Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Pandemic Vaccines: How Are We Going to Be Better Prepared Next Time?

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In response to the SARS-CoV-2 pandemic, we are currently witnessing the fastest vaccine development in history. While these vaccines will now make a significant impact on ending the pandemic, they were needed much earlier. Here I discuss how to ensure that vaccines will become available within 3-4 months after a new outbreak.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in late 2019 in Wuhan, China, and caused a global coronavirus disease 2019 (COVID-19) pandemic.[1] Since then more than one million people have died globally, millions have been infected, and in many countries we are seeing signs of societal disintegration. The global economy has taken a major hit and businesses in many areas including tourism, hospitality, and the airline industry are fighting for their survival or have already gone bankrupt. Daily life has become difficult, even for people who have not been infected or have lost loved ones. In addition, while countermeasures like social distancing, wearing face masks, and restrictions on large gatherings (especially indoors) can help to keep infections low if effectively implemented, the populations in many countries are getting tired and are often unwilling to comply to countermeasures, let alone complete lockdowns.

Vaccines against infectious diseases have been one of the greatest successes in human history, effectively reducing disease burden for many pathogens. They have even allowed us to eliminate a human virus (smallpox) and a livestock virus (Rinderpest virus) from the face of the earth. When the sequence of SARS-CoV-2 was made openly available by Chinese scientist on January 10, 2020, a race to develop a vaccine began.[2] This was not a race of vaccine candidates against each other, but a race against the virus. SARS-CoV-2 vaccine development is moving ahead at record speed. Based on important development work already done on other coronaviruses,[3] the first phase 1 trial was started on March 16, 2020,[4] the first individuals were enrolled in phase 3 trials in summer 2020, and results showing high effectiveness of two of these vaccines were recently reported. This speed of vaccine development is unprecedented, and the vaccines will likely be key in ultimately resolving this situation. They will also save millions of lives. However, vaccines were needed much earlier, as early as possible (Figure 1A). While it is unlikely that vaccines would have stopped the virus from going global, a well-prepared infrastructure capable of producing vaccines 3–4 months into the outbreak (in March or April) would have saved many lives and would likely have normalized the situation in many geographic areas by now (Figure 1B). Still, without vaccines, countries in the Northern hemisphere experience a strong increase in cases during the fall, even in countries that controlled the initial wave well. Here, I will try to provide a strategy that might allow us to be better prepared in the future from a vaccine perspective.

Overall Strategy

Many different viruses may cause a pandemic in the future, but we know which virus families have the most potential. And it is viruses that spread from human to human via the respiratory tract that we worry about the most, since this is a transmission route that is hard to stop. Viruses that use other transmission routes can be highly problematic as well but might be impacted much more by non-pharmaceutical interventions. From each of the identified virus families, which should certainly include the *Paramyxoviridae*, *Orthomyxoviridae*, and *Coronaviridae* families, a handful of

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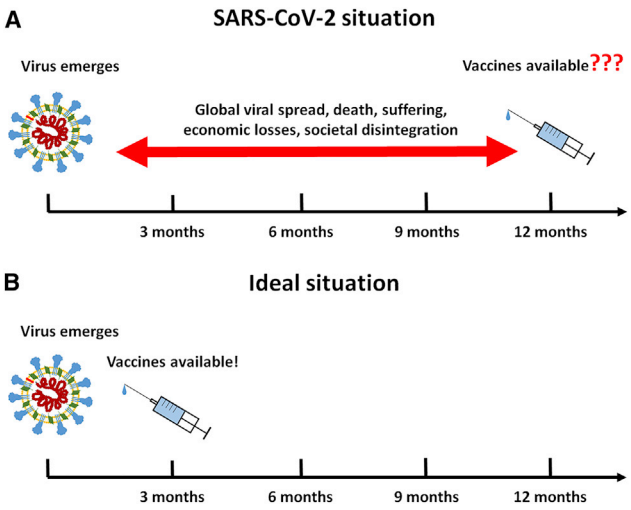

Figure 1. Overview of the Current Situation with SARS-CoV-2 and an Ideal Scenario from the Vaccinology Point of View

(A) Current, suboptimal situation and (B) ideal scenario.

