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Review

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in late 2019 in China and caused a coronavirus disease 2019 (COVID-19) pandemic. To mitigate the public health, economic and societal impacts of the virus, a vaccine is urgently needed. The development of SARS-CoV-2 vaccines was initiated in early January 2020 when the sequence of the virus became available and moved at record speed with one Phase I trial already starting in March 2020 and currently more than 180 vaccines in various stages of development. Phase I/II trial data is already available for several vaccine candidates and many have moved into Phase III trials. The data available so far suggests that effective and safe vaccines might become available within months rather than years.

In late December 2019, China reported cases of pneumonia with unknown etiology in the city of Wuhan[1]. The causative agent was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a betacoronavirus closely related to the SARS-CoV-1 from 2002-2004[2]. SARS-CoV-2 caused a sizable epidemic of coronavirus disease 2019 (COVID-19) in China and then spread globally and caused a pandemic. Coronaviruses are enveloped viruses with a large, single stranded positive sense RNA genome. Four coronaviruses, two alphacoronaviruses (NL63, 229E) and two betacoronaviruses (HKU1, OC43), circulate in humans and cause common colds[3]. It has been hypothesized that all four of these viruses are of zoonotic origin with OC43 being the potential etiologic agent of the 1890 'influenza' pandemic (Russian flu)[3,4]. Based on phylogenetic analysis, OC43 and bovine coronavirus (BCoV) split from a common ancestor around 1890, suggesting that possibility[4]. In addition, the aforementioned SARS-CoV-1 and the Middle Eastern CoV have caused zoonotic infections and epidemics with high case fatality rates in humans[3]. No vaccines against coronaviruses have ever been licensed for use in humans. Development of vaccines against hCoVs is of low priority given the mild disease they are causing. In addition, a vaccine would need to be quadrivalent and even then it would only prevent a minor proportion of colds (because the majority is caused by other viruses) and has therefore not been pursuit. Vaccines against SARS-CoV-1 were developed pre-clinically and two vaccines were also tested in Phase I trials[5,6]. But development stopped since the virus was eradicated from the human population and never reemerged after 2004. Vaccines against MERS CoV are actively being developed and have been supported by the Coalition for Epidemic Preparedness Innovations (CEPI). Through pre-clinical studies with SARS-CoV-1 and MERS CoV vaccines, the antigenic target for coronavirus vaccines has become pretty clear (Figure 1b)[7,8]. Most coronaviruses encode only one large surface protein, the spike protein (S), which is responsible for receptor binding and membrane fusion[9]. In the case of SARS-CoV-2 (and SARS-CoV-1), S binds to angiotensin converting enzyme 2 (ACE2) on host cells and is then endocytosed[10,11]. This step is followed by fusion of viral and endosomal membranes and release of the viral genome into the cytoplasm[9,12]. Antibodies binding to S, especially to its receptor binding domain (RBD), prevent attachment to the host cell and neutralize the virus. Therefore, and based on knowledge from SARS-CoV-1 and MERS-CoV vaccines[13], S was already identified as antigenic target for vaccine development at the very early stage.

Since the onset of the pandemic we have learned a lot about the immune response to SARS-CoV-2 after natural infection and these lessons have corroborated the initial assumptions. Antibodies directed to S, including ones targeting the RBD and with targets outside of the RBD, have been shown to neutralize the virus[14–18]. In addition, while the magnitude of the antibody response to S is very heterogenous, it looks so far like a normal antibody response to a respiratory virus with an initial plasmablast-derived boost of antibodies, followed by some decline and then a potential stabilization at a baseline maintained by long lived plasma cells[17,19,20]. Mucosal antibody responses are also induced by natural infection in humans[19,21]. In addition, it has been demonstrated that S is a strong target of CD4+ T-cells, while fewer CD8+ T-cells are induced by natural infection with SARS-CoV-2 in general[22]. In non-human primates (NHPs), infection with SARS-CoV-2 has been shown to protect from re-infection[23,24]. Vaccination experiments in the same model showed that neutralizing antibodies, but not T-cell responses, correlated with protection[25]. While neutralizing antibodies have now also been implicated as correlate of protection in an outbreak on a fishing vessel[26], it is important to note that natural infection induces both mucosal antibody responses (secretory IgA) as well as systemic antibody responses (IgG). The upper respiratory tract is mostly protected by secretory IgA while the lower respiratory tract is mostly protected by IgG[27–29]. Intramuscularly or intradermally injected vaccines induce mostly IgG but no secretory IgA[30]. It is therefore possible that most vaccines currently in development induce disease preventing or disease attenuating immunity but not necessarily sterilizing immunity (Figure 2).

In general, traditional vaccine development takes a long time and a development time of 15 years is common (Figure 1a). The process starts with exploratory work on vaccine design and evaluation in animal models, which can take years. This is then followed by a stage in which more formal preclinical experiments are conducted, a process for vaccine production is designed and formal toxicology studies are performed, a process that can also take several years. After that stage, an application for an investigational new drug (IND) is filed and Phase I clinical trials (testing in <100 individuals, approximately 2 years) are performed to test initial safety and to obtain some immunogenicity data. If the results are promising and funding is available, a vaccine candidate is then moved into Phase II clinical trials (testing in a few hundred individuals, also about 2 years) to determine immunogenicity,

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dose and optimal vaccine regimens. If the results of Phase II are promising, the decision might be made to move forward with very costly Phase III trials (in thousands of individuals, approximately 2 years) in which efficacy and safety are evaluated. If the results of the Phase III trials meet the pre-defined endpoints, a biologics license application (BLA) is filed with regulatory agencies (e.g. FDA or EMA). The licensing process can take another 1-2 years, especially if additional data is requested. Importantly, the whole process of vaccine development is slowed down by economic risk assessment at every step since it is very expensive. Vaccine development only moves forward from one step to another if the developer is convinced that the data look good, that the risk of failure is relatively low and that there is (still) a market for the vaccine.

The SARS-CoV-2 pandemic required quick action and development of vaccines in record time (Figure 1b). Data from SARS-CoV-1 and MERS CoV vaccine development saved time and the initial step of exploratory vaccine design was basically skipped. In many cases production processes were just adapted from existing vaccines or vaccine candidates and in certain cases pre-clinical and toxicology data from related vaccines could be leveraged. This led to the start of a first clinical trial already in March 2020 (NCT04283461). Clinical phases have been started in overlapping, staggered schemes with initial Phase I/II trials followed by rapid start of Phase III trials after interim analysis of Phase I/II data. Currently, several vaccine producers have already started commercial production at risk even without any Phase III trial results. While the licensure pathways are not completely clear yet, it is possible that reviews could be expedited and that vaccines may even be approved via emergency use authorization (EUA). The US Food and Drug Administration (FDA) has released a guidance document for development and licensure for COVID-19 vaccines which states that an efficacy of at least 50% will be required and also provides further details[31]. It is very important to point out that moving forward at financial risk has been the main factor for accelerated SARS-CoV-2 vaccine development, while no corners have or should be cut in terms of safety evaluation.

While vaccine development is moving forward at record speed, there are still many open questions. Vaccines will likely require two doses, and potentially booster doses at later time points, which means that at least 16 billion doses are needed to meet the global demand. Many of the vaccines described below are developed by entities that have never brought a vaccine to market or use technologies that have never resulted in a licensed vaccine. Therefore, unforeseen issues with scaling might cause delays. It is also not clear yet if bottlenecks with availability of e.g. syringes or glass vials will occur, how vaccines will be distributed globally and how rollout will occur within a country. Finally, vaccine enhanced disease has been reported in some animal models for certain vaccine candidates against SARS-CoV-1 and MERS CoV (Box 1). While so far no signals of enhanced disease have been found in animal models or humans, a safety signal pointing at enhanced disease would certainly derail development of a vaccine candidate and negatively impact on SARS-CoV-2 vaccine development in general.

Below I review what types of vaccines are in the pipeline as well as initial data from nonhuman primate studies, Phase I and Phase I/II trials.

