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

Fundamental Research 1 (2021) 131–138

Contents lists available at ScienceDirect

Fundamental Research

journal homepage: http://www.keaipublishing.com/en/journals/fundamental-research/

Review

# SARS-CoV-2 virus: Vaccines in development

Qingrui Huang[a], Jinghua Yan[a,b,*]

[a] CAS Key Laboratory of Microbial Physiological and Metabolic Engineering, Institute of Microbiology, Chinese Academy of Sciences, Beijing 100101, China
[b] University of Chinese Academy of Sciences, Beijing 101408, China

ARTICLE INFO

*Keywords:*
SARS-CoV-2
COVID-19
Vaccine
Clinical trial
Virus

ABSTRACT

The ongoing COVID-19 pandemic, caused by SARS-CoV-2, is an unprecedented challenge to humanity. Global herd immunity may be necessary before resumption of normal economic and societal activities. Since the beginning of the outbreak, the development of COVID-19 vaccines has proceeded at record speed using nearly all available platforms or strategies to maximize vaccine success. A total of 42 vaccine candidates have now entered clinical trials and encouraging data from several vaccine candidates in phase 1 or 2 clinical trials have been reported. In this review, we examine current COVID-19 vaccine candidates, discuss their strengths and weaknesses, summarize published clinical data and analyze future challenges.

## 1. Introduction

At the end of December 2019, a novel coronavirus designated as SARS-CoV-2 emerged and caused an outbreak of unusual virus pneumonia [1–5]. Because of its extraordinary transmissibility, coronavirus disease 2019, caused by this novel virus, rapidly caused a global pandemic and brought the world to a near standstill [6–9]. By late October 2020, the virus had accounted for more than 40 million laboratory-confirmed infections and 1 million deaths in 218 countries and territories, and still counting. In the absence of a vaccine, physical-distancing, face masks and other transmission-mitigation strategies have been implemented to manage COVID-19 [10,11]. While these strategies reduce the risk of infection they do not provide immunity to SARS-CoV-2 and individuals remain susceptible to the virus. Normal economic and social activities will not be resumed until global herd immunity is achieved. Due to the emergence of re-infection and the fact that even a 1% mortality rate to COVID-19 will kill millions of people globally, the dependence of humankind immunity on infection is unacceptable [12–14]. Therefore, safe and effective vaccines against COVID-19 are desperately needed.

As SARS-CoV-2 is a new virus, knowledge of what constitutes a safe and immunologically effective vaccine strategy is limited [15,16]. Nevertheless, the global pandemic required quick action and development of vaccines at record speed. Since the beginning of the pandemic, various vaccine platforms and strategies including live attenuated virus, inactivated virus, protein subunit, virus-vectored, mRNA and DNA vaccines, have been developed in parallel to maximize the potential success rate [17–32]. These efforts are encouraging and fruitful. According to the World Health Organization (WHO), there are currently 10 vaccine candidates being evaluated in phase 3 clinical trials, 34 in phase 1 or 2 clinical trials, and 154 in pre-clinical development. During COVID-19 vaccine development, a new pandemic vaccine development paradigm has been built and vaccine development time has been compressed from the typical 10–15 years to only 1–2 years. Results from phase 1 or 2 clinical trials of eight COVID-19 vaccine candidates have already been reported [33–42]. This review outlines strengths and shortfalls of every COVID-19 vaccine development platform, summarizes published clinical data, and analyzes the challenges ahead.

## 2. Target antigen for COVID-19 vaccines

SARS-CoV-2 is an enveloped, positive-sense RNA virus in the genus *Betacoronavirus* of the family *Coronaviridae* [43]. The virion envelope consists of membrane (M) and envelope (E) proteins, coated with a "crown"-like trimeric spike (S) protein. Nucleocapsid (N) proteins bound to the RNA genome constitute the virion core [44–46]. Similar to other human coronaviruses such as SARS-CoV, SARS-CoV-2 uses an S protein for entry into host cells [47–49]. The S protein can be functionally categorized into S1 and S2 subunits, which are separated by a protease cleavage site [48,50,51]. First, the receptor-binding domain (RBD) at the C terminus of the S1 subunit engages human angiotensin-converting enzyme 2 (hACE2) as the receptor, which subsequently causes fusion between the viral envelope and the host cell membrane through the S2 subunit [8,45,52–54]. RBD, S1 and the S protein (full-length or ectodomain) are capable of eliciting highly potent neutralizing antibodies and cellular immunity and have been widely selected as promising antigens for COVID-19 vaccine development [25,29,31,40,55,56].

The structures of the RBD alone, RBD-hACE2 and RBD-monoclonal antibody have been determined at high resolution by many research groups [57–59]. SARS-CoV-2 RBD contains two structural domains [58].

