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Perspective

SARS-CoV-2 vaccines: status report

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Abstract

SARS-CoV-2, the causal agent of COVID-19, first emerged in late 2019 in China. It has since infected more than 170,000 individuals and caused more than 6500 deaths globally. Here we discuss therapeutic and prophylactic interventions for SARS-CoV-2 with a focus on vaccine development and its challenges. Vaccines are being rapidly developed but will likely come too late to have an impact on the first wave of a potential pandemic. Nevertheless, important lessons can be learned for the development of vaccines against rapidly emerging viruses. Importantly, SARS-CoV-2 vaccines will be essential to reducing morbidity and mortality if the virus establishes itself in the population.

Introduction

On December 31st, several cases of pneumonia with unknown etiology were reported in Wuhan, China. The outbreak had started in early December or November (Huang et al., 2020) and numbers of cases rose quickly with more than 80,000 infections reported in China as of March 15th 2020, including more than 3000 deaths. At the time of this review the disease, termed COVID-19 (COronaVIrus Disease 2019), had become pandemic and spread to more than 157 countries including community transmission in countries like the United States, Germany, France, Spain, Japan, Singapore, South Korea, Iran and Italy and a large scale outbreak with more than 600 cases on the cruise ship Diamond Princess. As of March 15th, more than 170,000 cases and 6500 deaths have been reported globally, with rapid growth of numbers in many countries. The causative agent of the outbreak was swiftly identified as betacoronavirus with a genomic sequence closely related to that of the Severe Acute Respiratory Syndrome (SARS) coronavirus from 2003, earning the new virus the name SARS-CoV-2 (Gorbalenya et al., 2020; Wu et al., 2020; Zhou et al., 2020; Zhu et al., 2020). SARS-CoV-2 likely originated in bats but might have been amplified in an intermediate host. Initial work showed that it can use angiotensin converting enzyme 2 (ACE2) from bats, civet cats, swine, cats, ferrets, non-human primates (NHPs) and humans as a receptor (Letko and Munster, 2020; Wan et al., 2020; Zhou et al., 2020). Transmission of the infection to a pet dog in Hong Kong suggests that canine ACE2 can also be recognized by SARS-CoV-2. Pangolins, protected animals that are traded illegally in Asia and elsewhere, have been proposed as a potential amplifying host by some studies (Lam et al., 2020; Zhang et al., 2020). The initial reports from in China and elsewhere note that whereas most COVID-19 cases present mild to moderate pathology, approximately 20% percent of cases are severe (Chen et al., 2020; Guan et al., 2020; Huang et al., 2020; Team, 2020; Wang et al., 2020). The case fatality rate (CFR) seems to be age-dependent with a higher percentage in the elderly, and especially men, and an overall

interim CFR of approximately 1-3%. The number of individuals with undetected, mild cases could of course be much higher than the official case number which would lead to a lower infection fatality rate (IRF). South Korea, a country that put a massive effort into testing and has already tested tens of thousands of samples, reports much lower CFRs than countries without extensive testing like Japan, Iran or the United States. The CFR is disproportionally high in Italy (currently 7.3%), likely due to a large number of mild cases missed combined with a relatively older population and a healthcare system that is overwhelmed with cases. The reproductive number (R_0) of the infection, that is the number of cases directly generated by one case in a population where all individuals are susceptible to infection, is estimated to be 2-3 (Li et al., 2020). Given the severity of the disease, which in most age groups is above that of seasonal influenza or pandemic H1N1 (2009) influenza, vaccines and therapeutics to tackle this novel virus are urgently needed.

Coronaviruses, in brief

SARS-CoV-2 is part of the *Coronaviridae* family, which are named after their crown-like appearance under the under the electron microscope that is given by the surface glycoproteins that decorate the virus. The family includes two subfamilies: *Letovirinae* and *Orthocoronavirinae*. The *Orthocoronavirnae* include the genera *Alphacoronvirus*, *Betacoronavirus*, *Gammacoronavirus* and *Deltacoronavirus*. Alphacoronaviruses and betacoronaviruses typically infect only mammals, whereas gammacoronoviruses and deltacoronaviruses typically infect avian species and sometimes mammals as well (Cui et al., 2019). Coronaviruses are common human pathogens and two types of alphacoronaviruses (229E, NL63) and two types of betacoronaviruses (OC43, HKU1) circulate in humans and cause common cold. More pathogenic coronaviruses for humans include SARS-CoV-1, the Middle Eastern Respiratory Syndrome (MERS) CoV and now SARS-CoV-2, which are all betacoronaviruses.