Types of vaccines in development

More than 180 vaccine candidates based on several different platforms (Figure 3) are currently in development (Figure 4)[32]. The WHO maintains a working document that includes most of the vaccines in development and can be found online at https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines[32]. The platforms can be divided into 'traditional' approaches like inactivated or live virus vaccines, platforms that have recently resulted in licensed vaccines (recombinant proteins, vectored vaccines) and platforms that have never been used for a licensed vaccine (RNA and DNA vaccines).

Inactivated vaccines

Inactivated vaccines (Figure 3c) are produced by growing SARS-CoV-2 in cell culture, usually on Vero cells followed by chemical inactivation[33,34]. They can be produced relatively easily, however, their yield might be limited by productivity of virus in cell culture and the requirement for biosafety level 3 (BSL3) production facilities. Examples are CoronaVac (initially called PiCoVacc), developed by Sinovac Biotech Ltd. in China[34,35] (discussed below) as well as several other candidates developed in China, by Bharat Biotech in India and by the Research Institute for Biological Safety Problems in Kazakhstan. These vaccines are usually administered intramuscular and might be adjuvanted with alum or other adjuvants. Since the whole virus is presented to the immune system, immune responses are likely to target not only S but also the matrix, envelope and nucleoprotein. Several inactivated vaccine candidates have entered clinical trials with three Chinese candidates in Phase III and one Indian, a Kazakh and a Chinese candidate in Phase I/II clinical trials (Figure 4)[32].

Live attenuated vaccines

Live attenuated vaccines (Figure 3d) are produced by generating a genetically weakened versions of viruses that replicate to a limited extend, cause no disease but induce immune responses that are similar to the immune response induced by natural infection (Figure 2). Attenuation can be achieved by adapting the virus to unfavorable conditions (e.g. growth at lower temperature, growth in non-human cells) or by rationally modifying it (e.g. by codon de-optimization or by deleting genes responsible for counteracting innate immune recognition[36,37]). An important advantage of these vaccines is that they can be given intranasally and induce mucosal immune responses which can protect the upper respiratory tract (Figure 2), the major entry portal of the virus. In addition, since the vaccine virus is replicating in the vaccinee, the immune response will likely target both structural and non-structural genes with antibodies and cellular immune responses. Of course, there are also disadvantages to these vaccines including safety concerns and the need to modify the virus which is time-consuming if done in the traditional way and technically challenging when reverse genetics is used. Only three live attenuated vaccines are currently in pre-clinical development (Figure 3) including one that is attenuated by codon de-optimization in collaboration between Codagenix and Serum Institute of India[32].

Recombinant protein vaccines

Recombinant protein vaccines can be divided into recombinant S vaccines (Figure 3e), recombinant RBD vaccines (Figure 3f) and virus like particle (VLP) vaccines (Figure 3g). These recombinant proteins can be expressed in different expression systems including insect cells, mammalian cells, yeast and plants[15,32,38]. RBD-based vaccines can likely also be expressed in *E. coli*[39]. Depending on the expression system yields and posttranslational modifications vary. Also, specifically for recombinant spike, modifications like deletion of the polybasic cleavage site[40–42], inclusion of two (or more) stabilizing mutations[13,40,43,44], inclusion of trimerization domains as well as the mode of purification (soluble protein versus membrane extraction) might influence the generated immune response. The advantage of these vaccines is, that they can be produced without handling live virus. In addition, some recombinant protein vaccines, like FluBlok for influenza, have been licensed and there is considerable experience in producing them. However, there are also disadvantages. S is relatively hard to express and this will likely impact on production yields and how many doses can be produced[15]. RBD is easier to express. However, it is a relatively small protein when expressed on its own and while potent neutralizing antibodies bind to RBD, it lacks other neutralizing epitopes present on the full length spike. This might make RBD-based vaccines more prone to antigenic drift than vaccines that include the full length S. Many recombinant

protein vaccines are currently in pre-clinical development and several S and RBD vaccines have entered the clinical trials[32]. Of those, Novavax (described below) has reported NHP and Phase I data (Tables 1 and 2)[42]. One VLP vaccine, produced by Medicago, has also entered clinical trials[32]. Similar to inactivated vaccines, these candidates are typically injected and are not expected to result in robust mucosal immunity.

Replication inactive vectors

Replication inactive vectors (Figure 3h) represent a large group of vaccines in development. These are typically based on another virus that has been engineered to express the S and has been disabled from replication *in vivo* by deletion of parts of its genome. The majority of these approaches are based on adenovirus (AdV) vectors but modified vaccinia Ankara, human parainfluenza virus vectors, influenza virus, andeno-associated virus (AAV) and Sendai virus are used as well (Figure 3)[32,41,45–49]. The majority of these vectors are delivered intramuscularly, enter the vaccinees' cells and then express the spike protein to which the host immune system responds. These approaches have many advantages. Live SARS-CoV-2 does not have to be handled for production, there is significant experience with producing larger quantities of some of these vectors (an Ad26 prime MVA boost-based ebolavirus vaccine was recently licensed in the European Union) and they stimulate both B-cell and T-cell responses well. A disadvantage is that some of these vectors are impacted and partially neutralized by pre-existing vector immunity[46]. This is circumvented by using vector types that are either rare in humans[41], derived from animal viruses[47] or viruses that do not induce much immunity by themselves (e.g. AAV). In addition, vector immunity can be problematic when prime-boost regimens are used which can be circumvented by priming with one vector and boosting with another vector. Several of these replication incompetent vector vaccines are far in clinical development with ChAdOxnCoV-19[47] (chimpanzee AdV), Janssen (AdV26 – Phase III study not recruiting yet)[41], Cansino (AdV5)[45,46] (all described below for NHP and/or clinical results) and Gamaleya Research Institute (Ad5/Ad26)[50] being in Phase III clinical trials followed by ReiThera (gorilla AdV) in Phase I trials (Figure 4 and Tables 1 and 2)[32].

Replication active vectors

Replication active vectors (Figure 3i) are typically derived from attenuated or vaccine strains of viruses that have been engineered to express a transgene, in this case the S protein. In some cases, animal viruses that do not replicate efficiently and cause no disease in humans are used as well. This approach can result in more robust induction of immunity since the vector is propagating to some extend in the vaccinee and often also triggers a strong innate immune response. Some of these vectors cane also be given via mucosal surfaces which might trigger mucosal immune responses (Figure 2). Currently, only two replication active vectors are in Phase I clinical trials including an engineered measles vaccine strain developed by Institute Pasteur and Themis (now acquired by Merck) as well as an influenza virus based vector by Beijing Wantai Biological Pharmacy (Figure 4)[32]. However, several others including vectors based on vesicular stomatitis virus[51], horsepox and Newcastle disease virus[52,53] are currently in development[32]. NDV-based approaches are very interesting since these viruses grow to high titers in eggs and could be produced using the global influenza virus vaccine production pipeline. In contrast to measles and VSV, they are probably also safe enough to administer them intranasally which could lead to mucosal immunity.

Inactivated virus vectors

Some vaccines in the pipeline rely on viral vectors that display S on their surface but are then inactivated before use (Figure 3j)[32]. The advantage here is that the inactivation process makes the vectors safer since they cannot replicate, not even in an immunocompromised host. While the amount of antigen that is presented to the immune system with regular viral vectors is not easily controlled, antigen amounts can be easily standardized in inactivated vectored vaccines, similar to inactivated or recombinant protein vaccines. Examples include NDV-based vaccines that display S on their surface (which can be produced like influenza vaccines)[54] as well as rabies vectors[32]. These technologies are currently in the preclinical stage.

DNA vaccines

DNA vaccines (Figure 3k) are based on plasmid DNA that can be produced in large scale in bacteria. Typically, these plasmids contain mammalian expression promotors and the S gene which is expressed in the vaccinee upon delivery. The huge advantage of these technologies is the possibility of large scale production in *E. coli* as well as the high stability of plasmid DNA. However, DNA vaccines often show low immunogenicity and have to be delivered via delivery devices to make them efficient. The need for such delivery devices, like electroporators, limits their use. Four different DNA vaccines are currently in Phase I/II clinical trials (Figure 4)[32].

