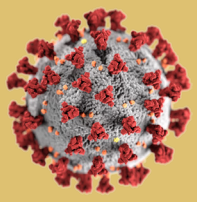
South Africa and the **COVID-19**



vaccine debate

Prof Burtram C Fielding

Scientists, public health experts and politicians have been telling us that, to stop Covid-19, we need to embark on a massive vaccine rollout. But do we really need to vaccinate more than 70% of our population to stop this virus? What is the science telling us?

What do we know about the Covid-causing virus?

To make sense of the need for a vaccine, we need to look at this "new" or novel coronavirus first. The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the virus behind Covid-19, is only the seventh human coronavirus identified. This virus is not nearly as deadly as two of its "cousins", SARS-CoV and MERS-CoV, which had a 10% and 35% death rate, respectively. According to global statistics, only about 15-18% of all Covid-19 cases develop into severe or critical cases that require treatment with oxygen, with about 5% of all Covid-19 cases requiring intensive care. And thankfully "only" about 2.0-3.5% of Covid-19 cases die. We now know with some certainty that advanced age (older than 60); being male; and the presence of other pre-existing medical conditions such as obesity, diabetes, heart disease, certain chronic lung diseases and kidney disease are among the major factors linked to severe Covid-19 and an increased risk of death. This does not suggest that young children, the youth and women are immune to the disease. They can and do catch the virus – even if they don't always exhibit the associated symptoms – and can and do pass it on to others. Importantly, only those who develop severe Covid-19 are at risk of dying.

Why are people dying of Covid-19?

It is not SARS-CoV-2 that kills directly, but rather it is the body's own response to the virus that causes damage to the body. In all viral infections, the infected person's built-in immune system, once alerted to the presence of the invading virus – identified by the body as a foreign substance – is activated and, in healthy individuals, launches an attack against said antigen. The main purpose of the immune response is to stop the spread and movement of the virus throughout the body. If the pathogen manages to evade the first-line physical barriers and enters the body, the chemical and cellular immune response is activated. It is then that the body releases cells (notably B cells and T cells) that attack the pathogen, or produces special proteins known as antibodies. Think of these antibodies as the sentinels of the immune system; they attach themselves to the virus, and attract cells that then destroy said antigen.

Typically this immune response is carefully regulated by the body, to ensure that it destroys only the virus, and not the host itself – that is, humans. With Covid-19, however, the immune system "overreacts". This leads to the blood-clotting system malfunctioning, as well as to the overproduction and release of inflammatory proteins known as cytokines. This results in the formation of blood clots and what's known as hyperinflammation, respectively. Hyperinflammation throughout the body, in particular the organs, can lead to multiple organ damage and failure. On the other hand, blood clots forming in blood vessels can obstruct blood flow, and could result in deep-vein thromboses in the legs, clots in the lungs, and stroke-causing clots in the brain.

Because the body's immune system, inflammation and clotting are linked, anything that causes the regulation of these systems to get out of whack, and the balance between the three to be off, can lead to severe or critical Covid-19, and in some cases, death.

Can we save lives in the absence of effective Covid-19 vaccines?

To effectively treat Covid-19, we need to be able to identify individuals at risk of developing severe or critical Covid-19 early in the clinical development of the disease. Then, equally importantly, we need drugs that are effective in treating the disease. How far have we advanced to address these two issues?

As mentioned, we know which part of the population is at greater risk of developing severe Covid-19; and keep in mind that not everyone in these risk groups will develop severe Covid-19 – just about 15% do in the end. Then, when someone becomes infected, we can just analyse the combination of various early symptoms, predict who is at greater risk of developing critical Covid-19, and have some idea of who is at increased risk of dying. Used together with the presence of certain bio-markers in patients – biological molecules found in body fluids or tissues that are a measure of body processes and/or indication of disease – we can predict, with a high degree of accuracy, not only the risk of illness (morbidity), but also the risk of death (mortality) of individual patients eight to ten days in advance. This should provide clinicians with enough time to start pharmaceutical interventions.