* Corresponding author.
*E-mail address:* yanjh@im.ac.cn (J. Yan).

https://doi.org/10.1016/j.fmre.2021.01.009

Available online 22 January 2021

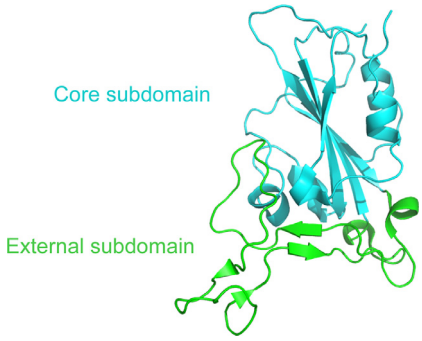


**Fig. 1.** The structure of SARS-CoV-2 RBD (PDB:6LZG) [58].

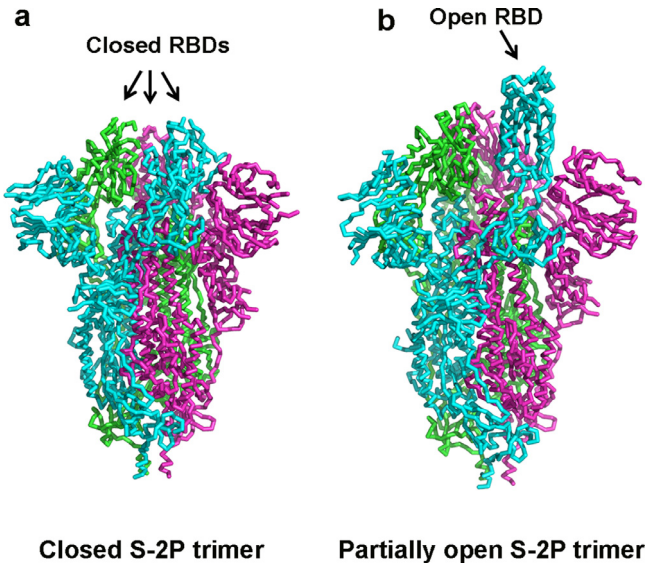


**Fig. 2.** The two distinct conformational states of SARS-CoV-2 S trimer [57]. (a) Closed SARS-CoV-2 S trimer with all RBDs closed (PDB:6VXX). (b) Partially open SARS-CoV-2 S trimer with one RBD at the trimer apex open (PDB:6VYB).

One is the conserved core subdomain with five antiparallel $\beta$ strands, and the other is the external subdomain which is dominated by a disulfide bond-stabilized flexible loop and responsible for the recognition of hACE2 (Fig. 1) [57,58]. The Cryo-EM structure of SARS-CoV-2 S trimer revealed that two dominant distinct conformational states exist, one is closed S trimer, and the other is partially open S trimer with one of the three RBDs rotated up in a receptor-accessible conformation (Fig. 2) [57,60]. These findings provided important structural information about the vaccine antigens [43,52,61–63]. However, in addition to the S protein, other proteins, such as the N protein, M protein and non-structural proteins may be potential vaccine antigens and act by inducing a more balanced immune response between humoral and cellular immunity.

## 3. COVID-19 vaccine candidates in development

### 3.1. Live attenuated vaccines

Live attenuated vaccines are based on an attenuated strain of virus that can induce a host immune response by limited replications *in vivo* but not lead to disease. The attenuation strategies generally include adaption of viruses to unfavorable conditions such as low temperature or rational gene modifications involving codon de-optimization and deletion of certain genes associated with replication or eluding human immune recognition [64,65]. An advantage of such vaccines is that they mimic natural infections and can stimulate potent cellular response aside of induction of virus neutralizing antibodies. The disadvantage to these vaccines is the safety concern about virus reverse mutations in vaccinated individuals. To date, only three SARS-CoV-2 live attenuated vaccine candidates have reached pre-clinical stages, including one (developed by Codagenix and the Serum Institute of India) by using the CodaVax technology platform which attenuates the virus through codon de-optimization.

### 3.2. Inactivated vaccines

Purified inactivated vaccines are widely used for prevention of diseases caused by viruses such as the influenza virus and the poliovirus [66–68]. Selection for a seed virus strain, characterized by highly efficient proliferation and high genetic stability, is the first step for developing SARS-CoV-2 inactivated vaccines. The selected strain is then propagated in cell cultures, usually vero cells followed by inactivation using chemicals such as $\beta$-propiolactone. After optimized purification steps including chromatography, pure inactivated vaccine preparations are obtained. Because of the whole virus being presented to the immune system, an advantage of inactivated vaccines is that the elicited immune response will target not only the S antigen but also other structural or non-structural proteins including the M, E and N proteins. The inclusion of other viral antigens might induce a more balanced response involving both humoral and cellular immunity. However, pulmonary immunopathology induced by SARS-CoV vaccine candidates, either directly mediated by a Th2 immune response or as a result of antibody-dependent enhancement (ADE) [69–72], warrants a careful investigation of the safety of these vaccines against SARS-CoV-2. Certain epitopes, which readily induce high-binding but low-neutralizing antibodies, are prone to elicit an ADE effect. Thus, the inactivated vaccine type may have a high ADE risk because of the maximal epitopes included. In addition, the requirement for biosafety level 3 (BSL3) production facilities during SARS-CoV-2 propagation might be a limitation to inactivated vaccine production.