RNA vaccines

Finally, RNA vaccines (Figure 3l) are a relatively recent development. Similar to DNA vaccines, the genetic information for the antigen is delivered instead of the antigen itself. The antigen is then expressed in the vaccinee's cells. Two technologies exist: Either mRNA (with modifications) or a self-replicating RNA are used. mRNA usually requires higher doses than self-replicating RNA, which amplifies itself[55]. The RNA is usually delivered via lipid nanoparticles (LNPs). RNA vaccines have shown great promise in recent years and many of them are in development. Promising preclinical results have been published with a number of candidates[43,56–58] and Pfizer and Moderna are currently the frontrunners and have vaccines in Phase III trials (Figure 4, Tables 1 and 2), Curevac and Arcturus are in Phase I/II trials and a candidates by Imperial College and the Chinese Liberation Army is in Phase I[32,59,60]. Advantages of the technology are that the vaccine can be produced completely *in vitro*. However, the technology is new and it is unclear which issues will be encountered for large scale production and long term storage stability (frozen storage is required). In addition, these are injected vaccines which are unlikely to induce strong mucosal immunity (Figure 2).

Results from NHPs

Several animal models for SARS-CoV-2 have been developed including mice expressing human ACE2, either via adenovirus transduction or by genetic engineering[61,62], mouse models with mouse adapted SARS-CoV-2 strains[63–67], ferrets[68–70] as well as hamsters[71–73] and non-human primates (especially rhesus macaques)[23,33,74–81]. The hamster model can mimic severe disease as seen in a proportion of humans while the NHP model more reflects mild to moderate infection. For vaccines far in clinical trials limited hamster data is available but many of the vaccine candidates have been tested in NHPs allowing for more direct comparisons. As indicated in Table 1, these comparisons have to be taken with a grain of salt for several reasons: Challenge doses and routes vary, vaccine regimens and schedules vary as well. Importantly, while all studies report neutralization data, differences in assays can introduce huge biases. Furthermore, most studies did not determine the level of infectious virus in the upper and lower respiratory tracts and measured viral RNA or subgenomic RNA by PCR instead.

Sinovac was the first company to test their β-propiolactone inactivated vaccine (Figure 3c) in the rhesus macaque model (it is now in Phase III trials)[32,34]. The vaccine was formulated based on total protein content and adjuvanted with aluminium hydroxide and then given three times in a one week interval at a 3 ug and 6 ug dose. A challenge was performed one weeks post boost with 10^6 the 50% tissue culture infectious dose ($TCID_{50}$) virus via the intratracheal (i.t) route. The authors found

that this vaccination regimen induced low to moderate neutralizing antibody titers but protected the lower respiratory tract (LRT) from challenge without evidence of vaccine enhanced respiratory disease (Table 1). Of note, viral RNA was found at very low copy numbers in the 3ug (low dose group) in the LRT and viral RNA was found in both groups in the throat swaps but at much lower copy numbers than in the controls. In the same paper the authors also demonstrate that antiserum from vaccinated mice and rats showed cross-neutralization against diverse SARS-CoV-2 isolates.

Another β-propiolactone inactivated vaccine candidate (Figure 3c) by Beijing Institute of Biological Products Ltd. (currently in Phase III trials)[32] was also evaluated in NHPs (cynomolgus macaques) but as a two dose vaccination regimen in a two week interval at 2ug and 8ug of vaccine with aluminium hydroxide as adjuvant[33]. They developed relatively high antibody titers in the 1:200 range post boost and where challenged 10 days post boost with 10^6 $TCID_{50}$ of SARS-CoV-2 i.t. The results were similar to Sinovac with complete protection of the lung but detectible titers in throat swaps (Table 1).

ChAdOxnCoV-19, developed by University of Oxford, AstraZeneca and Serum Institute of India is based on a nonreplicating chimpanzee adenovirus (Figure 3i) expressing a wild type version of the spike protein (no stabilizing mutations, polybasic cleavage site present, Tables 1 and 2)[49]. This vaccine was tested in rhesus macaques in a prime only and a prime boost regimen at $2.5x10^{10}$ viral particles (VP) given intramuscularly. Prime and boost were given in a 4 week interval and animals were challenged 4 weeks after the last vaccination. Animals in both groups induced moderate neutralizing antibody titers (1:5-1:40 after the prime, 1:10-1:160 after the boost) and both groups were protected from lung disease post challenge (combined intranasally (i.n.), i.t., ocular and orally) and also mostly from viral replication in the lung as assessed by copies of subgenomic RNA. However, animals did not seem to control viral replication in the upper respiratory tract. In addition, T-cell responses were detected (Table 1).

Another nonreplicating adenovirus vector vaccine (Figure 3i), based on AdV26, has been developed by Janssen and tested in rhesus macaques (Table 1)[41]. Several constructs were tested in a single shot regimen of 10^{11} VP given i.m. of which the most successful included the full length version of S with the polybasic cleavage site removed and with two stabilizing prolines introduced (named S.PP)[10,13]. Animal were challenged with 10^5 $TCID_{50}$ of SARS-CoV-2 i.n. and i.t. six weeks post vaccination. The S.PP construct, which was ultimately moved forward into clinical trials, achieved neutralization titers in the 1:100 range in week 4 post boost. Challenged S.PP animals showed no trace of subgenomic RNA in the lung and only one animal out of six had a low PCR signal in the upper respiratory tract. In addition, antibody titers in these animal did not rise post infection, indicating sterilizing immunity. Other constructs tested in parallel fared less well but all induced some degree of protection with no sign of enhanced disease. CD8+ T-cell responses were also assessed but were not particularly high, especially in the S.PP group (Table 1).

An mRNA vaccine (Figure 3l), mRNA-1273, which was developed by the Vaccine Research Center (VRC) at NIH and Moderna, was tested in a 10ug and 100ug dose prime-boost regimen with a 4 week interval in rhesus macaques (Table 1)[57]. The vaccine induced considerable neutralizing antibody levels, which especially in the high dose, reached impressive titers in the 1:1000 range already after the prime. Neutralization titers reached geometric mean titers (GMTs) or 1:501 and 1:3481 in the low and high dose post boost. CD4+ T-cells and T_{FH} responses were detected as well. Post challenge with $7.6x10^5$ plaque forming units (PFU) of virus via the i.n. and i.t. route, animals were almost completely protected from challenge in the lower respiratory tract except for single animals in each group that showed low subgenomic copy numbers. The upper respiratory tract of the low dose group showed virus subgenome copies similar to the control group but viral replication in the high dose group was mostly controlled, except for three out of eight animals on day 1 post infection and one out of eight animals on day 4 post infection.

Novavax has tested their recombinant spike protein based vaccine (Figure 3e) with Matrix-M adjuvant in cynomolgus macaques in three different doses (2.5 ug, 5 ug and 25 ug) in a 3 week prime boost interval via the intramuscular route (Table 1)[82,83]. Animals were then challenged on day 37 with 10^4 TCID of virus in/it. Animals in vaccinated groups reached neutralizing titers in the 17,920 - 23,040 range and were protected in the lower and upper respiratory tract except for one animal (out of four) in the low dose group which had detectible subgenomic RNA in the bronchoalveolar lavage on day 2. Since no subgenomic RNA could be detected in the high dose group, this suggest sterilizing immunity. The Novavax vaccine candidate has been tested in Phase I and was now advanced into Phase II trials[42].