I will not look at all the possible drugs used in the treatment of severe Covid-19. Instead, let's look at two relatively cheap drug options that have received widespread support, and that are readily available in South Africa. Dexamethasone, a steroid widely used to treat inflammation, was the first drug shown to save lives in people ill with Covid-19, in what University of Oxford scientists called a "major breakthrough". Trials show dexamethasone reduces death rates by a third among seriously ill patients. The South African Department of Health (SADoH) issued an advisory to "recommend the use of dexamethasone (or an equivalent steroid) for all Covid-19 patients on ventilators or requiring non-invasive supplementary oxygen".

Researchers report that hospitalised Covid-19 patients treated with blood thinners (usually low molecular weight heparin) have improved clinical outcomes and this is associated with lower death rates. In fact, the SADoH guidelines recommend "the use of blood thinners for all hospitalised patients with Covid-19. The blood thinner can be given in two different doses: low-dose to reduce the risk of blood clots developing and high-dose to treat blood clots that have already developed."

It is important to note that these drugs are used to treat severe or critical Covid-19 in patients requiring hospitalisation and ventilation only, and are not recommended for routine use in mild to moderate Covid-19 cases.

What is "herd immunity"?

The World Health Organisation (WHO) defines herd immunity, or "population immunity", as "the indirect protection from an infectious disease that happens when a population is immune either through vaccination or immunity developed through previous infection". In other words, it's really about preventing the spread of a disease. Depending on how contagious a disease is, between 60% and 90% of a given population must have some form of immunity to stop the disease-causing organism from spreading. In South Africa, scientists estimate that we need 60% to 70% of our population to be immune to Covid-19 to stop the spread. How does immunity from natural infection compare to immunity from vaccination? To achieve herd immunity against Covid-19 in South Africa and minimise deaths, should we be looking at vaccination only, or should we be looking at a vaccine-natural infection combination approach?

Some scientists speculate that compared to natural infection, Covid-19 vaccines offer "better" protection, with possibly longer periods of protection. Yet, with the vaccine having been developed and rolled out over only the past few months, how much do we know about immunity from Covid-19 vaccines?