Coronaviruses have a very large (30kb +) single stranded positive sense RNA genome encoding for a number of open reading frames. One frame encodes the spike or S protein, a class I fusion protein that mediates attachment of the virus to cell surface receptors followed by uptake into endosomes (for most coronaviruses). Proteolytic cleavage of the spike protein and fusion of viral and endosomal membranes triggers release of viral RNA into the cytosol (reviewed in (Fehr and Perlman, 2015)). The RNA contains a 5' cap structure and a 3' poly(A) tail that allows expression of the replicase, which is encoded by approximately two thirds of the genome. The other third codes for the structural and accessory proteins. The replicase is expressed as two polyproteins - pp1a and pp1ab; these include up to 16 nonstructural proteins (nsp). The nsps are generated by processing of pp1a and pp1ab by 2-3 different viral proteases encoded within the replicase. Many of the nsps then assemble into the replicase-transcriptase complex that - in the host cell cytosol - produces anti-sense genome, new viral genome and subgenomic RNA that serves as mRNA. Structural proteins S, matrix protein (M) and envelope (E) are then generated and inserted into the endoplasmatic reticulum and follow the secretory pathway to the endoplasmic reticulum-Golgi intermediate compartment (ERGIC). A minority of coronaviruses also encode a hemagglutinin esterase (HE). In many coronaviruses the S protein is also cleaved into two subunits, S1 and S2, often by furin-like proteases. RNA genome associates with nucleoprotein and then buds into the (ERGIC), forming virus particles. After assembly, virions are transported to the cell surface in vesicles and are exocytosed. A number of accessory proteins are also expressed which seem to be important for pathogenesis, but not all are functionally characterized.

Therapeutics for SARS-CoV-2 infections

Clinical trials with the nucleotide analog remdesivir (NCT04257656, NCT04252664, NCT04280705 etc.) and protease inhibitors (NCT04255017, NCT04276688 etc.) as well as other treatment options are currently ongoing in China and the US and trial results are expected within weeks. Remdesivir works against coronaviruses closely related to SARS-CoV-2 in animal models as well as against the related MERS CoV including in non-human primates (Agostini et al., 2018; Brown et al., 2019; de Wit et al., 2020; Sheahan et al., 2017; Sheahan et al., 2020). Remdesivir was also tested for treatment of ebolavirus infections in humans (and found less successful than other treatments (Mulangu et al., 2019)), and therefore safety data already exists for this therapeutic agent; this should accelerate the process of clinical testing against SARS-CoV-2. Remdesivir's mechanism of action as nucleotide analogue is not completely clear but it likely either terminates RNA synthesis or leads to incorporation mutagenesis, or both (Agostini et al., 2018). In addition, a combination of the two licensed HIV inhibitors, lopinavir and ritonavir, is also being tested in clinical trials (e.g. NCT04264858 etc.). Lopinavir is a *bona fide* protease inhibitor while ritonavir was initially designed as protease inhibitor but was found to boost the half-life of lopinavir by inhibiting cytochrome P450 (Hull and Montaner, 2011). The combination was compassionately used as treatment for SARS-CoV-1 in 2003-2004 and showed some promise (Chu et al., 2004). Effectiveness of the combination was limited in mice but appreciable in non-human primate models of MERS-CoV (Chan et al., 2015; Sheahan et al., 2020). The mechanism of action of lopinavir is not completely clear but it likely inhibits one or more of the coronavirus proteases. Other treatment options with ongoing or planned clinical trials include dosing of recombinant human ACE2 to neutralize the virus and prevent lung damage (NCT04287686) as well as the use of the antiviral arbidol, a fusion inhibitor (Kadam and Wilson, 2017; Teissier et al., 2011). Another interesting option is the use of convalescent serum as treatment and clinical trials to test this are currently ongoing in China (NCT04264858, placebo control, not recruiting yet). Similarly, polyclonal human IgG derived from transgenic cows could be used as well since this strategy has been successful for MERS-CoV in animal models (Luke et al., 2016) and was tested for safety in clinical trials already (NCT02788188). Many of these trials will have results within months and if remdesvir (produced by Gilead) and/or lopinavir-plus-ritonavir (produced by AbbVie as Kaletra and Aluvia, respectively) show effectiveness, they could potentially be used widely within a short time frame. Compassionate use of these drugs has already been reported for SARS-CoV-2 infections (Holshue et al., 2020; Lim et al., 2020).

