural incidence of infection will be reduced over time. More significant in our view is the spread of new variants.

Essentially, all the vaccines approved so far display reduced efficacy against the new mutants to varying degrees. In this context, BioNTech (Pfizer) has undertaken an interesting project, a new study into the development of a third vaccine shot to achieve enhanced efficacy against these mutants. In the matter of a possible third booster dose, it is worrying that all the major regulatory authorities in the world have more or less decided that no new approval procedures will be necessary, regardless of how much the vaccine in question has been modified. In parallel, BioNTech has published a study on efficacy against the mutants, from which it is still not clear just how effective its vaccine will be. The results appeared in *The New England Journal of Medicine*.

Also of interest in this context is a highly controversial project in England – a "human challenge" in which volunteers between the ages of 18 and 30 are infected with the SARS CoV-2 virus without prior vaccination. Setting aside for one moment the fact that long-term damage can also occur in young and healthy people, we consider this project to be useful in obtaining a significantly higher validity basis for the development of vaccines, by contrast with the so-called empirical studies conducted so far.

Israel is a country that is of great interest to us at the moment. The vaccination rates here are very high. Although the BioNTech/Pfizer vaccine has produced the best results in terms of reduced infectivity, it is still possible for a vaccinated person to carry and transmit the virus, and with all other vaccines, this probability is even higher. For example, arrangements have been made to stage concerts in Tel Aviv, which may only be attended by persons who have been vaccinated, but because it is still possible for the virus to be passed on, FFP2 masks will have to be worn.

As for what is happening elsewhere in the global pandemic, the southern hemisphere is about to enter its autumn, and the numbers are rising sharply again, in contrast to the north. In Brazil, for example, up to 3,000 deaths a day are forecast in the coming days and weeks – up from 1,500 at present.

Indeed, we still have the full spectrum of possibilities as to how the pandemic will unfold. It is quite possible that the virus will weaken itself through mutation and virtually disappear in the northern hemisphere this summer, meaning that the pandemic is already more or less over. Ministers in the UK and governors in the USA (especially Florida and Texas) are making confident forecasts in this regard. And the Russian government has issued an official statement predicting this outcome for the pandemic.

In theory, we agree that this is one possibility. At the other extreme, however, is a course of events in which the current run of mutations continues. These have so far tended to become more transmissible than the original Wuhan virus and are associated with greater complications. The already reduced effectiveness of vaccines continues to manifest itself. This is because of political considerations in various countries, where governments have felt pressurized to adopt vaccines with poor efficacy or to extend the interval between first and second doses. The consequence is partial immunity, which merely opens up the way for escape mutations, thereby significantly prolonging the pandemic with considerably more complications. Indeed, Professor Ugur Sahin, CEO of BioNTech, recently conceded that he could not rule out the formation of a “super mutant”.

In this other extreme scenario, success stories such as those from pharmaceutical giant Merk become all the more significant. Having abandoned their efforts to create a vaccine, they are now focusing on the development of Covid-19 drugs which may play a major role in the future; when resistance to antibodies builds up due to escape mutations, it is important that there are medications that are antivirally effective against SARS CoV-2. The two drugs that have

so far been unveiled and which we have been monitoring for some time, molnupiravir and MK-711, certainly seem to offer good prospects.

At the moment, the vaccine situation can be summed up as follows:

Unlike BioNTech, the scientists at **Moderna** have so far published only statements based on their own findings but without any valid data on the efficacy of their vaccine against the currently known mutants. As regards a booster vaccine, should the pandemic continue this year, they have so far not produced any information on the "Next Generation Program". Furthermore, the continuing infectivity rate among individuals who have received the Moderna vaccine is significantly higher than that of BioNTech.

The efficacy of the **Johnson & Johnson** vaccine is officially only 72%, which is considerably lower than the published rates for the mRNA-based versions. In any case, all vector-based vaccines are generally less effective. The Johnson & Johnson vaccine has one big advantage in that its approval came relatively late. Its clinical phase 3 was partially conducted in Latin America and in South Africa, which meant that it had a greater exposure to the new mutants than the earlier vaccines. They reported much lower success rates in South Africa, but still above the 50% threshold for approval laid down in World Health Organization guidelines. The Johnson & Johnson vaccine has the further advantage that only one shot is needed. The disadvantage, however, is that production is only just starting up. As we have seen with the vaccines approved so far, the initial production tends to include defects, and because of side-effects from the first batches, they should be avoided.