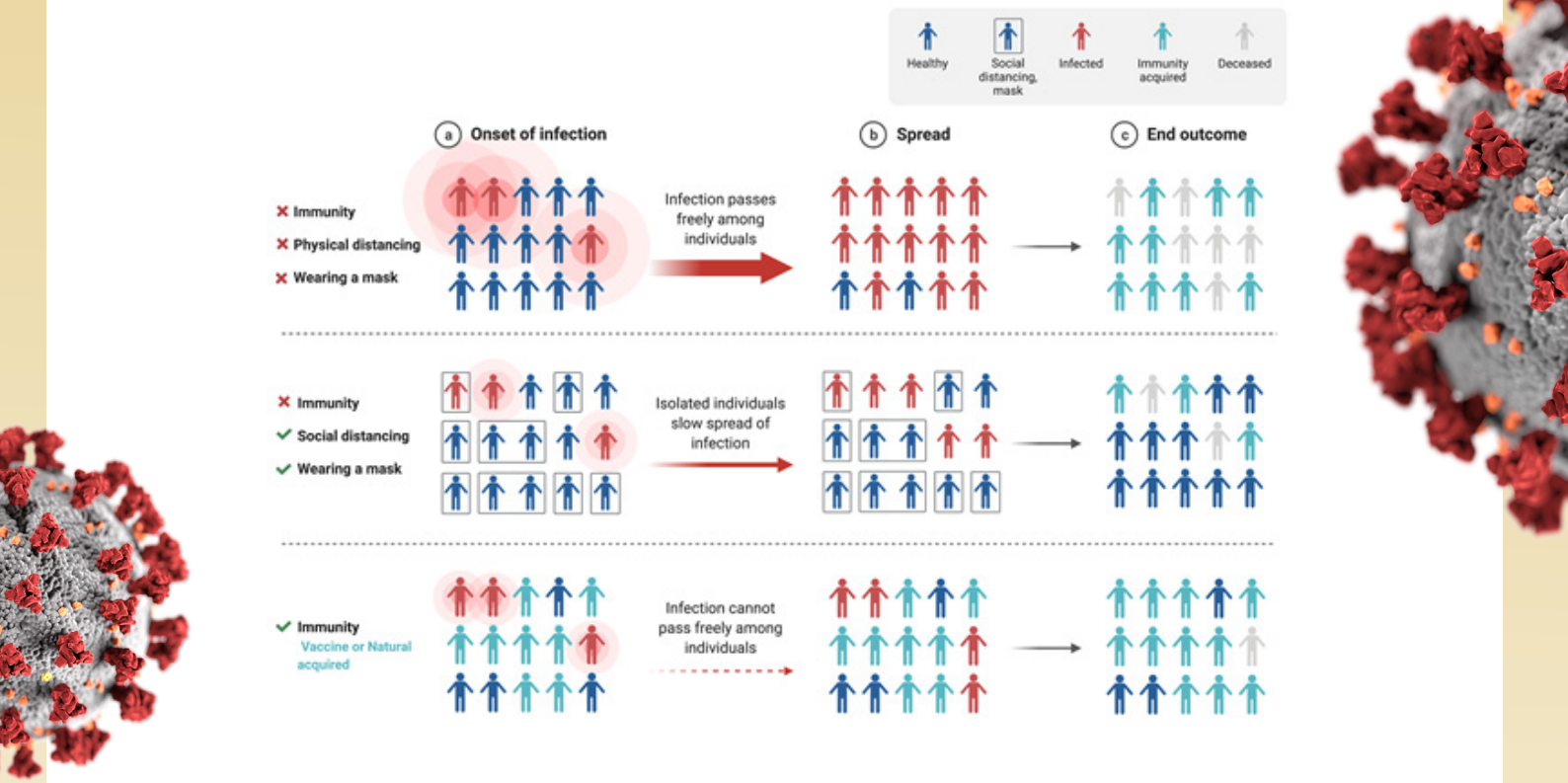


Figure 1: The principles of herd immunity and safety measures explained (Created with BioRender.com. Based on "Principles of Herd Immunity and Social Distancing", by BioRender.com (2021). Retrieved from https://app.biorender.com/biorender-templates)

Unfortunately, the answer to this question is that we know very little. We do not know if immunity from either will last months or, hopefully, years. For now, only time and further research will tell. Obviously researchers are hoping for long-term immunity, and there is a growing consensus that we will likely see immunity lasting one to three years. In reality, though, the duration "could be longer or shorter" and will only be determined by studying people who have received the vaccine.

And don't forget that we have immune data from the other six human coronaviruses. For the four "common cold" coronaviruses, immunity typically lasts between one and three years; this means that people can be infected multiple times over the course of their lives. For the two more deadly coronaviruses, SARS-CoV and MERS-CoV, antibodies last for one to three years, but the T and B cells – the determinants of long-term immunity – appear to last from five years to decades. Very importantly, too, whereas the current Covid-19 vaccines use one viral protein to stimulate an immune response, natural infections also stimulate antibody production against various other viral proteins; these other antibodies have also previously been shown to play a central role in immunity.

Will we see the same for SARS-CoV-2 as we see for the other human coronaviruses? Does this mean that natural immunity will offer better protection against SARS-CoV-2 variants? Does this mean that it will offer better long-term protection? We simply do not know yet, and only time will tell.

What is meant by vaccine "effectiveness" and "efficacy"?