Beijing Institute of Biological Products Company Limited, together with China CDC and Peking Union Medical College, developed a SARS-CoV-2 inactivated vaccine with alum as adjuvant (BBIBP-CorV) [33]. A randomized, double blinded placebo-controlled phase 1/2 trial of this vaccine has been reported (ChiCTR2000032459). A total of 192 healthy adults (18–80 years) and 448 adults (18–59 years) were enrolled in phase 1 and 2 trials, respectively. In phase 1, subjects were separated into two age groups (18–59 years and ≥ 60 years) and the developers tested three doses, 2, 5, and 8 $\mu$g of BBIBP-CorV in a prime-boost vaccination regimen within a 4-week internal. In phase 2, a single-dose schedule of 8 $\mu$g and a two-dose schedule of 4 $\mu$g with internals of 2, 3, or 4 weeks were investigated. In both trials, all of the adverse reactions were mild or moderate in severity and no serious adverse events were reported. The phase 1 trial indicated that neutralizing antibody titers in adults receiving 4 $\mu$g doses at two weeks post boost reached 211.2 in the young group and 131.5 in the elderly group, respectively. The lower neutralizing antibody titer in the elderly group indicates the need for an increased dose and/or more potent adjuvant. In the phase 2 trial, two-dose immunization of the 4 $\mu$g vaccine with internals of 3 or 4 weeks achieved higher neutralizing antibody titers than the single 8 $\mu$g dose or 4 $\mu$g dose with a two-week internal. This indicated the benefit of increasing the internal time between prime and boost injections. During the revision of the manuscript, BBIBP-CorV has been reported of a protection efficacy of 78.4% and been approved for use in China.

Interim evaluation of randomized, double-blind, placebo-controlled, phase 1 and 2 clinical trials of an alum-adjuvanted inactivated vaccine candidate (developed by Wuhan Institute of Biological Products and Sinopharm) was also reported (ChiCTR2000031809) [34]. The phase 1 trial with 96 adults (aged 18–59 years) tested three doses, 2.5, 5, and 10 $\mu$g with three injections, 4 weeks apart. The phase 2 trial used 224 adults (aged 18–59 years) and a 5 $\mu$g dose in a prime-boost vaccina-

tion regimen with 2- and 3-week internals. The vaccine was well tolerated and showed excellent safety in both trials. In the phase 1 trial, the geometric mean titers of neutralizing antibodies at 2 weeks post 3 injections reached 316 (low-dose group), 206 (medium-dose group), and 297 (high-dose group), respectively. In the phase 2 trial, similar to the results of BBIBP-CorV, neutralizing titers in the 3-week internal group (247) were higher than those in the 2-week internal group (121).

Another inactivated vaccine candidate with alum as the adjuvant (CoronaVac, also designated as PiCoVacc, developed by Sinovac and the Chinese Academy of Medical Sciences), was the first COVID-19 vaccine candidate evaluated in the rhesus macaque model [17]. The developer found that three immunizations within the one-week internal at 3 $\mu$g and 6 $\mu$g doses could induce moderate neutralizing antibody titers and protect macaques from virus infection in the lower respiratory tract following SARS-CoV-2 challenge without evident antibody-dependent enhancement of infection. The three vaccine candidates mentioned above are currently being evaluated in phase 3 clinical trials. Other inactivated vaccine candidates involving one Kazakh, one Indian and one Chinese candidate are currently in phase 1 or 2 clinical trials (Table 1).