What do we know about betacoronavirus vaccine design?

During the 2009 H1N1 influenza virus pandemic, vaccine producers switched their production pipelines quickly from producing trivalent seasonal influenza virus vaccines to monovalent pandemic vaccines. This was basically just a change of strains and established and approved processes, established release criteria and existing correlates of protection could be used (Krammer and Palese, 2015). Still, it took six months until the vaccine was ready to be distributed and used and came too late to make an impact on the second pandemic wave which took place in the US in Fall of 2009. This time we are facing a new challenge in the form of a virus that has just now emerged in humans, and the response will be more complex since there are no existing vaccines or production processes for coronavirus vaccines.

Vaccine technology has significantly evolved in the last decade including the development of several RNA and DNA vaccine candidates, licensed vectored vaccines (e.g. Ervebo, a vesicular stomatitis virus vectored ebolavirus vaccine, licensed in the European Union), recombinant protein vaccines (e.g. Flublok, an influenza virus vaccine made in insect cells, licensed in the US) and cell

culture-based vaccines (e.g. Flucelvax, an influenza virus vaccine made in mammalian cells). SARS-CoV-2 was identified in record time and its genomic sequence was swiftly made widely available by Chinese researchers (Wu et al., 2020; Zhou et al., 2020; Zhu et al., 2020). Also, we know from studies on SARS-CoV-1 and the related MERS-CoV vaccines that the spike protein on the surface of the virus is an ideal target for a vaccine. This protein interacts, in the case for SARS-CoV-1 and 2, with the receptor ACE2 and antibodies targeting the spike can interfere with this binding, thereby neutralizing the virus (**Figure 1**). The structure of the spike protein of SARS-CoV-2 was solved in record time at high resolution, further contributing to our understanding of this vaccine target (Lan et al., 2020a; Wrapp et al., 2020). Therefore, we have a target antigen that can now be incorporated into advanced vaccine platforms.

Several vaccines for SARS-CoV-1 were developed and tested in animal models including recombinant spike protein-based vaccines, attenuated and whole inactivated vaccines as well as vectored vaccines (Roper and Rehm, 2009). The majority of these vaccines protect animals from challenge with SARS-CoV-1, although most do not induce sterilizing immunity. In some cases, vaccination with the live virus results in complications, including lung damage and infiltration of eosinophils in the mouse model (e.g. (Bolles et al., 2011; Tseng et al., 2012)) and liver damage in ferrets (e.g. (Weingartl et al., 2004)). In another study vaccination with inactivated SARS-CoV-1 led to enhancement of disease in one nonhuman primate while it protected 3 animals from challenge (Wang et al., 2016). The same study identified certain epitopes on S as protective while immunity to others seemed to be enhancing. However, in almost all cases vaccination is associated with greater survival, reduced virus titers and/or less morbidity as compared to unvaccinated animals. Similar findings have been reported for MERS-CoV vaccines (Agrawal et al., 2016; Houser et al., 2017). Therefore, while vaccines for related coronaviruses are efficacious in animal models, we need to ensure that the vaccines which are developed for SARS-CoV-2 are sufficiently safe.

Another consideration for effective coronavirus vaccine development might be waning of the antibody response. Infection with human coronaviruses does not always induce long-lived antibody responses and re-infection of an individual with the same virus is possible as shown in human challenge studies (Callow et al., 1990). Antibody titers in individuals that survived SARS-CoV-1 or MERS-CoV infections often waned after 2-3 years (Liu et al., 2006; Wu et al., 2007) or were weak to begin with (Choe et al., 2017). Despite that, re-infections are unlikely in the short term. Of note, reinfections after days of recovery have been reported recently but appear to be the consequences of false negatives (Lan et al., 2020b)). However, they could happen when humoral immunity wanes over months and years. An effective SARS-CoV-2 vaccine will need to overcome these issues in order to protect in a scenario where the virus becomes endemic and causes recurrent seasonal epidemics.