When a vaccine is developed, we ask the questions "Does the vaccine work?" (efficacy) and "Does the vaccine help people?" (efficiency). Efficacy, which is tested under very specific conditions, in which people are randomly assigned to "treatment" vs "no-treatment" groups, does not necessarily equal effectiveness, and could overestimate the impact of a vaccine's impact in "real-world conditions". Once the efficacy of a vaccine has been established, its effectiveness is determined in observational studies, where factors such as other medications people are taking, underlying chronic co-morbidities, viral mutants, the age of those vaccinated, and how the vaccine is stored and administered under everyday conditions, can reduce how effective the vaccine is at preventing disease. In South Africa, we are now seeing in real time how the difference between "efficacy" and "effectiveness" for the University of Oxford/AstraZeneca vaccine is playing out. The vaccine, which had a reported efficacy of 95% against the wild-type (original) SARS-CoV-2, now has a reported 25% effectiveness in younger people infected with a SARS-CoV2 mutant. A virus cannot replicate – make more of itself – without a host; in this case, the host is us. Each time the virus enters a human cell, it first has to make more of its own genetic material, which will ultimately be used to make more copies of the virus. This type of virus does not have the ability to correct mistakes when it copies its own genetic material, and these resultant changes are known as mutations. This a natural process and the majority of the mutations will not result in changes to how the virus behaves in the host. Every so often, though, a mutation arises that could provide the virus with a selective advantage in the host, such as allowing the virus to enter human cells more easily, or to evade the body's immune cells. Viruses with these small genetic changes (or mutations) are known as "variants". This is what we have observed first-hand in some parts of the world where variants have been identified. Data now show that some of these variants can enter human cells "better" and spread "easier" between people. Worryingly, some research groups have reported that antibodies from vaccines and natural infections are not as effective against some variants as they are against the original virus, rendering some vaccines less effective in certain demographics of our population. Thankfully, as far as we know, none of the current variants cause more severe Covid-19.