### 3.3. Protein subunit vaccines

Protein subunit vaccines are a popular platform to develop vaccines against infectious viruses such as influenza virus, hepatitis B and varicella-zoster virus [66]. When combined with an adjuvant, protein subunit vaccines usually have good safety and immunogenicity profiles. The great amount of production experience gained from currently licensed vaccines is also an advantage [55]. SARS-CoV-2 protein subunit vaccines can be classified into three categories, RBD-based vaccines, S-based vaccines and virus-like particle (VLP) vaccines. The antigen expression systems involve yeast cells, mammalian cells, insect cells and plants. Depending on the expression systems, glycosylation modifications vary and may influence the immune response [73]. As a relatively small protein, RBD faces the challenge of low immunogenicity. Strategies for improving its immunogenicity may be needed. A dimeric form of RBD has been reported to significantly enhance neutralizing antibody response [55]. Recombinant New Coronavirus Vaccine (CHO Cell) based on the dimeric RBD was developed by our team in collaboration with Anhui Zhifei Longcom Biopharmaceutical. This vaccine has completed the phase 2 clinical trial with excellent safety profiles and immunogenicity, and is scheduled to begin a phase 3 trial. In comparison to RBD, wild-type S is metastable and difficult to manufacture on a large scale *in vitro*. This may impact vaccine yields in the future [61]. Modifications of the deletion of the polybasic cleavage sites and inclusion of two (S-2P) or six proline substitutions can stabilize the S protein, and significantly improve its yields and the immune response generated [74]. Several vaccine candidates including two protein subunit candidates (NVX-CoV2373 and MVC-COV1901) selected the S-2P mutant as the antigens [35]. There are currently 15 protein subunit vaccine candidates in clinical trials and many more in pre-clinical development (Table 1).

Of these, NVX-CoV2373 (developed by Novavax) is a recombinant nanoparticle vaccine, constructed from the full-length S-2P antigen (mentioned above) with a saponin-containing Matrix-M adjuvant. Data from a randomized, placebo-controlled, phase 1 trial in 131 adults (aged 18–55 years) using this vaccine candidate has been published (NCT04368988) [35]. The trial evaluated two doses of this vaccine (5 and 25 $\mu$g) with two intramuscular injections, 3 weeks apart. There were no severe adverse events reported, and the geometric mean neutralizing antibody $IC_{>99\%}$ titers at 2 weeks post boost approached 3906 (5 $\mu$g group) and 3305 (25 $\mu$g group), respectively. Both of these exceeded the levels observed in symptomatic COVID-19 patients (983). In addition, the Matrix-M adjuvant could skew the immune response toward the Th1 phenotype. This vaccine candidate is currently being evaluated in phase 3 clinical trials (Table 1).

### 3.4. Virus-vectored vaccines

Replication-deficient virus vectors are increasingly being explored as antigen carriers for developing vaccines against infectious diseases [75]. Such vectors are typically disabled from replication by deletions of certain parts of the virus genome and they are engineered to express the targeted antigen protein, in this case SARS-CoV-2 RBD or S protein. Human and chimpanzee adenoviruses (AdV) are the most popular choices in these approaches. The major advantages of these platforms include safety profiles, considerable experience of scalable manufacturing of some of these vectors, and potent stimulation of both humoral and cellular immunity. A disadvantage is that pre-existing vector immunity in humans could weaken vaccine-elicited immune responses by neutralizing partial vectors. The use of rare serotypes (e.g. chimpanzee adenoviruses) in human populations can circumvent this problem. In prime-boost immunization regimens, boosting with one different vector to priming can also escape impact of priming-induced neutralizing antibodies. ChAdOxnCoV-19 (chimpanzee adenovirus, developed by the University of Oxford and AstraZeneca), a recombinant Ad5 vectored COVID-19 vaccine (Ad5, developed by CanSino and Beijing Institute of Biotechnology), Gam-COVID-Vac (Ad26 priming and Ad5 boost, developed by Gamaleya Research Institute) and Ad26.COV2.S (Ad26, developed by Janssen) are currently in phase 3 clinical trials and eight other virus-vectored COVID-19 vaccine candidates have also entered phase 1 or 2 clinical trials (Table 1).

A phase 1/2, single-blind, randomized controlled trial of S-encoding ChAdOx1 nCoV-19 vaccine in 1077 participants (age of 18–55 years), with licensed MenACWY vaccine (a meningitis vaccine) as a placebo, has been reported (NCT04324606) [76]. The majority of participants received one single injection of ChAdOx1 nCoV-19 at a dose of $5 \times 10^{10}$ viral particles or the placebo. Ten individuals were immunized in a prime-boost regimen with a 4-week internal. Although no serious adverse events related to ChAdOx1 nCoV-19 were reported, local and systemic reactions were more common in the SARS-CoV-2 vaccine group than those in the meningitis vaccine group, indicating a worse safety profile. Neutralizing antibody titers from a subgroup of 35 participants were measured using three live SARS-CoV-2 neutralizing assays (a plague reduction neutralization assay, $PRNT_{50}$; a microneutralisation assay, $MN_{50}$; and CPE-based neutralizing assay, $IC_{100}$), and the medium titters reached 218, 51, and among 4–16 range, respectively. The boost dose increased the titters in the latter two assays to 136 ($MN_{50}$) and 29 ($IC_{100}$), respectively. Interferon-$\gamma$ ELISpot responses peaked at 856 spot-forming cells per million peripheral blood mononuclear cells (PBMC) at 2 weeks post vaccination with a background of 50–100 spot-forming cells per million PBMCs, indicating that a cellular immunity was induced. During the revision of the manuscript, ChAdOx1 nCoV-19 (brand name: AZD1222) has been approved for emergency use in England.