SARS-CoV-2 infection causes the most several pathology in individuals above 50 years of age. The reason for this is not completely clear but many infections have milder manifestations in naïve younger individuals than in naïve older individuals. Since older individuals are more affected, it will be very important to develop vaccines that protect this segment of the population. Unfortunately, older individuals typically respond less well to vaccination due to immune-senescence (Sambhara and McElhaney, 2009). For influenza – which is also problematic for older adults - there are specific formulations for this segment of the population that include more antigen or an adjuvant (DiazGranados et al., 2013; Tsai, 2013). Protection in older individuals appear to require higher neutralization titers against influenza virus as compared to younger individuals (Benoit et al., 2015), and this issue might also need to be addressed for SARS-CoV-2. In case

vaccination in older individual is not effective, they could still benefit indirectly if vaccination is able to stop transmission of the virus in younger individuals.
Only a small number of SARS-CoV-1 vaccines made it to phase I clinical trials before funding dried up due to the eradication of the virus from the human population due to non-pharmaceutical interventions when case numbers were still small. Results from these trials, performed with an inactivated virus vaccine and a spike-based DNA vaccine, are encouraging since the vaccines were safe and induced neutralizing antibody titers (Lin et al., 2007; Martin et al., 2008). Some neutralizing monoclonal antibodies isolated against SARS-CoV-1, like CR3022 (ter Meulen et al., 2006; Tian et al., 2020), can cross-react to the receptor binding domain of SARS-CoV-2. This suggests that SARS-CoV-1 vaccines might cross-protect against SARS-CoV-2. However, since these vaccines have not been developed further than phase I, they are currently not available for use. Vaccines against MERS-CoV, also targeting the MERS-CoV spike protein, are in pre-clinical and clinical development including vaccines based on Modified Vaccinia Ankara vectors, adenovirus vectors and DNA-based vaccines and several of them are supported by the Coalition for Epidemic Preparedness Innovation (CEPI) (Yong et al., 2019). However, it is unlikely that MERS-CoV vaccines induce strong cross-neutralizing antibodies to SARS-CoV-2 due the phylogenetic distance between the two viruses. Nevertheless, we can still learn a lot from these vaccines about how to move forward with SARS-CoV-2 vaccine design (Pallesen et al., 2017).

The current pipeline for SARS-CoV-2 vaccines

The development of vaccines for human use can take years, especially when novel technologies are used that have not been extensively tested for safety or scaled up for mass production. Since no coronavirus vaccines are on the market and no large scale manufacturing capacity for these vaccines exists yet (**Table 1**), we will need to build these processes and capacities. Doing this for the first time can be tedious and time-consuming (**Figure 1**). CEPI has awarded funds to several highly innovative players in the field and many of them will likely succeed in eventually making a SARS-CoV-2 vaccine. However, none of these companies and institutions have an established pipeline to bring such a vaccine to late stage clinical trials that allow licensure by regulatory agencies and they also do not currently have the capacity to produce the number of doses needed. An mRNA-based vaccine, which expresses target antigen *in vivo* in the vaccine after inhjection of mRNA encapsulated in lipid nanoparticles, co-developed by Moderna and the Vaccine Research Center at the National Institutes of Health is currently the furthest along with a phase I clinical trial recently started (NCT04283461). Curevac is working on a similar vaccine but is still in the pre-clinical phase. Additional approaches in the preclinical stage include recombinant protein based vaccines (focused on the spike protein, e.g. ExpresS2ion, iBio, Novavax, Baylor College of Medicine, University of Queensland, Sichuan Clover Biopharmaceuticals etc.), viral vector based vaccines (focused on the spike protein, Vaxart, Geovax, University of Oxford, Cansino Biologics etc.), DNA vaccines (focused on the spike protein, Inovio, Applied DNA Sciences etc.), live attenuated vaccines (Codagenix with Serum Institute of India etc.) and inactivated virus vaccines (**Figure 1 and Table 1**). All of these platforms have advantages and disadvantages (**Table 1**) and it is currently not possible to predict which strategy will be faster or more successful. Johnson&Johnson (https://www.jnj.com/latest-news/what-you-need-to-know-about-coronavirus-and-a-potential-johnson-johnson-vaccine) and Sanofi (http://www.news.sanofi.us/2020-02-18-Sanofi-joins-forces-with-U-S-Department-of-Health-and-Human-Services-to-advance-a-novel-coronavirus-vaccine) recently joined efforts to develop SARS-CoV-2 vaccines. However, J&J is using an experimental adenovirus vector platform that has not resulted in a licensed vaccine yet.

Sanofi's vaccine, to be made using a process similar to the process used for their approved FluBlok recombinant influenza virus vaccine (Zhou et al., 2006), is also months – if not years – away from being ready to be used in the human population.