What are the Covid-19 vaccines considered for South Africa?

Vaccines are meant to mimic natural infections and aim to trick the body into activating its immune system. So, similar to natural infections, the antibodies and immune cells generated after vaccination will protect the body when exposed to the actual virus. The first batch of Covid-19 vaccines currently considered in South Africa all rely on their acting upon the SARS-CoV-2 Spike protein (S). The S is the viral protein that sticks out of the virus's surface, giving it its "crown-like" appearance when viewed under a very specialised electron microscope. This is also the virus protein that binds to the human cell protein (ACE2), allowing the virus to enter the cell. These vaccines employ different technological approaches to prime the body's immune system to recognise and fight SARS-CoV-2. But, in the end, all of them are aimed at stimulating the production of neutralising antibodies in the body; these antibodies are aimed at preventing the virus from entering the cell by binding to the virus S and preventing attachment of the virus to the human cell receptor, ACE2.

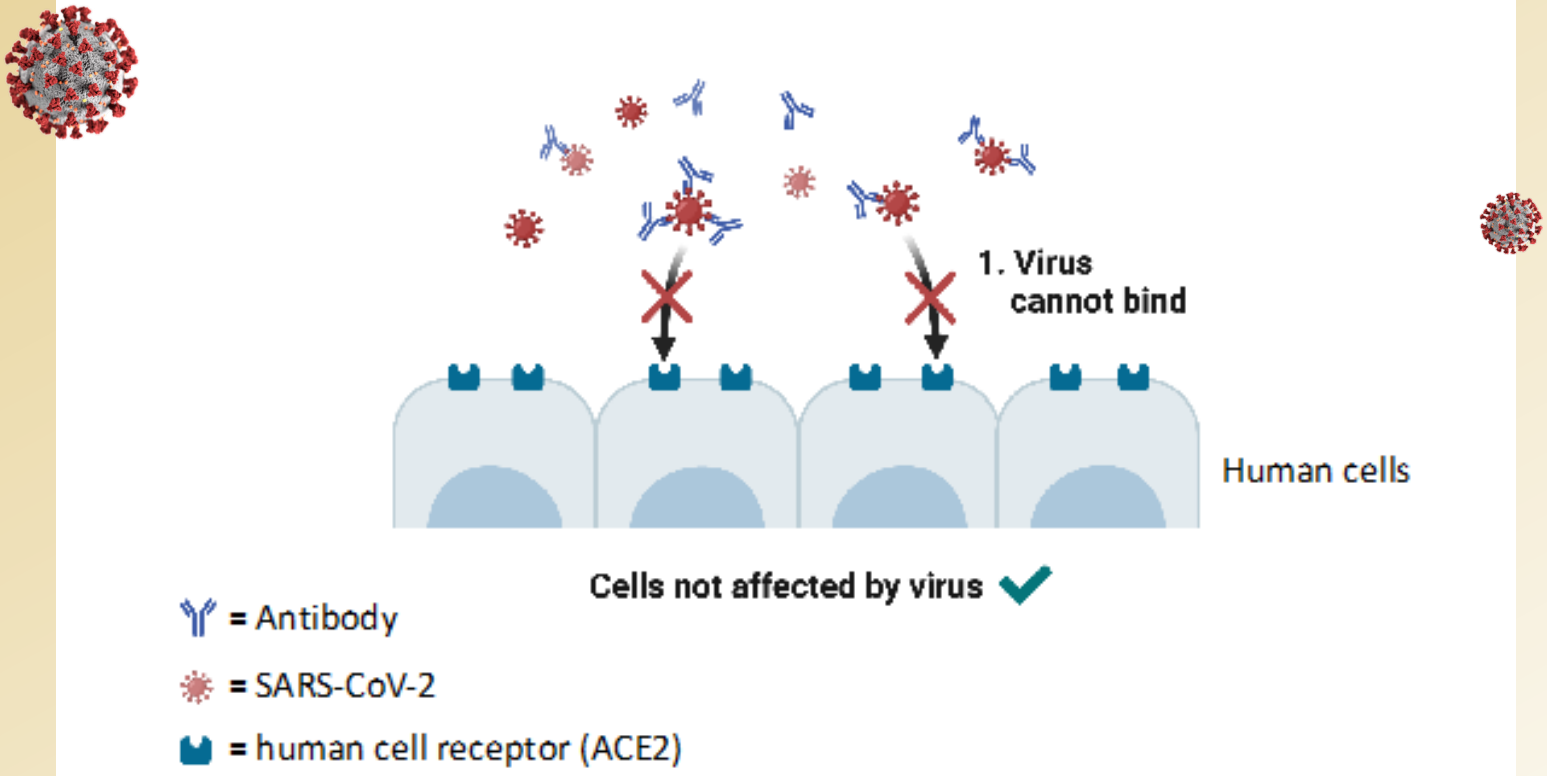


Figure 2: Neutralising antibodies prevent the virus from entering the cell (Created with BioRender.com. Based on "Recruitment of T and B Cells by Antigen-presenting Cells (APCs)" by BioRender.com (2021). Retrieved from https://app.biorender.com/biorender-templates)

The Pfizer/BioNTech and Moderna vaccines use the same type of technology. These are mRNA vaccines that code for the coronavirus's S and are encapsulated in a lipid nanoparticle. After it is injected, the recipient's cells then make S, and the body also produces antibodies to S. Whereas the Pfizer/BioNTech vaccine has to be stored at -70°C, Moderna's vaccine can be kept in a standard refrigerator for up to 30 days, and can be stored for up to six months at -20°C.

The AstraZeneca, Johnson & Johnson and Sputnik V vaccines depend on technology based on an inactivated common cold virus. They contains the genetic material of S. The AstraZeneca vaccine can be stored and transported in normal refrigerated conditions – about 2° to 8°C – for at least six months. Whereas the other four vaccines mentioned above require two doses, about four weeks apart, the J&J vaccine requires a single dose.

SinoVac is different from the other Covid-19 vaccines considered for use in South Africa in that it an inactivated SARS-CoV-2 vaccine. Unfortunately, based on current data, these vaccines do not effectively protect us from SARS-CoV-2 infection and, in about 30% of cases, do not prevent those infected from spreading the virus. They are effective in preventing Covid-19, though, especially the severe and critical forms of the disease. And because the vaccines do not protect from infection or spread, the potential for the emergence of virus variants is still a possibility.