Results from Phase I/II clinical trials

In an amazing race against time, 35 vaccines have made it so far into clinical trials with 9 being now in Phase III trials (Figure 4)[32]. As mentioned above, and due to the high speed of vaccine development in this area, I am referring to the WHO working document that includes most of the vaccines in development (https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines)[32]. The first Phase I trial with the Moderna/VRC vaccine started already in March 2020, barely 3 months after SARS-CoV-2 was reported for the first time. Several of the candidates described above with data in NHP experiments (Table 1), as well as candidates for which no NHP data is available yet, have already released data from their Phase I, Phase I/II or Phase II trials. Here we will discuss these findings in with the focus on neutralizing antibody responses, T-cell responses where available and safety data. Again, while neutralizing antibody titers are compared, it is important to point out that the assays to measure neutralizing antibodies vary vastly and comparisons have to be taken with a grain of salt.

Sinovac's CoronaVac

Sinovac very recently reported results from a randomized, double blinded placebo controlled Phase II trial (NCT04352608) with their inactivated vaccine (Figure 3c) CoronaVac (the name PiCoVacc was used in the manuscript describing the NHP results, Table 1) in 600 healthy adults (18-59 years of age)[35]. They used two doses, 3 ug or 6 ug, adjuvanted with aluminium hydroxide in a 2 week or 4 week prime-boost regimen. PBS was used as a placebo control (Table 2). Immunogenicity readouts included RBD enzyme-linked immunosorbent assays (ELISAs) and neutralization assays (cytopathic effect (CPE)-based) with authentic SARS-CoV-2. The safety profile of the vaccine was excellent and both doses were comparable to placebo. No grade 3 adverse reactions were reported. The 2-week interval with both doses resulted in low neutralization titers with GMTs around 1:30, the 4 week interval fared slightly better in the 1:60 range 28 day post boost. Overall, more than 90% of individuals seroconverted. Of note, the authors also stratified the titers by age. 18-39 year olds had clearly higher antibody responses than older individuals, suggesting that perhaps higher doses or different adjuvants might be needed for the elderly. This vaccine candidate is currently being evaluated in Phase III clinical trials in adults and the elderly (NCT04456595)[32].

CanSino's AdV5-based vaccine

CanSino is developing an nonreplicating AdV5-based vaccine (Figure 3i) expressing the unmodified spike protein. No NHP data is currently publicly available for this candidate, but CanSino was the first to publish clinical trial results from their Phase I trial[45] followed by data from a randomized, double blinded placebo controlled Phase II trial (NCT04341389)[46]. Of note, this vaccine is currently licensed to be used in the Chinese military. The vaccine was tested as one shot vaccine in two doses, $5x10^9$ virus particles and $1x10^{11}$ VPs in 508 healthy adults

aged 18 and above (Table 2). Both cellular responses and neutralizing antibody responses 28 days post vaccination were assessed. Neutralization assays were performed with authentic SARS-CoV-2 but no details about the assay procedure are given, T-cell responses were evaluated with an IFN-γ enzyme linked immunospot (ELISpot) assay with overlapping S peptides on peripheral blood mononuclear cells (PBMCs). Antibody responses to RBD were monitored as well. Neutralizing antibody responses were low with GMTs between 1:19.5 (59% seroconversion) and 1:18.3 (47% seroconversion) for the high and low doses. T-cell responses were below the limit of detection in 506 out of 508 individuals on day 0 but increased to 11 (90% response) and 10 (88% response) spot forming units (SFU) per 10^5 PBMCs in the high and low dose groups. Importantly, the authors found that pre-existing immunity to AdV5 and age (older people have a higher likelihood to have AdV5 immunity) correlated with lower immune responses to the vaccine. In terms of safety, the vaccine appeared to be relatively reactogenic, especially in the higher dose. Fever, fatigue and headache were common, injection site pain was reported in >50% of individuals. Grade 3 adverse reactions (mostly fever) were reported in 9% of individuals in the high dose group and 1% in the low dose group. This vaccine candidate at a dose of $5x10^5$ VP is currently being evaluated in Phase III clinical trials (NCT04526990, NCT04540419 etc.).

AstraZeneca's ChAdOxnCoV-19

Based on their longstanding experience with the nonreplicating ChAdOx1 vector (Figure 3i), the University of Oxford together with AstraZeneca and Serum Institute of India, is developing ChAdOxnCoV-19 which expresses a full length wild type version of the spike protein. They recently reported preliminary results from a Phase I/II single-blind randomized control trial in 1077 participants aged 18-55 (NCT04324606)[47]. The vast majority of participants in the vaccine group received a single dose of $5x10^5$ VPs but a small cohort of 10 individuals also received a booster dose 28 days post-prime (Table 2). A meningitis vaccine was used in the placebo control group which allows for comparisons of the safety profile with a licensed vaccine. Antibody responses were tracked using several binding assays as well as three different neutralization assays, all performed with authentic SARS-CoV-2. Cellular immune responses were measured using an IFN-γ ELISpot with PBMCs stimulated using a peptide pool spanning the S. To determine neutralizing antibody responses, a subgroup of 35 individuals was analyzed. Using a 50% plaque reduction neutralization titer ($PRNT_{50}$) assay, a microneutralization (MN) assay with IC_{80} as readout and a virus neutralization assay based on CPE 28-day post vaccination titers were 1:218 (median titers, 100% seropositivity), 1:51 (median titer, 91% seropositivity) and in the 1:4-1:16 range (62%, this assay measures potentially an equivalent to IC_{100}), respectively. A booster dose increased the titers in the latter two assays to 1:136 (100%) and 1:29 (100%). Of note, pre-existing immunity to SARS-CoV-2 was found in a small number of participants (4%). Cellular immunity peaked at day 14 with 856 SFU per 10^6 cells and waned to 424 SFU by day 56. Background cellular immunity was found mostly in the 50-100 SFU per 10^6 PBMCs range. The most common side effects were fatigue (>70%) and headache (>60%). Feeling feverish or having an elevated temperature was relatively common. The booster dose seemed to be better tolerated but since it was only given to 10 individuals, this has to be taken with a grain of salt. Overall, ChAdOxnCoV-19 had a worse safety profile than the licensed meningitis vaccine used in the placebo arm, independently if paracetamol was given to alleviate side effects or not. This vaccine candidate is currently being evaluated in Phase III clinical trials in several countries as one-dose or two-dose regimen (ISRCTN89951424, NCT04516746).

Moderna's mRNA-1273

Moderna and the VRC recently reported preliminary data from a Phase I open label dose escalation trial with their mRNA-based vaccine (Figure 3l) candidate mRNA-1273 (NCT04283461) in 45 healthy individuals 18-55 years of age[59]. As discussed above, mRNA-1273 is an mRNA vaccine delivered via LNPs and expressing the full length spike protein with two stabilizing mutations. Three doses were evaluated in a prime-boost regimen with a 4-week interval including 25ug, 100ug and 250ug or RNA (Table 2). Readouts included full length S ELISA, pseudovirus and virus neutralization assays as well as assessment of different T-cell populations via intracellular cytokine staining (ICS) using a S peptide pool for stimulation. Less than 50% of participants induced antibodies that could neutralize pseudotyped particles after the prime. However, at day 43 (15 days post boost) 50% inhibitory dilution (ID_{50}) GMTs of 1:112.3, 1:343.8 and 1:332.2 were recorded for the representative groups. More informative, $PRNT_{80}$ values with authentic SARS-CoV-2 reached 1:339.7 and 1:654.3 in the 25 and 100ug groups (data for the 250 ug group was not provided), within the range of convalescent samples from COVID-19 patients. T-cell responses were analyzed in detail and good CD4+ responses were detected in the 25 and 100 ug groups with a T_{h1} polarization. CD8+ T-cell responses were measured but low, as expected for the SARS-CoV-2 S. Adverse events were dose dependent and most common in the highest dose. Solicited systemic events were reported in 33%, 67% and 53% after the prime and 54%, 100% and 100% after the booster dose in the 25, 100 and 250ug doses. While fever was not detected after the prime, it was found in 40% and 67% of the 100 and 250 ug doses. This vaccine candidate is currently being evaluated at the 100ug dose in Phase III clinical trials in adults and older adults (NCT04470427).