CanSino published the first COVID-19 clinical trial results from the phase 1 trial with their recombinant Ad5 vectored COVID-19 vaccine, expressing wild-type full length S protein [36]. Data from a randomized, double-blind, placebo-controlled, phase 2 trial in 508 adults (aged 18 and older) was also reported (NCT04341389)[37]. In the phase 2 trial two doses were tested, $5 \times 10^9$ and $1 \times 10^{11}$ virus particles, each as one shot. Results showed that 9% of participants in the high-dose group and 1% in the low-dose group reported grade 3 adverse reactions (mostly fever). This indicated that the vaccine was relatively reactogenic, especially when delivered at a high dose. SARS-CoV-2 neutralizing antibody titers approached 18.3 in the low-dose group and 19.5 in the high-dose group, respectively, representing low immunogenicity. High pre-existing anti-Ad5 immunity and increasing patient age were found to negatively impact the neutralizing antibody response. Moreover, both doses induced cellular immunity as evidenced in an interferon-$\gamma$ ELISpot assay.

**Table 1**
The development of vaccine candidates in clinical trial.

| Platform | Vaccine | Developer | Location | Antigen | Adjuvant | Route | Number of dose | Phase |
|---|---|---|---|---|---|---|---|---|
| Inactivated virus | CoronaVac | Sinovac | China | Whole-virus inactivated | Alum | IM | 2 | Phase 3 NCT04456595 |
| | BBIBP-CorV | Beijing Institute of Biological Products Company Limited | China | Whole-virus inactivated | Alum | IM | 2 | Phase 3 ChiCTR2000034780 NCT04560881 |
| | Inactivated vaccine | Wuhan Institute of Biological Products | China | Whole-virus inactivated | Alum | IM | 2 | Phase 3 ChiCTR2000034780 ChiCTR2000039000 |
| | BBV152 | Bharat Biotech | India | Whole-virus inactivated | Aluminum hydroxide gel (Algel) or a novel TLR7/8 agonist adsorbed Algel (Algel-IMDG) | IM | 2 | Phase 1/2 NCT04471519 CTRI/2020/09/027674 |
| | QazCovid-in® | Research Institute for Biological Safety Problems | Rep of Kazakhstan | Whole-virus inactivated | Not available | IM | 2 | Phase 1/2 NCT04530357 |
| | Inactivated vaccine | Institute of Medical Biology, Chinese Academy of Medical Sciences | China | Whole-virus inactivated | Not available | IM | 2 | Phase 1 NCT04412538 |
| | Inactivated vaccine | Beijing Minhai Biotechnology | China | Whole-virus inactivated | Not available | IM | 1, 2 or 3 | Phase 1 ChiCTR2000038804 |
| Platform | Vaccine | Developer | Location | Antigen | Adjuvant | Route | Number of dose | Phase |
| Protein subunit | ZF2001 | Anhui Zhifei Longcom Biopharmaceutical | China | Dimeric RBD (CHO cells) | Alum | IM | 2 or 3 | Phase 2 NCT04466085 |
| | KBP-COVID-19 | Kentucky Bioprocessing Inc | America | RBD (tobbaco plants) | Not available | IM | 2 | Phase 1/2 NCT04473690 |
| | Soberana 01 | Instituto Finlay de Vacunas | Cuba | RBD | Adjuvant | IM | 2 | Phase 1 IFV/COR/04 |
| | COVID-19 recombinant vaccine (Sf9) | West China Hospital, Sichuan University | China | RBD (insect cells) | Alum | IM | 2 | Phase 1 ChiCTR2000037518 |
| | UB-612 | COVAXX, United Biomedical | America | RBD fused to Fc domain of human IgG1, combined with SARS-CoV-2 peptide pool | AdjuPhos® (CpG1 plus alum) | IM | 2 | Phase 1 NCT04545749 |
| | COVAX19 | Vaxine Pty Ltd, Medytox | Australia | S (insect cells) | Advax-SM | IM | 2 | Phase 1 NCT04453852 |
| | Sclamp (COVID-19) Vaccine | University of Queensland | Australia | Molecular clamp stabilized S (mammalian cells) | MF59 | IM | 2 | Phase 1 ACTRN12620000674932p |
| Platform | Vaccine | Developer | Location | Antigen | Adjuvant | Route | Number of dose | Phase |
| Protein subunit | NVX-CoV2373 | Novavax | America | S with cleavage site deleted and two stabilizing proline mutations (insect cells) | Saponin-containing Matrix-M | IM | 2 | Phase 3 2020-004123-16 |
| | Recombinant protein vaccine | Sanofi Pasteur, GSK | France | S (insect cells) | No adjuvant or AS03 | IM | 2 | Phase 1/2 NCT04537208 |
| | SCB-2019 | Clover Biopharmaceuticals , GSK, Dynavax | China | Trimeric S protein (mammalian cells) | No adjuvant, AS03 or CpG1018 plus Alum | IM | 2 | Phase 1 NCT04405908 |
| | MVC-COV1901 | Medigen Vaccine Biologics Corporation, NIAID, Dynavax | China Taiwan | S with cleavage site deleted and two stabilizing proline mutations (insect cells) | CpG 1018 plus alum | IM | 2 | Phase 1 NCT04487210 |
| | HBsAg VLPs | SpyBiotech, Serum Institute of India | India | RBD-HBsAg | Not available | IM | 2 | Phase 1/2 AC-TRN12620000817943 |
| | CoVL | Medicago | Canada | Coronavirus-like particle | No adjuvant, AS03 or CpG1018 | IM | 2 | Phase 1 NCT04450004 |
| Platform | Vaccine | Developer | Location | Antigen | Adjuvant | Route | Number of dose | Phase |
| Virus vectored | ChAdOxnCoV-19 | University of Oxford, AstraZeneca | England | Replication-deficient chimpanzee Ad-based S | No | IM | 1 | Phase 3 ISRCTN89951424 NCT04516746 NCT04540393 CTRI/2020/08/02717 |