representative strains with the highest pandemic potential should be selected for vaccine production. Up to 50–100 different viruses could be selected and this would broadly cover all phylogenies that may give rise to pandemic strains. Importantly, the more we know about viruses circulating in animals and their pathogenicity, the easier it will be to choose relevant strains (Figure 2). If this sounds farfetched, we should consider that the number "2" in SARS-CoV-2 indicates that this virus is genetically related to SARS-CoV-1, the virus responsible for the SARS outbreak in 2003.[5] We have experienced SARS-CoV-1 and in the past researchers have warned us of the possible emergence of similar viruses very explicitly.[6,7] It should be possible to choose candidates that are close to viruses that might emerge in the human population. The idea is that once viruses are selected, vaccines can be produced in different platforms and tested in phase 1 and phase 2 trials with some of the produced vaccine being stockpiled. This would likely cost 20–30 million US dollars per vaccine candidate resulting in a cost of 1–3 billion US dollars. In parallel, correlates of protection for related human viruses can be investigated (e.g., for human coronaviruses in the case of *Coronaviridae*). Production capacity can be built to allow rapid production of at least 2 billion doses per year using different vaccine platforms. If a new virus hits, the vaccine closest to the new strain is selected, a strain change is performed, vaccine production starts immediately, and phase 3 trials are initiated within a month. First readouts from the phase 3 trials would be expected likely post-second vaccination, and the vaccine could receive an emergency use authorization based on a correlate of protection 2 months after initiation of the trial. While initial trials continue, vaccine rollout is initiated, and production is ramped up.

Surveillance and Understanding Pathogenesis

For such a scenario, it is crucial to understand which viruses circulate in different animals and different ecosystems. This, of course, includes wild animals like bats and aquatic birds, which have been the reservoir for several of the past pandemic viruses. It also includes domestic animals in different production systems. For example, pigs were the reservoir for the H1N1 virus that caused the 2009 pandemic[8] and camels have transmitted Middle Eastern Respiratory Syndrome (MERS)-CoV to humans on a regular basis.[9] Despite ongoing global surveillance efforts, including surveillance in many animal species for influenza viruses led, for example, by the Centers of Excellence for Influenza Research and Surveillance (CEIRS)[10] and in bats in Southeast Asia for coronaviruses, led by EcoHealthAlliance,[11] among others, we need to increase these efforts substantially. More information is needed, especially in areas where there is close and frequent contact between animals and humans. These efforts might be complicated by external factors, such as political considerations, and would certainly need a substantial investment for systematic and sustainable support, but the effort needs to be made. Knowing which viruses are circulating among livestock and wild animals is helpful, but we also need to better understand the genome sequence data. Indeed, instead of just collecting sequences, viruses need to be isolated and their pathogenicity must be tested in suitable animal models. This will then allow us to identify pathogenicity markers that can then be recognized by just looking at the sequence. Examples include the predicted binding to human angiotensin converting enzyme 2 (ACE2) for *Sarbecoviruses* and binding to α-2.6 linked sialic acid and specific polymerase polymorphisms for influenza virus. This knowledge will allow us to select viruses for vaccine development that are as close as possible (potentially even identical) to viruses that may cause future pandemics.

Vaccine Development and Clinical Trials

In recent years, and especially since the beginning of 2020, we have learned a lot about different vaccine platforms and how they perform in terms of immunogenicity, safety, stability, and scalability. The currently ongoing phase 3 trials are the biggest vaccine platform comparison experiment ever done in history. Within the coming months, we will have a clear picture of which vaccine