Pfizer's BNT162b1 and BNT162b2

Pfizer, in collaboration with the German company BioNTech, has recently published data from an ongoing Phase I/II randomized, placebo-controlled, observer-blind dose escalation study with BNT162b1 in 45 healthy adults, 18-45 years of age (NCT04368728)[60]. BNT162b1 is an mRNA-based, LNP delivered vaccine (Figure 3l) that expresses a trimeric version of the RBD that is held together by a T4 foldon. Three doses, 10, 30 and 100ug of RNA were tested in a prime-boost vaccination regiment with a 3 week interval (Table 2). ELISA binding to RBD and neutralization of a SARS-CoV-2 reporter virus (IC_{80}) was tested. Three weeks post dose 1, neutralization titers were in general low (similar to the mRNA-1273). Seven days post dose 2, GMTs of 1:168 and 1:267 were detected (the 300ug group was not boosted due to an unfavorable safety profile). At 14 days post boost titers reached 1:180 and 1:437, respectively. Convalescent serum was tested side by side and reached 1:94. However, it is unknown how representative these sera were. Systemic adverse events after the prime seemed to be dose dependent and included fever, especially in the 100ug dose group (50%), fatigues, headache and chills. Similar to mRNA-1273, side effects were more common after the booster dose with more than 70% of participants reporting fever in the 30ug dose. One participant reported grade 3 fever in the 30ug group and sleep disturbance was reported as severe adverse event by one participant in the 100ug dose. Participants in the 100ug dose did not receive a booster dose due to tolerability profiles of the 100ug dose post prime and the 30 ug dose post boost. In and additional study, Pfizer recently reported a direct comparison between BNT162b1 and BNT162b2 (NCT04368728). BNT162b2 is similar to BNT162b1 but encodes a full length S protein with the two proline mutations. While antibody titers between the two candidates were basically comparable, BNT162b2 showed a more favorable safety profile. The trial also included a group of older individuals (65-85 years). Reactogenicity for both vaccines was lower in this group compared to younger individuals but antibody titers were also lower (GMTs at approximately 40% of the younger individuals) (Table 2)[84]. BNT126b2 was selected to move forward and is now in a Phase III study in healthy adults and the elderly (NCT04368728).

Novavax' NVX-CoV2373

Novavax has recently published a primary analysis of the results from their randomized, observer blind placebo controlled Phase I trial

with NVX-CoV2373 in 131 healthy adults aged 18-59 (NCT04368988)[42]. Novavax is using a recombinant version of the full length S (Figure 3e) with the polybasic cleavage site deleted and the two stabilizing proline mutations expressed in insect cells and purified by membrane extraction. This leads to rosette formation of S via its hydrophobic tails (similar to Sanofi's FluBlok recombinant HA-based vaccine) which was termed 'nanoparticle' by Novavax. The antigen was formulated with or without the saponin-containing adjuvant Matrix-M and given at doses of 5 or 25ug in a 3 week interval prime boost regimen (Table 2). A prime-only scenario was also tested. Immunogenicity was assessed by ELISA and using a microneutralization assay with authentic SARS-CoV-2 (ID_{99} as readout) as well as by ICS for CD4+ stimulated with S peptides. The group receiving the unadjuvanted vaccine showed basically no response after the prime and barely responded after the boost with a GMT neutralization titer of 1:41 14 days post boost. Both the adjuvanted 5 and 25 ug doses had intermediate responses after the prime and reached very high GMT titers of 1:3906 and 1:3305 respectively with 100% seroconversion post boost. The adjuvanted prime-only 25 ug group reached a titer of 1:128 at the same time point (which is 35 days post-prime) with two individuals not seroconverting. These data show both the value of including an adjuvant and of a prime-boost regimen while a dose response was not appreciable. CD4+ responses were evaluated 7 days post boost and both adjuvanted groups showed a robust T_{h1} polarized response. Local reactogenicity and systemic events were milder after the first dose than after the second dose and were mostly driven by the adjuvant. Malaise, fatigue and headache were the most common side systemic side effects but fever was rare. Two participants had severe events after the first vaccination (malaise, fatigue, headache) and eight after the second vaccination (tenderness at injection site, muscle pain, nausea/vomiting, joint pain, malaise, fatigue and headache). This candidate now advanced into Phase II trials (NCT04533399).

Clinical trials summary

In summary, there is a gradient of immunogenicity in terms of neutralizing antibodies with inactivated and AdV5 vaccine on the lower end, ChAdOx and the mRNA candidates in the medium range and the recombinant protein vaccine at the high end. Of course, different assays and readouts (ID_{50}, ID_{80}, ID_{99}, ID_{100}, different assays) were used and results are therefore hard to compare. In terms of tolerability, the inactivated vaccines and recombinant protein vaccines seem to perform relatively well, followed by the mRNA vaccines which show increased reactogenicity after the second vaccination followed by the AdV vectored vaccines. In addition to the data discussed above, Phase II data for a candidate from Gamaleya Institute comprised of a prime boost regimen with nonreplicating AdV5 and AdV26 vaccines (Figure 3i) expressing the S were recently also published[50].

Outlook

With nine vaccine candidates in Phase III trials already and encouraging data from many candidates in NHPs and Phase I, II or I/II trials the situation can be described as cautiously positive. However, there are many unknowns moving forward. Phase III trial results need to show that the vaccines are effective and safe in a larger population. Currently, based on NHP data and on a small study on a fishing vessel[25,26], it is speculated that neutralizing antibodies could be a correlate of protection. However, this still has to be shown in humans and other factors including cellular immune responses might play a protective role as well.

Importantly, all current vaccines in clinical trials are administered intramuscularly. While that route induces strong IgG responses which protect the lower respiratory tract, it does not drive secretory IgA responses which protect the upper respiratory tract, which is something natural infection does. Small amounts of IgG can be found in the URT as well but they depend on very high serum titers. It is therefore conceivable, and this is supported by evidence from NHP experiments, that most vaccines will only protect from lower respiratory tract infection but might not be inducing sterilizing immunity in the URT. This could lead to vaccines that, while protecting from symptomatic disease, might still allow for transmission of the virus. Potentially, the amount of virus shed in this case might be less and shedding might last for a shorter period of time. However, sterilizing immunity in the URT would be preferred. Live attenuated vaccines or viral vectors that can be applied intranasally would likely also lead to a strong mucosal immune response. Unfortunately, very few vaccines suitable for intranasal vaccination are being developed and none is in clinical trials.

In addition, we do not know how long vaccine immunity will persist. Currently, we see what looks like a 'normal' immune response after natural infection with some but not drastic waning of antibodies over time. It is at this time unknown if vaccine induced immune responses are longer or shorter lived than immune responses induced by natural infection. However, booster doses every few years are given for many vaccines and waning of immunity over longer periods of time would not have a major negative impact.

Another unknown is how well elderly individuals, who are most at risk, will respond to the vaccine. From the Sinovac inactivated vaccine and from Pfizer's two mRNA candidates it already becomes clear that they respond less well and different vaccine formulations or even special prime-boost regimens might be needed to drive up immune responses in this age group. Of note, elderly individuals often need to achieve higher neutralization titers than younger individuals, at least for protection from influenza virus[85,86]. Potentially, vaccine with higher reactogenicity that might induce a stronger interferon/antiviral response (mRNA vaccines, AdV vectors or even VSV-vectored vaccines) might improve titers in this age group. In addition, high dose vaccines[87] or heterologous prime boost regimens (e.g. a virus vectored prime followed by an adjuvanted protein vaccine boost)[88] have been successfully used to increase immune responses for influenza virus vaccines and could be used here.

Another important point is tolerability, especially when considering vaccinating children since they usually show more reactogenicity. Given that many of the vaccine candidates have relatively strong side effects, low dose vaccines might be needed for this age group, especially for AdV and mRNA based vaccines. On the positive side, reactogenicity of Pfizer's BNT162b and BNT162b1 vaccines was reduced in older adults making them more suitable for this age group.