(*continued on next page*)

**Table 1** (*continued*)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Recombinant Ad5 vectored COVID-19 vaccine | CanSino, Beijing institute of Biotechnology | China | Replication-deficient human Ad5-based S | No | IM | 1 | Phase 3 NCT04526990 NCT04540419 |
| | Gam-COVID-Vac | Gamaleya Research Institute | Russia | Replication-deficient human Ad26 (priming), Ad5 (boost)-based S | No | IM | 2 | Phase 3 NCT04530396 NCT04564716 |
| | Ad26.COV2.S1 | Janssen Pharmaceutical Companies | America | Replication-deficient human Ad26-based S1 | No | IM | 2 | Phase 3 NCT04505722 |
| | GRAd-COV2 | ReiThera, LEUKOCARE, Univercells | Italy, Germany, Belgium | Replication-deficient Simian Ad-based S | No | IM | 1 | Phase 1 NCT04528641 |
| | VXA-COV2-1 | Vaxart | America | Replication-deficient human Ad5-based | No | Oral | 2 | Phase 1 NCT04563702 |
| Platform | Vaccine | Developer | Location | Antigen | Adjuvant | Route | Number of dose | Phase |
| Virus vectored | MVA-SARS-2-S | Ludwig-Maximilians, University of Munich | Germany | Replication-defective MVA-based S | No | IM | 2 | Phase 1 NCT04569383 |
| | V590-001 | Merck Sharp & Dohme, IAVI | Germany | Replication-competent VSV-based S | No | IM | 1 | Phase 1 NCT04569786 |
| | TMV-083 | Institute Pasteur, Themis, University of Pittsburg CVR, Merck Sharp & Dohme | France | Replication-competent measles-vector based | No | IM | 1 or 2 | Phase 1 NCT04497298 |
| | DelNS1-2019-nCoV-RBD-OPT1 | Beijing Wantai Biological Pharmacy, Xiamen University | China | Replication-competent intranasal flu-based-RBD | No | IM | 1 | Phase 1 ChiCTR2000037782 |
| | hAd5-S-Fusion+N-ETSD | ImmunityBio, NantKwest | America | Replication-deficient human Ad5-based S fusion protein and nucleocapsid with an enhanced T-cell stimulation domain | No | SC | 2 | Phase 1 NCT04591717 |
| | Ad5-nCoV | CanSino Biological Inc | China | Replication-deficient human Ad5-based | No | IM or mucosal | 2 | Phase 1 NCT04552366 |
| Platform | Vaccine | Developer | Location | Antigen | Adjuvant | Route | Number of dose | Phase |
| mRNA | mRNA-1273 | Moderna, NIAID | America | S-2P | No | IM | 2 | Phase 3 NCT04470427 |
| | BNT1626b1, BNT1626b2 | BioNTech, Fosun Pharma, Pfizer | Germany | Trimeric RBD, S-2P | No | IM | 2 | Phase 3 NCT04368728 |
| | CVnCOV | CurVac | Germany | Not available | No | IM | 2 | Phase 1 NCT04449276 |
| | ARCT-021 | Arcturus/Duke-NUS | America | Self-replicating mRNA that encodes for the prefusion spike protein | No | IM | Not available | Phase 1/2 NCT04480957 |
| | LNP-nCoVsaRNA | Imperial College London | England | S | No | IM | 2 | Phase 1 SRCTN17072692 |
| | ARCoV | Abogen | China | RBD | No | IM | 2 | Phase 1 ChiCTR2000034112 |
| DNA | INO-4800 | Inovio Pharmaceuticals, International Vaccine Institute | America | S | No | ID | 2 | Phase 1/2 NCT04447781 NCT04336410 |
| Platform | Vaccine | Developer | Location | Antigen | Adjuvant | Route | Number of dose | Phase |
| DNA | DNA vaccine | Cadila Healthcare Limited | India | DNA plasmid vaccine | No | ID | 3 | Phase 1/2 CTRI/2020/07/026352 |
| | GX-19 | Genexine Consortium | Korea | Not available | No | IM | 2 | Phase 1/2 NCT04445389 |
| | AG0301-COVID19 | Osaka University, AnGes, Takara Bio | Japan | Not available | Yes | IM | 2 | Phase 1/2 NCT04463472 NCT04527081 |
| Peptides | EpiVacCorona | FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo | Russia | SARS-CoV-2 pepetides conjugated a carrier protein | Alum | IM | 2 | Phase 1 NCT04527575 |
| | pVAC-SARS-CoV-2 | University Hospital Tuebingen | Germany | SARS-CoV-2 pepetide cocktail based on human HLA II binding screening | ISA 51 VG plus CpG | SC | 1 | Phase 1 NCT04546841 |