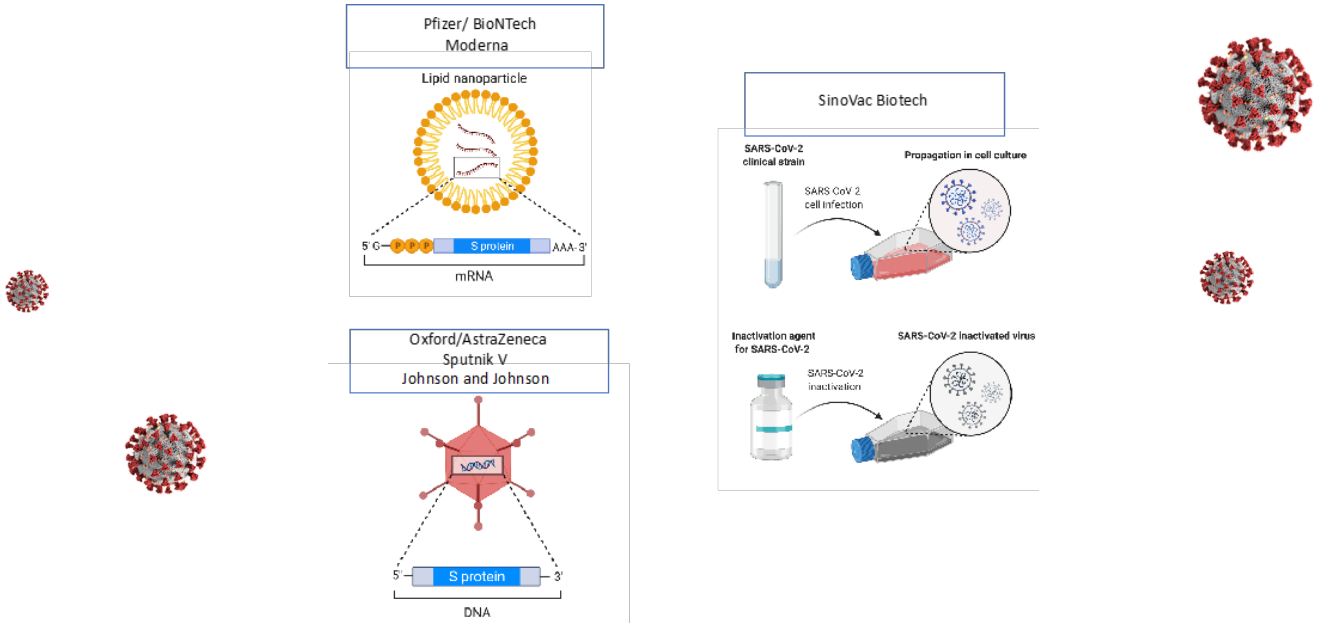


Figure 3: Vaccines considered for use in South Africa (Created with BioRender.com. Based on "Covid-19 Vaccine Candidate: BNT162 (a1, b1, b2, c2) (BioNTech)", "Covid-19 Vaccine Candidate: AZD1222 (University of Oxford & AstraZeneca" and "Covid-19 Vaccine Candidate: CoronaVac (Sinovac Biotech)" by BioRender.com (2021). Retrieved from https://app.biorender.com/biorender-templates)

Who should be vaccinated?

In general, vaccines are more effective in younger people than the elderly and young children, because the immune system in young adults is more robust; this often results in vaccines being less effective in the latter two. Some public health experts and politicians claim that because of the nature of the Covid-19 pandemic "no one may be safe until everyone is safe", and that as long as we allow the virus to infect many people, we will "allow mutations and increase the risk of death". Hence they argue that herd immunity may not be achieved if we do not vaccinate everyone, including children and pregnant or lactating women.

Traditionally, we would only consider vaccinating children if: (1) the disease has the potential to cause severe and widespread illness or deaths in children; (2) there is a residual pool of young hosts spreading a deadly disease to others; (3) a subgroup of children, with pre-existing medical conditions, are vulnerable to the disease-causing organism; and (4) the disease has resulted in the suspension of educational, social and athletic activities crucial to normal development. In children, Covid-19 symptoms are mostly mild, and a very low death rate has been reported. Moreover, deaths are almost exclusively linked to serious co-morbidities and in infants under one year of age.

There is global evidence that the closure of educational, social and athletic activities have not significantly prevented the spread of Covid-19 among children. In fact, we now see that other community- and household-based factors are chiefly responsible for the spread of the disease in children. Even though children can be infected and spread the virus to others, they are not the main source of spread. So, based on previous vaccination criteria, as well as current evidence, the large-scale Covid-19 vaccination of children appears not to be warranted.

As for the long-term safety of the vaccines, we simply to not have the data. In fact, the vaccines have not been tested on children and pregnant or lactating women, so we do not know what the potential long-term effects could be on the baby in the latter cohort. The vaccines have just not been around long enough.

So should you take the vaccine?

In the end, for people to make an informed consent decision about taking the vaccine or not – as for any other medical procedure – they need access to all available data. In my opinion, in the end, to vaccinate or not should be based on a risk-based approach. Everyone should weigh their risk of developing severe or critical Covid-19 with the potential risks, even though potentially small, associated with the vaccines; whichever outweighs the other, should inform your decision to vaccinate or not.

Finally, there is a growing consensus that herd immunity will not be achieved for Covid-19. It is my opinion that we should minimise the spread of the virus for as long as possible by maintaining the personal prevention measures of wearing a mask, sanitising our hands, physical distancing and self-isolating when feeling ill. But, equally important, we should protect those at high risk of developing severe and critical Covid-19 by vaccinating them. Once we have an adequate vaccine protection in this cohort – the elderly, with co-morbidities, as well as frontline medical workers – we could ease the use of the personal prevention measures with confidence.

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