Furthermore, it is not clear how vaccines will be rolled out and distributed globally, once licensed. Even within countries, distribution and rollout are not clear yet. It is likely that in many countries first doses will be used to immunize high risk groups and healthcare workers but this needs to be discussed and established. In the beginning of September 1st, the US National Academies of Sciences, Engineering, and Medicine published a draft document for public comment to discuss this important topic[89].

Assuming that two shots per person are needed, 16 billion doses of vaccine have to be produced. It is encouraging to see that many vaccine producers have good candidates in development and that there is high diversity in terms of vaccine platforms and geographic location of the producers since no single company will be able to produce the amount of vaccine needed. Even supply of syringes, glass vials etc. might become a bottleneck since this large number of doses needed is not trivial. A specific concern here are vaccine producers that have never before licensed a vaccine and produced it at large scale for the market (e.g. Moderna or Novavax) or vaccine based on platforms that have never been produced at large for the market scale (mRNA, DNA). Suring scale up, manufacturing and distribution of these candidate's unforeseen challenges may arise due to limited experience with technologies or organizational structures. In the case of mRNA vaccines, the need for frozen storage and distribution already provides challenges, especially in low income countries were even regular cold chains are hard to maintain.

For the vaccines in clinical trials for which Phase I/II data is available, we observe both an immunogenicity and reactogenicity gradient. In terms of immunogenicity, AdV5-based vaccines seem to rank lowest, followed by inactivated and ChAdOx1 based vaccines, mRNA vaccines, and finally adjuvanted, protein-based vaccines performing best. Reactogenicity seems lowest in inactivated and protein based vaccines, followed by mRNA vaccines, with vectored vaccines having the highest rate of side effects. It is highly likely that the AstraZeneca, Moderna and Pfizer vaccine candidates, which are along the furthest in the US and Europe, all show sufficient efficacy and will be licensed if sufficiently safe. However, it may also be that these vaccines will later on be replaced by vaccines that show similar efficacy but have reactogenicity profiles that are more tolerable. In addition, it is hard to predict how availability and production capacity will shape the global landscape of SARS-CoV-2 vaccines. While likely not being licensed in the US and Europe, it is very likely that AdV5-based and inactivated vaccines produced in China, as well as different vaccine candidates produced in India and elsewhere will play a major role to satisfy the global demand for SARS-CoV-2 vaccines.

Despite all the challenges discussed here, we are in the process of developing vaccines as countermeasure against COVID-19 at record speed and it is certainly possible that vaccines with safety and efficacy proven in Phase III trials might already enter the market in 2020.

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Competing interests The Icahn School of Medicine at Mount Sinai has filed patent applications for SARS-CoV-2 serological assays and NDV-based SARS-CoV-2 vaccines.

Additional information
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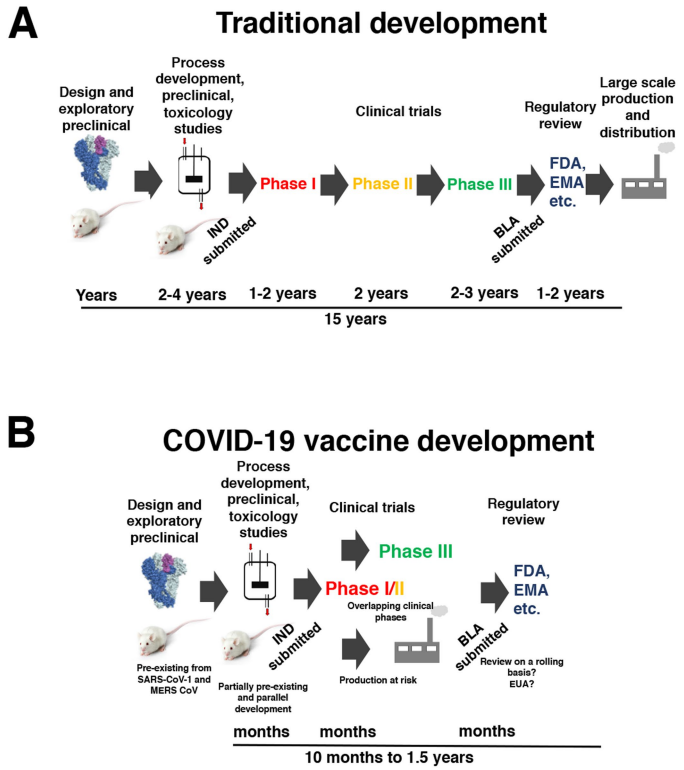

Fig. 1 | Traditional and accelerated vaccine development pipelines. A shows the traditional pathway vaccines take which can take 15 years or longer starting with a lengthy discovery phase in which vaccines are designed and exploratory preclinical experiments are conducted. This is usually followed by a phase in which more formal preclinical experiments and toxicology studies are performed and in which production processes are developed. During this process an investigational new drug (IND) application is filed followed by Phase I, II and III trials. Once results are available from Phase III trials and if they meet predetermined endpoints, a biologics license application (BLA) is filed, reviewed by regulatory agencies and finally the vaccine is licensed. After that point, large scale production begins. **B** shows the accelerated timeline followed for COVID-19. Due to knowledge gained with SARS-CoV-1 and MERS CoV vaccine development the discovery phase was skipped. Existing processes were adopted, and Phase I/II trials were started. Phase III trials were initiated after interim analysis of Phase I/II results with several clinical trial stages going in parallel. In the meantime, vaccine producers started large scale GMP production at risk. The exact licensing pathway (e.g. via an initial EUA) is not clear yet.

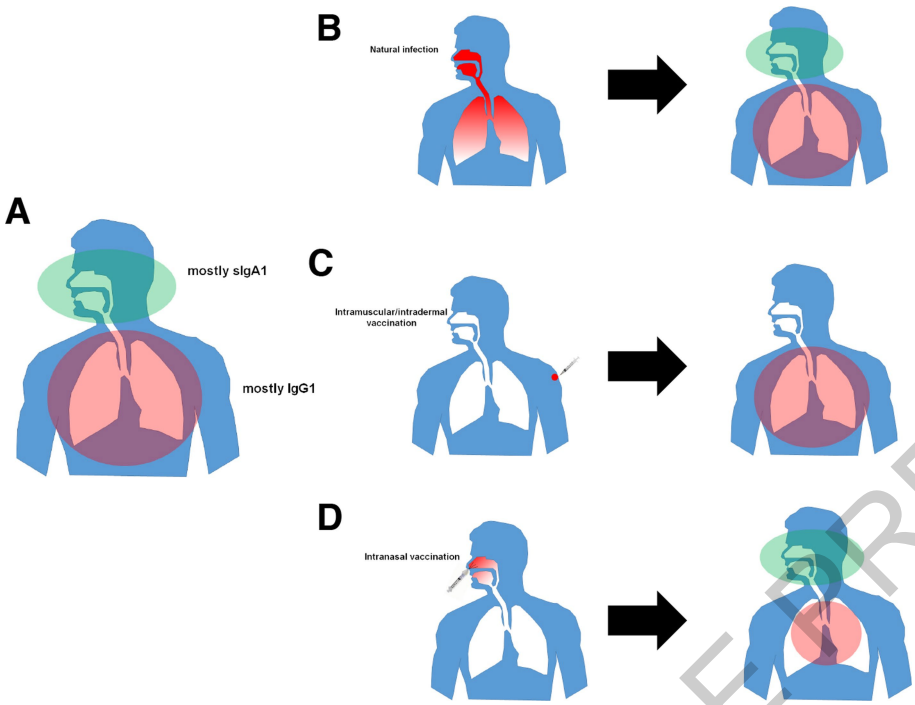

Fig. 2 | Mucosal and systemic immune responses to natural infection with respiratory viruses and vaccination. A The lower human respiratory tract is mostly protected by IgG (IgG1 is most prevalent) which is the main type of antibody in serum and which is transported into the lung. The upper respiratory tract is mostly protected by secretory IgA1 (sIgA1). **B** Natural infection with respiratory viruses induces both a systemic immune response, dominated by IgG1, as well as a mucosal immune response in the upper respiratory tract based on sIgA1. This process can lead to sterilizing immunity for many respiratory viruses. **C** Intramuscular or intradermal vaccination leads in many cases to a strong induction of serum IgG but not to an induction in mucosal IgA. While some IgG can also found on the mucosal surfaces of the upper respiratory tract, the lack of sIgA often leaves an individual vulnerable to reinfection of the upper respiratory tract. **D** Intranasal vaccination can efficiently induce mucosal antibody responses, thereby potentially providing sterilizing immunity in the upper respiratory tract. Systemic immune response are however often lower with this type of vaccination. Currently, all SARS-CoV-2 vaccine candidates in clinical development are given intramuscularly and very few of the >180 vaccine candidates in development are designed to induce mucosal immunity. While mucosal immunity might not be required to protect from sever or even symptomatic disease, it might be required to achieve optimal protection from infection and onward transmission of SARS-CoV2.