### *3.5. mRNA vaccines*

mRNA is a relatively new vaccine development platform. Following antigen-encoding mRNA entering cell cytoplasm, antigen is produced by vaccinees' cells and immune responses are elicited [43]. In contrast to conventional vaccines that require antigen production in eggs or cell culture, mRNA vaccines usually have substantial advantages of versatility, rapid development and potent immunogenicity, especially when delivered by lipid nanoparticles [77–83]. Many mRNA vaccine candidates against infectious diseases or cancer have shown great promise in clinical trials in recent years [78]. A number of COVID-19 mRNA vaccine candidates have also been developed and produced promising results in

preclinical studies [26–28,43,84]. BNT162b2 (a candidate of BioNTech in collaboration with Pfizer) and mRNA-1273 (a candidate of Moderna) are among the most advanced candidates in clinical trials (Table 1). Several other mRNA vaccine candidates including one developed by CurVac and one by the Chinese Liberation Army are also in phase 1 or 2 clinical trials (Table 1). However, given that there has been no previous mRNA vaccine licensed for market, some issues might be encountered about large-scale production and long-term storage stability of the vaccine. mRNA-1273 is an mRNA vaccine encapsulated in lipid nanoparticles (LNPs) that encodes the full-length spike protein with two stabilizing proline mutations (S-2P). Moderna conducted the first COVID-19 phase 1 clinical trial with this vaccine in 45 healthy adults, 18–55 years of age, and published its interim results (NCT04283461) [40]. Three doses of 25 $\mu g$, 100 $\mu g$, and 250 $\mu g$ in a prime-boost immunization regimen with 4 weeks separation were evaluated. Systemic adverse events were more common following the second vaccination and 0%, 40% and 57% of the participants in the dose-escalation groups, respectively, had fever after the boost vaccination, whereas none of participants reported fever after the prime dose. As to immunogenicity, authentic virus-neutralizing activity was tittered as $PRNT_{80}$ and the authors found that the geometric mean $PRNT_{80}$ titers reached 339.7 in the 25-$\mu g$ group and 654.3 in the 100-$\mu g$ group, respectively. Both were within the range of convalescent serum specimens. $CD4^+$ T cell responses with a strong Th1 bias were elicited by the vaccine. This vaccine candidate is now in the phase 3 clinical trial with the 100 $\mu g$ dose in adults and elderly individuals.

BioNTech, together with Pfizer, has published safety and immunogenicity data of BNT1626b1, a LNPs-formulated mRNA encoding SARS-CoV-2 RBD fused with a T4 fibritin trimerisation domain, from a placebo-controlled, observer-blinded Phase 1/2 trial (NCT04368728) [41]. The trial in 45 healthy adults (aged 18–55 years) was designed to assess three doses (10, 30 and 100 $\mu g$) in a prime-boost immunization regimen with a 3-week internal. Systemic adverse events increased with dose escalation and, similar to mRNA-1273, adverse events also increased in participants after the boost dose in comparison with those following the first dose. SARS-CoV-2 neutralizing geometric mean $NT_{50}$ titers in sera at 2 weeks post boost reached 180 in the 10 $\mu g$ group and 437 in the 30 $\mu g$ group, respectively, compared to 94 for a panel of COVID-19 convalescent human sera. The developers recently presented additional data from a USA clinical trial with a direct comparison between BNT1626b1 and BNT1626b2, which is similar to BNT1626b1 but encodes S-2P (NCT04368728) [42]. Although the neutralizing antibody titers elicited by the two vaccine candidates were comparable, BNT1626b2 showed less systemic reactogenicity, particularly in elderly adults, and it was selected to enter a phase 3 study.