Understanding the timeframes

Why does this take so long? As mentioned above, there are currently no approved human coronavirus vaccines. In addition, many technologies used (production platforms, vectors etc.) are new and need to be tested thoroughly for safety. The target for the vaccine, the spike protein, has been identified and vaccine candidates are being generated. This is usually followed by two important steps that are typically needed before bringing a vaccine into clinical trial. First, the vaccine is tested in appropriate animal models to see if it is protective. However, animal models for SARS-CoV-2 might be difficult to develop. The virus does not grow in wild type mice and only induced mild disease in transgenic animals expressing human ACE2 (Bao et al., 2020). Other potential animal models include ferrets and NHPs for which pathogenicity studies are currently ongoing. Even in the absence of an animal model that replicates human disease, it is possible to evaluate the vaccine since serum from vaccinated animals can be tested in *in vitro* neutralization assays; post-challenge safety data should also be collected in these cases, to assed for complications such as the ones seen in cases of SARS-CoV-1 and MERS CoV vaccines. Second, vaccines need to be tested for toxicity in animals, e.g. in rabbits. Usually viral challenge is not part of this process since only the safety of the vaccine itself will be evaluated. This testing, which has to be performed in a manner compliant with GLP (good laboratory practice), typically takes 3-6 months to complete. For some vaccine platforms parts of the safety testing might be skipped if there is already sufficient data available for similar vaccines made in the same production process.

Vaccines for human use are produced in processes that comply with current Good Manufacturing Practice (cGMP) to ensure constant quality and safety of vaccines. This requires dedicated facilities, trained personnel, proper documentation and raw material that was also produced in cGMP quality. These processes have to be designed or amended to fit SARS-CoV-2 vaccines. For many vaccine candidates in the preclinical phase such processes do not exist yet and have to be developed from scratch.

Once sufficient pre-clinical data is available and initial batches of the vaccine have been produced in cGMP quality, clinical trials may be initiated. Typically, clinical development of vaccines starts with small phase I trials to evaluate the safety of vaccine candidates in humans. These are then followed by phase II trials (formulation and doses are established, initial prove of efficacy) and finally by phase III trials in which the efficacy and safety of a vaccine needs to be demonstrated in a larger cohort. However, in an extraordinary situation like the current one this scheme might be compressed and an accelerated regulatory approval pathway might be developed. If efficacy is shown, a vaccine may be licensed by regulatory agencies.

Another important point is that production capacity to produce sufficient amounts of cGMP quality vaccine needs to be available. For vaccines based on existing vaccine platforms, e.g. inactivated or live attenuated vaccines, this can be relatively easily achieved since existing infrastructure can be used (**Table 1**). For vaccines based on novel technologies, e.g. mRNA, this capacity needs to be built and this typically also takes time. While it would be beneficial if even a limited amount of doses would be available to protect health care workers and the most vulnerable segments of the population, the ultimate goal should be to make vaccine available to the global population. This will be challenging. Even for influenza virus vaccines, for which many production facilities exist

in high income as well as low and middle income countries, the demand in the case of a pandemic would by far exceed the production capacity.
Finally, it also takes time to distribute vaccines and administer them. To vaccinate a large proportion of the population would likely take weeks. Given that the population is currently completely naïve to SARS-CoV-2, it is highly likely that more than one dose of the vaccine is needed. Prime-boost vaccination regimens are typically used in that case and the two vaccinations are usually spaced 3-4 weeks apart. It is likely that only 1-2 week after the second vaccination protective immunity will be achieved. This therefore adds another 1-2 months to the timeline. Even if shortcuts for several of the steps mentioned above can be found, it is unlikely that a vaccine would be available earlier than 6 months after the initiation of clinical trials. Realistically, SARS-CoV-2 vaccines will not be available for another 12-18 months.
What are potential solutions for these long-time frames in the future? One possibility is to build production capacity, if possible globally distributed, that can be activated in the event of a new emerging viruses. From today's perspective only very few types of viruses are likely to cause respiratory disease that leads to rapid global spread. Surveillance in the animal reservoir paired with virus characterization studies can identify members of virus families that have potential to cause pandemics. Vaccine candidates using these isolates could then be produced, tested in animals to determine mechanisms of protection and tested in humans to establish safety of the vaccines. It is unlikely that exactly the same viruses that are chosen as vaccine candidates will later cause outbreaks. However, if the vaccine candidate is sufficiently closely related, sequences for the vaccines could be quickly switched and the vaccines for the newly emerging viruses could be swiftly produced and moved to late stage clinical trials right away (while large scale production is ramped up globally). In addition, stockpiled vaccines based on the initial candidates could be deployed, even if slightly mismatched to the strain causing the outbreak (a strategy that is currently used for H5 and H7 avian influenza virus vaccines). This would allow a response within a few weeks and could potentially stop a virus locally before it becomes pandemic. An alternative, but also very challenging solution would be the development of broadly protective vaccines that cover whole virus families or genera. This effort is currently ongoing for influenza viruses (Erbelding et al., 2018) and could potentially also be applied to coronaviruses, or at least betacoronaviruses. Both of these options are costly and require global political will and vision.