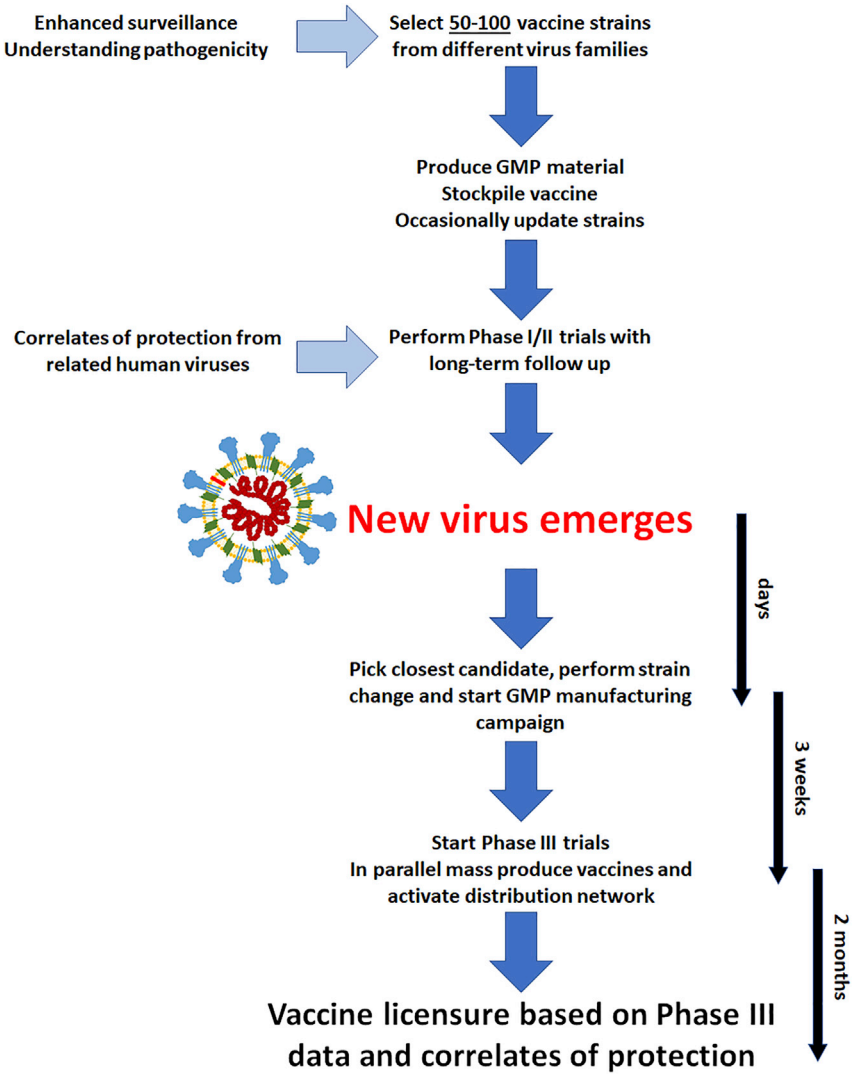

Figure 2. Schematic of a Vaccinology-Based Strategy Toward Better Pandemic Preparedness

platforms performed best. From these platforms, we can then pick 1–2 per selected virus, produce GMP (good manufacturing practice - the vaccine production quality needed for human trials) quality material, and go into phase 1 trials to assess initial safety. But we cannot stop there. SARS-CoV-1 vaccine development advanced to phase 1 trials for two candidates but this did not help us much with the current pandemic [12,13]. We also need to conduct larger (1000 participants or more) phase 2 trials with each of these candidates. This should include different doses and different age groups, similar to trials that have now been performed for SARS-CoV-2.[2] During these phase 2 trials we should strive to understand both the safety profile and the immune responses to these vaccines, including detailed exploratory analysis. Importantly, we should follow these individuals longer than usual. Ideally, follow-up times of 10–20 years should be considered. This would answer questions regarding the longevity of the immune responses, and it would certainly increase public trust in the safety of these vaccines. One of the most frequent concerns of the public is that a vaccine may appear safe in the short term but might have unknown long-term side effects. By extending these trials out for years, crucial questions regarding both safety and immunogenicity could be addressed.

Correlates of Protection

However, in the absence of a circulating pathogen, phase 3 efficacy trials are of course not possible. Licensing of vaccines based on protection data of animals may be a possible path forward, but it will leave a lot of open questions. What can be done, however, is to study in detail correlates of protection against similar viruses that already circulate in humans. As an example, we could have studied in detail which type of immune response is needed to protect us from infection/reinfection with OC43, NL63, HKU1, or 229E—all coronaviruses circulating in humans. While some studies have been performed,[14] a firm correlate of protection has not been pinned down. It is likely that neutralizing antibodies against coronaviruses do in fact correlate with protection in humans, but since this has not been shown in adequately sized and diverse populations, we cannot base vaccine licensure on a correlate and must perform much larger, more labor-intensive, and longer field efficacy studies. However, having a correlate of protection for a closely related virus and animal data suggesting protection based on that correlate as well would allow us to base short and much smaller phase 3 trials on immunogenicity readouts alone. Again, this needs investments in research; for example, through family cohort studies across the globe.[15] The advantage here is, that in the same studies, correlates of protection against many pathogens and in different age groups could be measured in parallel.

Vaccine Production Capacity

As outlined above, vaccines using different platforms for our selected virus candidates need to be initially produced in GMP quality to support phase

1 and phase 2 trials. In addition, material for limited stockpiles should also be produced and occasionally be replaced with fresh vaccine batches. This does not present a major challenge, since relatively small amounts are needed. But in case of an emerging pandemic, billions of doses will be needed within months, which requires a huge production capacity. This is a problem that is not easy to solve. We need vaccine production plants around the globe that can shift to pandemic vaccine production within days. Some of this infrastructure exists already, depending on the vaccine platform chosen. However, it is likely that this capacity needs to be increased significantly. Many of these production plants will not produce product most of the time but will still need to be kept fully prepared. Building and maintaining this infrastructure will likely be very costly, but currently it is the only way to guarantee that production capacity is ready when needed. It will also be important to secure global supply chains and store appropriate glass vials, syringes, etc., in quantities required to package at least 2 billion doses. Finally, distribution pathways need to be established and plans for global vaccine distribution need to be drawn up and agreed on.