This is another argument in favor of **BioNTech**, which has now reached a stage of maturity, as its first two large production runs have already been used up, mainly due to the high vaccine consumption in the USA since the new president took office. Now there is a third production version, which comes with an unofficial upgrade. This is being produced at the Pfizer plant in Ghent, Belgium, at the new BioNTech plant in Marburg, Germany, and at the Pfizer plant in Michigan. So, we can expect this upgraded version from BioNTech to reach the market in 1-2 weeks at the latest. This version has already been adapted to deal with the new mutants, but its effectiveness remains limited, especially with regard to the South African variant. The mRNA technology of the BioNTech vaccine lends itself to upgrading, whereas it will prove more difficult to develop a booster vaccine for the vector-based Johnson & Johnson.

We now have a wealth of data on the **AstraZeneca** vaccine and the effect of delaying the second dose. There are already early reports that have shown some kind of resistance building up in people who have been vaccinated. Overall, this trend is very worrying. If many people are infected who are only partially but not yet properly immune, the probability increases that the virus can take hold and resistant variants appear.

It is clear that all vaccines currently approved for use have limited effectiveness against the mutants that have emerged so far. If an approval process were to be run today with the Brazilian or South African variant in Clinical Phase 3, it would emerge that none of the currently available vaccines has an efficacy of more than 50%, which is the licensing threshold employed by the WHO.

On the one hand, there is a race between the vaccines that go into battle against the mutations, and on the other hand, there is a race between the SARS CoV-2 mutations themselves. Which will prevail? The received wisdom is that the relatively weak mutations will prevail. This is quite possible, in which case we can expect the pandemic to end sooner rather than later.

For various reasons, we do not concur with this prognosis at present. As mentioned earlier, all mutations to date have turned out to be more transmissible and also more complex. The three main variants causing concern are the Brazilian (P.1, 501Y.V.3), the South African (B.1.351, 501Y.V2) and the one that was first observed in the south-east of England (B.1.1.7, 501Y.V1). B.1.1.7 is considered to be the more harmless of the three. Because of the E484K mutation at the spike protein observed at various sequencing sites in Bristol, Southampton and Liverpool, we have to assume for the time being that the mutation event will become more infectious and also more complicated, with the more dangerous mutations prevailing over the weaker ones.

We are involved as consultants in a mass vaccination project in the Austria province of Tyrol where the South African variant has gained a foothold. This pilot project is a very interesting opportunity for us to see first-hand how well the different vaccines actually work. At the same time, it is also important to observe immunity that arises naturally from an infection. The findings from South Africa in particular are interesting. It turns out that people who became infected with the more virulent SARS CoV-2 mutant formed antibodies against both the more infectious variant and the original virus. From this, we can deduce that infection with a highly virulent mutant also offers subsequent protection against the underlying form of the virus. This is one of the main reasons why we are holding back from making recommendations on vaccination to Premium clients who have a very low risk profile. In other words, we are waiting for a vaccine that will be successful against the most dangerous variants and, taking a long-term perspective, will also immunize against all subsequent and weaker variants.

Conversely, vaccines that have a lower efficacy anyway and which were tested for the original variant right at the beginning of the pandemic pose exactly the opposite problem. The same applies to the point in time when a client was deemed to have a low-risk profile. It should also be noted that the pandemic is not over until

it can be downgraded to an epidemic. Ultimately, the infection event will continue worldwide for a lengthy period of time and there will also be escape mutations, which in turn will cause a new cycle of immunity gained from vaccination and/or infection to start all over again.

A similar problem exists with a survived infection. The question of whether you should still be vaccinated after an infection can be answered as follows: Basically, antibodies are formed in response to the virus variant that caused the infection, which means that an individual who has survived infection naturally has a lower immunity against new mutants, as would be the case if they had been vaccinated. The best estimate is that antibodies degrade within a period of three to six months, depending on the severity of the infection. For this reason, we monitor any infection of our Salvagene Premium clients to determine which variant was involved. As part of our C19 Aftercare Protocol, we also monitor antibody function to gauge how quickly this breaks down, leading to reduced immunity.

As mentioned above, if you become infected with the more dangerous variant, then you should be immune to the other variants. Therefore, we do not see the need to be vaccinated after infection by one of the more dangerous variants has been overcome. On the other hand, vaccination makes sense if you have first been infected with a weaker variant. It must, however, be borne in mind that antibodies formed during the initial infection and antibodies from a vaccine may produce cross-reactions. The situation in this regard remains unclear.

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