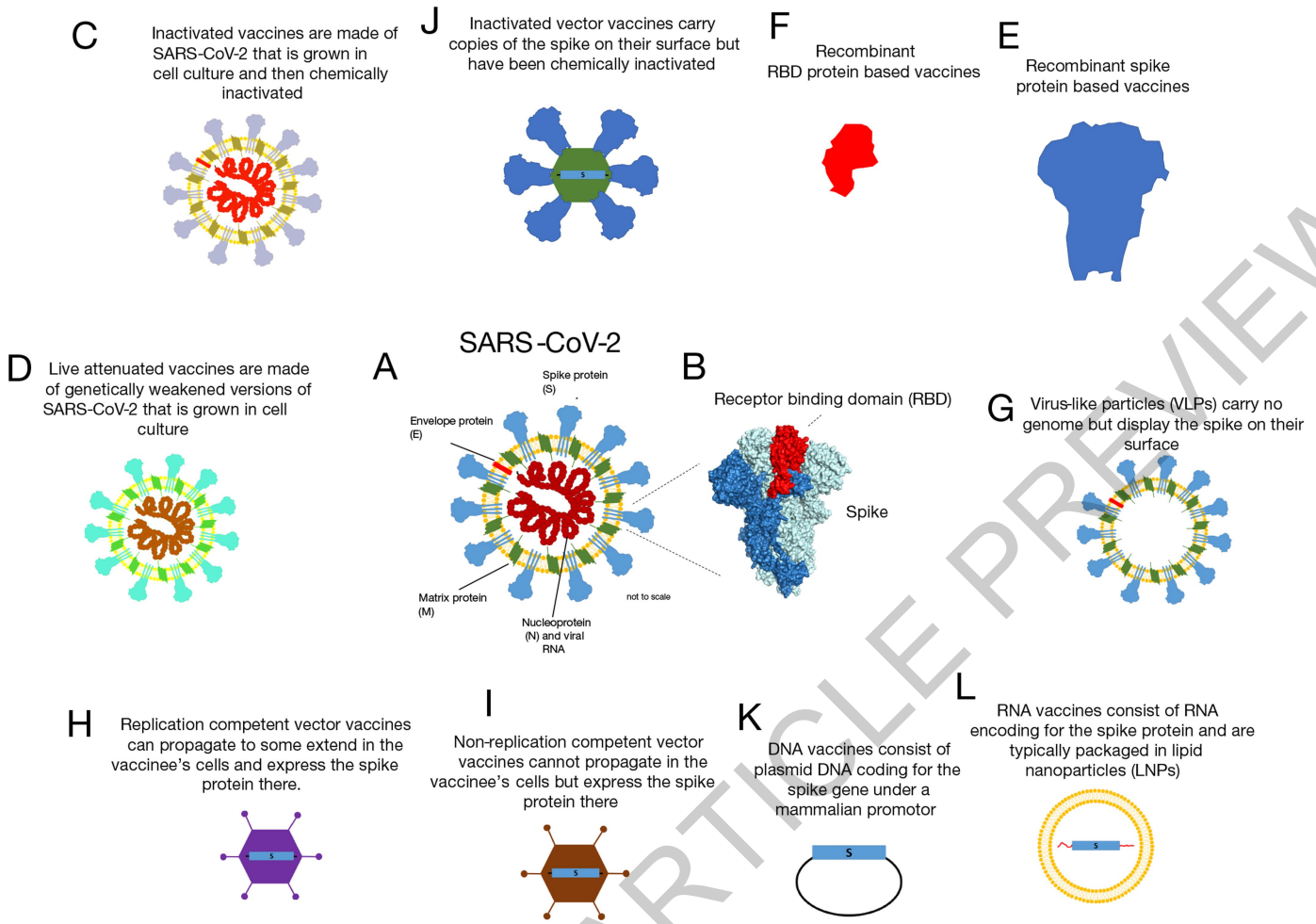

Fig. 3 | Vaccine platforms used for SARS-CoV-2 vaccine development. **A** shows a schematic of the structural proteins of the SARS-CoV-2 virion including the lipid membrane, the genomic RNA covered by the NP on the inside, the envelope and matrix proteins and the spike protein on the virus surface. **B** shows the structure of the spike protein with one monomer highlighted in dark blue and its receptor binding domain (RBD) shown in red. Current SARS-CoV-2 vaccines include inactivated virus vaccines (**C**), live attenuated vaccines (**D**), recombinant protein vaccines based on the spike (**E**), RBD (**F**) or virus-like particles (**G**), replication competent vectors (**H**), replication incompetent vectors (**I**), inactivated vectors that display spike on their surface (**J**), DNA vaccines (**K**) as well as RNA-based vaccines (**L**).

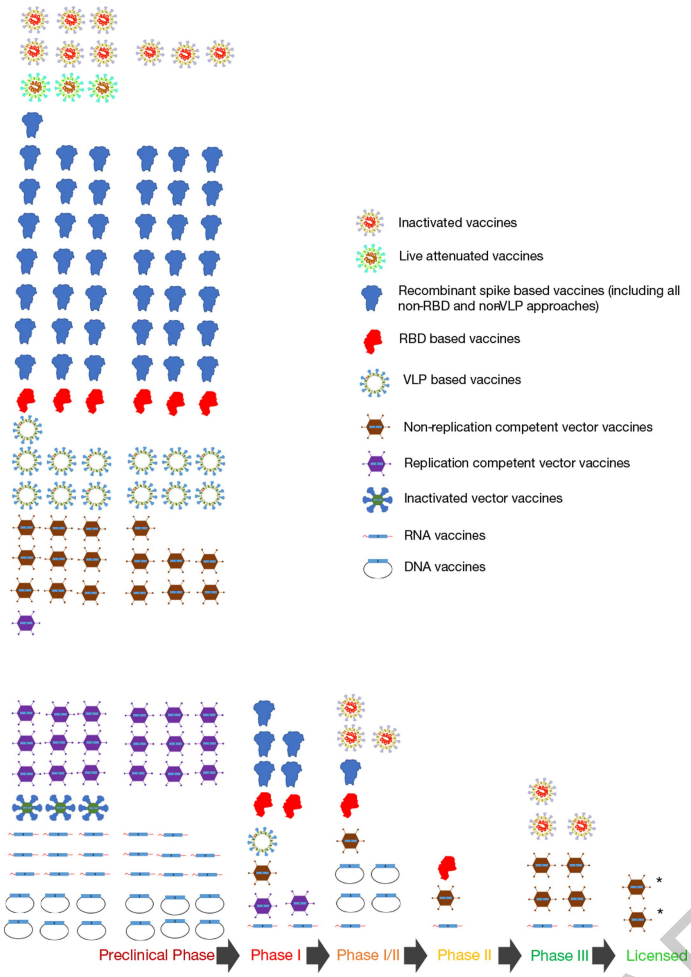

Fig. 4 | Overview of the COVID-19 vaccine development landscape with different vaccine platforms distributed over the different development phases. *licensed vaccines include a vaccine candidate produced by CanSino which is currently in use in the Chinese military and the vaccine by Gamaleya Research Institute in Russia which was licensed without a Phase III trial.