Concluding remarks

Considering the deep dive stock markets have taken in recent weeks and given the expected impact of a pandemic on the economy, funding for vaccine production infrastructure that would allow a swift response to emerging viruses looks like a great investment. However, without a pandemic looming such investments have rarely been made in the past, except for H5 and H7 subtype influenza viruses. Now would be the right time to consider investing in vaccines against emerging viruses that can lead to loss of human lives and also burden the global economy. An investment of a few billion dollars would allow us to have sufficient surveillance, appropriate vaccine candidates and infrastructure ready that could churn out vaccines for use in the global population quickly and effectively, potentially stopping an emerging virus in its tracks. In addition, we need well developed emergency plans that allow us to develop, test, produce and distribute vaccines within weeks, not months or years. This would need tight coordination between pharmaceutical companies, governments, regulatory agencies and the WHO as well as novel and out of the box approaches to cGMP production, release processes, regulatory science and clinical trial design.

For SARS-CoV-2, vaccines may come too late to make an impact on the first wave of this pandemic. However, they might be very useful if additional waves occur later in time or in a post-pandemic scenario in which SARS-CoV-2 continues to circulate as a seasonal virus. In addition, lessons learned from handling this outbreak will certainly allow us to be better prepared in the future. The viruses will keep coming.

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Table 1: Overview of vaccine production platforms and technologies for SARS-CoV-2

Platform	**Target**	**Existing, licensed human vaccines using the same platform**	**Advantages**	**Disadvantages**
RNA vaccines	Spike protein	No	No infectious virus needs to be handled; vaccines typically very	Safety issues with reactogenicity have been reported

			immunogenic, rapid production possible	
DNA vaccines	Spike protein	No	No infectious virus needs to be handled; easy scale up; low production costs; high heat stability; has been tested in humans for SARS-CoV-1; rapid production possible	Needs specific delivery devices to reach good immunogenicity
Recombinant protein vaccines	Spike protein	Yes for baculovirus (influenza, HPV) and yeast expression (HBV, HPV)	No infectious virus needs to be handled; adjuvants can be used to increase immunogenicity	Global production capacity might be limited; antigen/epitope integrity needs to be confirmed; yields need to be high enough
Viral vector-based vaccines	Spike protein	Yes for VSV (Ervebo) but not for other viral vectored vaccines	No infectious virus needs to be handled; excellent pre-clinical and clinical data for many emerging viruses including MERS-CoV	Vector immunity might negatively impact on vaccine effectiveness (depending on the vector chosen)
Live attenuated vaccines	Whole virion	Yes	Straight forward process used for several licensed human vaccines; existing infrastructure can be used	Creating infectious clones for attenuated coronavirus vaccine seeds takes time due to large genome size; safety testing will need to be extensive
Inactivated vaccines	Whole virion	Yes	Straight forward process used for several licensed human vaccines; existing infrastructure can	Large amounts of infectious virus need to be handled (could be mitigated by using an attenuated seed

			be used; has been tested in humans for SARS-CoV-1; adjuvants can be used to increase immunogenicity	virus); antigen/epitope integrity needs to be confirmed

Figure 1: Overview of potential SARS-CoV-2 vaccine platforms. The structure of a coronavirus particle is depicted on the left with the different viral proteins indicated. The spike protein is the major target for vaccine development. The spike structure shown is based on the trimeric SARS-CoV-1 spike (PDB 5XL3). One trimer is shown in dark blue with the receptor binding domain, a main target of neutralizing antibodies, highlighted in purple. The other two trimers are shown in light blue. Currently, SARS-CoV-2 vaccine candidates based on different vaccine platforms are developed and for some of them pre-clinical experiments have been initiated. For one mRNA-based candidate a clinical trial will start to enroll volunteers shortly (NCT04283461). However, many additional steps are needed before these vaccines can be used in the population and this process might take months, if not years. [1]For some candidates, GMP processes have already been established. [2]Clinical trial design might be altered to move vaccines through clinical testing quicker.