Phase III Trials and Rollout

Now, imagine the following scenario: a pneumonia with unknown etiology emerges somewhere. Days later the sequence is published, and the disease is found to be caused by a new virus. Not surprisingly, the virus is found to be closely related to a virus used in one of the tested vaccines. A strain change for this vaccine (or multiple vaccines if different platforms were used in parallel) is performed and production is ramped up. The first batches, which become available 3 weeks after discovering the virus, are immediately used in a phase 3 trial. Since a correlate of protection was determined for a closely related virus, the correlate can be used to measure vaccine efficacy. Assuming a prime-boost regimen with a three-week interval and peak antibody measurements 3 weeks post boost, results from the phase 3 trial will be available 2.5–3 months after the identification of the virus. This initial approval would likely be through an emergency authorization. During the time needed to get the first phase 3 trial results, production is ramped up globally and distribution chains have been activated. Three months after emergence of the new virus, vaccine rollout starts. In an alternative scenario, the virus that emerges is identical or nearly identical to one of the developed vaccines. In this case initial stockpiles could already be used for the phase 3 trials, which would buy a few additional weeks of time.

Regulatory Considerations

There are many regulatory and ethical complications with the above concept, even if all funding and technical issues were addressed. It is unlikely that a full license for such a vaccine would be granted based on a correlate of protection and getting emergency approval would also require regulatory flexibility. Once a vaccine is authorized to be used, it might be seen unethical to withhold the vaccine from placebo recipients in the control group of the phase 3 trial. However, this group is needed to determine efficacy based on protection, especially in the long term. To allow for this, regulatory agencies will need to find creative solutions around this problem, which is also currently causing issues with emergency use authorization of SARS-CoV-2 vaccines. In addition, regulatory processes need to be aligned globally. Initial phase 3 trials would likely be launched in a small number of countries, and therefore, other nations' regulatory bodies will need to be able to defer to the agencies in these countries. This certainly is a barrier that we are also seeing during the SARS-CoV-2 pandemic. For example, inactivated SARS-CoV-2 vaccines developed and trialed in China are unlikely to be licensed in the US or Europe. A more technical regulatory question is about assays for batch release of vaccines. Here, it often takes a long time until specific reagents are available. The key to address this issue is to use platform vaccine technologies and analytical tools that do not rely on specific reagents.

Conclusions

Many measures need to be taken to mitigate or even prevent the next pandemic. These include better surveillance systems, global pandemic response plans that are executed, development of broadly acting antivirals, and further development of diagnostics and non-pharmaceutical interventions. Here, I have focused on the contribution that vaccine development can make on pandemic preparedness. Many points made above might sound familiar. We have implemented some of them for influenza viruses. We have good surveillance systems for influenza viruses, we stockpile vaccines for zoonotic subtypes, we test those vaccines in clinical trials, and we do have a correlate of protection. I strongly believe, and this might be controversial, that if this pandemic had been caused by an influenza virus strain, we would be in a much better position. However, even for influenza virus the system needs to be scaled up and alternative solutions—for example, universal influenza virus vaccines like the ones currently developed by the Collaborative Influenza Vaccine Innovation Centers (CIVICs)—need to be added to the arsenal. In 2017, the Coalition for Epidemic Preparedness Innovations (CEPI) was founded with the goal to develop, produce, and trial vaccines against emerging viruses. CEPI supported a strong portfolio

including vaccines against MERS-CoV and many new vaccine platforms. CEPI catalyzed the quick development of SARS-CoV-2 vaccines and had the organization been founded 10 years earlier, we would likely already have vaccines on the market now. But CEPIs funding and mandate are limited. The US only recently contributed to it, and the amount was roughly equivalent to the cost of buying one fighter jet. CEPI would be an ideal vehicle for implementing a plan as outlined above, but this would require massive increases in funding and a mandate to create an Über-CEPI. Of course, plans similar to the one outlined above could be implemented using many other platforms and organizational structures as well.

The above plan has many flaws, would cost billions of dollars to implement, and might be entirely unfeasible from a regulatory, political, or technical perspective. It is meant to initiate discussions about how we can protect ourselves better in the future. It is unclear how much its implementation would cost and if governments would be able and willing to pay for it. However, it would not be unreasonable to assume that large international corporations would also have an interest in financing better preparedness, since inevitably they will also suffer huge financial losses from another pandemic. We know that influenza virus pandemics roughly occur four times every hundred years. In addition, we have recently seen the emergence of SARS-CoV-1, MERS-CoV, Nipah virus, and now a SARS-CoV-2 pandemic. Close contact with wild animals or livestock is required for zoonotic infections, and the increase in animal farming, hunting, and ecosystem destruction will likely lead to an increase in spillovers in the future. It is clear that the viruses will keep coming, likely at a faster pace. We need to be prepared for the next one.

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DECLARATION OF INTEREST

Mount Sinai has licensed SARS-CoV-2 serological assays to commercial entities and has filed for patent protection for serological assays as well as SARS-CoV-2 vaccines. F.K. is listed as an inventor on the pending patent applications.

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