Table 1 | Overview of NHP results

Company (reference)	Vaccine (type)	Dose range (route)	Neut titer after prime	Neut titer after boost	Neut titer after 2nd boost	T-cell response	Challenge dose (route)	URT protection	LRT protection	Species
Sinovac[34]	PiCoVacc (Inactivated virion + aluminum hydroxide)	3-6ug (i.m.)	None[a]	1:10 range[a]	1:50 range[a]	Not assessed	10^6 $TCID_{50}$ (i.t.)	Partiall[c]	High dose: yes; low dose: incomplete[c]	Rhesus macaques
Beijing Institute of Biological Products Ltd[33].	BBIBP-CorV (Inactivated virion + aluminum hydroxide)	4-8 ug (i.m.)	1:100 range[a]	1:200 range[a]	-	Not assessed	10^6 $TCID_{50}$ (i.t.)	Partiall[c]	Complete[c]	Cynomolgus macaques
AstraZeneca[49]	ChAdOx1nCOV-19 (non-rep AdV)	2.4x10^{10}VP 1x or 2x (i.m.)	1:5-40 range[a]	1:10-160 range[a]	-	Yes	2.6x10^6 $TCID_{50}$ (i.t., oral, i.n., ocular)	None (1x)[d] None (2x)[d]	Partial (1x)[d] Complete (2x)[d]	Rhesus macaques
Janssen[41]	Ad26COVS1 (non-rep AdV)	1x 10^{11}VP (i.m.)	1:100 range[b]	-	-	Low	10^5 $TCID_{50}$ (i.n, i.t.)	Complete in S.PP group[d]	Complete in S.PP group[d]	Rhesus macaques
Moderna[57]	mRNA-1273 (mRNA via LNPs)	2x 10-100 ug (i.m.)	Not assessed using authentic SARS-CoV-2	1:501 - 1:3481 range[b]	-	Yes, CD4, T_{FH}	7.5x10^5 $TCID_{50}$ (i.n., i.t.)	None (10ug)[d] Partial (100ug)[d]	Partial (10ug)[d] Complete (10ug)[d]	Rhesus macaques
Novavax[83]	NVX CoV2373 (S protein + Matrix M)	2x 2.5ug-25ug	-	17,920 - 23,040 range[a]	-	Not reported	10^4 (i.n., i.t.)[e]	Partial (low dose) [d] Complete (two higher doses)[d]	Complete[d]	Cynomolgus macaques

[a]based on microneutralization assay with CPE as readout

[b]based on microneutralization assay with a SARS-CoV-2 reporter virus, 50% reduction of relative light units is the readout

[c]based on vRNA copy numbers

[d]based on subgenomic RNA copy numbers

[e]units not specified

Table 2 | Overview of Phase I/II results

Company (reference)	Vaccine (type)	Dose range (route)	Neut titer after prime	Neut titer after boost	T-cell response	Registration #
Sinovac[35]	CoronaVac (inactivated SARS-CoV-2+aluminium hydroxide)	3-6ug (i.m.) 2x (0/14 or 0/28)	Not determined	1:30-1:60 range[a]	Not measured	NCT04352608
CanSino[46]	Ad5 nCoV (non-rep AdV5 expressing S)	$5x10^{10}$, 10^{11} VP (i.m.)	1:18.3-1:19.5 range[b]	-	Yes	NCT04341389
AstraZeneca[47]	ChAdOx1nCOV-19 (non-rep chimpanzee AdV expressing S)	$5x10^{10}$ VP 1x or 2x (i.m.)	Median 1:218[c] Median 1:51[d] Median 1:4-1:16[e]	Median 1:136[d] Median 1:29 [d]	Yes	NCT04324606
Moderna[59]	mRNA-1273 (mRNA)	2x 25, 100, 250 ug (i.m.)	Low	1:112.3 (25ug)[f] 1:343.8 (100ug)[f] 1:332.2 (250ug)[f] 1:339.7 (25ug)[g] 1:654.3 (100ug)[g]	Good CD4+ and low CD8+ response	NCT04283461
Pfizer[60]	BNT162b1 (mRNA)	2x 10, 30, 100 ug (i.m.)	Low	1:180 (10ug)[h] 1:437 (30 ug)[h]	Not measured	NCT04368728
Pfizer[84]	BNT162b1 (mRNA) and BNT162b2 (mRNA)	2x 10, 20, 30 ug	Low	Day 28[h] BNT126b1/18-55 years: 1:168 (10ug) 1:267 (30ug) BNT126b1/65-85 years: 1:37 (10ug) 1:179 (20ug) 1:101 (30ug) BNT126b2/18-55 years: 1:157 (10ug) 1:363 (20ug) 1:361 (30ug) BNT126b2/65-85 years: 1:84 (20ug) 1:147 (30ug)	Not measured	NCT04368728
Novavax[90]	NVX CoV2373 (Matrix-M) Spike protein 'rosettes;	2x 2.5ug-25ug (i.m. +/- Matrix-M) 1x 25ug (i.m. + Matrix-M)	1:128 (25ug + Matrix-M)[i]	1:3906 (5ug + Matrix-M) [i] 1:3305 (25 ug + Matrix-M) [i] 1:41 (25 ug unadjuvanted) [i]	CD4+	NCT04368988

[a]based on microneutralization assay with CPE as readout
[b]neutralization assay based on authentic SARS-CoV-2 but not described in detail
[c]based on $PRNT_{50}$ assay with authentic SARS-CoV-2
[d]based on MN assay with authentic SARS-CoV-2 with ID_{80} as readout
[e]based on a virus neutralization assay with CPE as readout
[f]based on pseudotyped particle entry inhibition ID_{50}
[g]based on PRNT80 with authentic SARS-CoV-2
[h]based on microneutralization assay with a SARS-CoV-2 reporter virus, ID_{80} of relative light units is the readout
[i]based on microneutralization assay with authentic SARS-CoV-2 (ID_{99})

Box 1

Vaccine enhanced disease

While enhanced disease is usually associated with flaviviruses, pre-existing immunity induced by natural infection or vaccination to feline coronavirus (FCoV) can lead to antibody-dependent enhanced disease. This occurs mostly under experimental conditions but seems to be rare in the field[91]. Vaccination with formalin inactivated vaccines, DNA-based vaccines, RNA-based vaccines, VLP-based vaccines and MVA-vectored vaccines against SARS-CoV-1 has resulted in complications like increased infiltration of eosinophils (suggesting a T_{h2} type immunopathology) into the lung or liver damage after challenge with the virus in different animal models[92–95]. It has been speculated that enhanced disease is driven by non-neutralizing antibodies to S, but has also been shown to be triggered by N-based vaccines[93,96,97]. *Bona fide* antibody dependent enhancement for SARS-CoV-1 even by neutralizing antibodies has been shown *in vitro* while the same antibodies then protected *in vivo*[98]. In addition, several vaccine candidates against SARS-CoV-1 induced protective immunity in animal models without signs of enhanced disease. Enhanced disease has also been reported in rabbits after natural infection and re-challenge with MERS-CoV in the absence of neutralizing antibodies[99]. Mice vaccinated with an inactivated MERS-CoV vaccine and then challenged with infectious virus showed enhanced infiltration of easinophiles into the lung even despite the presence of neutralizing antibodies. Of note, as with many SARS-CoV-1 vaccines, these mice controlled the virus better than animals in the control group[100]. The mechanism behind this phenomenon is still unclear and the data is murky. In this context it is also important to note that enhanced disease is not necessarily based on antibody dependent enhancement but could be caused by other mechanisms as well. It seems, given the right circumstances, enhanced disease induced by natural infection or vaccination can be forced in animal models. However, even in animal models there is currently no evidence for SARS-CoV-2 enhanced disease. Nevertheless, monitoring for the occurrence of this phenomenon pre and post marketing of vaccines is paramount, especially once titers start to wane.