During the revision of the manuscript, both mRNA-1273 and BNT1626b2 have been approved for emergency use based on primary analysis of phase 3 clinical data, which demonstrated their acceptable safety profiles and protection efficacies of 94.1% and 95%, respectively.

### 3.6. DNA vaccines

DNA vaccines are based on plasmids that contain a transgene of interest to encode the target antigen in vaccinees' cells. The huge advantages of DNA vaccines include versatility, rapid development, ease of large-scale manufacturing, and high stability [31,85]. However, unlike mRNA vaccines, DNA vaccines need to be delivered into cell nuclei where transcription occurs to express the antigen. There is a potential safety risk of integration into the host genome, which may lead to insertion mutations. Delivery devices, such as electroporators, may be required, which could limit vaccine use. Moreover, DNA vaccines usually show low immunogenicity and need repeated administrations [85]. There are four COVID-19 DNA vaccine candidates in phase 1 or 2 clinical trials (Table 1). Of those, the S-encoding INO-4800 vaccine candidate (developed by US Inovio Pharmaceuticals) can induce a protective immunity in rhesus masques after 2 injections.

## 4. Conclusion and perspective

The lengthy COVID-19 global pandemic has stimulated a frenetic search for a safe and efficacious vaccine. The global efforts in research and development for COVID-19 vaccines are unprecedented. Since the outbreak began, a handful of vaccine candidates have entered phase 1, 2 and 3 clinical trials within a period of only 6 months. According to published data from several candidates in phase 1, 2 or 1/2 trials, inactivated vaccine and protein subunit vaccines are well tolerated, the mRNA vaccine shows an increased reactogenicity following the second injection, and the Ad5 vectored vaccine seems to perform the worst. As clinical trials have used different assays and readouts ($ID_{50}$, $ID_{80}$, $ID_{99}$ and $ID_{100}$) to determine neutralizing antibody titers, it is difficult to compare immunogenicities of vaccine candidates. However, inclusion of convalescent patient sera as an assay control in some clinical trials makes comparisons easier and more accurate. The neutralizing antibody titers from low to high are as follows: Ad5 vectored vaccine, mRNA vaccine, and protein subunit vaccine. The cellular immunity elicited by the vaccine might play a protective role as well. Although the clinical data seem encouraging, there will be still many challenges moving forward. For example, there are few vaccine candidates in clinical trials designed to elicit IgA, which can protect the upper respiratory tract [22,86]. In fact, IgG, which can be efficiently induced by current clinical vaccine candidates and the IM administration, only protects the low respiratory tract [22]. This means that vaccine candidates may not be able to provide sterilizing immunity. Even though COVID vaccines may be developed successfully, it will be difficult to manufacture enough doses (to achieve global herd immunity, billions of vaccine doses will be needed) and the equal and effective distribution of vaccine doses will be a daunting challenge.

## Author contributions

Jinghua Yan and Qingrui Huang carried out the concepts, design and definition of intellectual content. Qingrui Huang conducted literature search and manuscript preparation. Jinghua Yan carried out manuscript editing. Both authors have read and approved the content of the manuscript.

## Declaration of Competing Interest

The authors declare that they have no conflict of interest.

## Acknowledgments

This work was supported by the Strategic Priority Research Program of the Chinese Academy of Sciences (XDB29040201), the National Natural Science Foundation of China (NSFC) (81901680), and National Key Research and Development Project (2020YFC0842300).

## Reference

[1] N Zhu, D Zhang, W Wang, et al., A novel coronavirus from patients with pneumonia in China, 2019, N. Engl. J. Med. 382 (8) (2020) 727–733.
[2] P Zhou, XL Yang, XG Wang, et al., A pneumonia outbreak associated with a new coronavirus of probable bat origin, Nature 579 (7798) (2020) 270–273.
[3] JA Juno, HX Tan, WS Lee, et al., Humoral and circulating follicular helper T cell responses in recovered patients with COVID-19, Nat. Med. (2020).
[4] C Shan, YF Yao, XL Yang, et al., Infection with novel coronavirus (SARS-CoV-2) causes pneumonia in Rhesus macaques, Cell Res 30 (8) (2020) 670–677.
[5] SH Sun, Q Chen, HJ Gu, et al., A mouse model of SARS-CoV-2 infection and pathogenesis, Cell Host Microbe 28 (1) (2020) 124–133.
[6] X Chi, R Yan, J Zhang, et al., A neutralizing human antibody binds to the N-terminal domain of the Spike protein of SARS-CoV-2, Science 369 (6504) (2020) 650–655.
[7] R Shi, C Shan, X Duan, et al., A human neutralizing antibody targets the receptor binding site of SARS-CoV-2, Nature (2020).
[8] J Hansen, A Baum, KE Pascal, et al., Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail, Science 369 (6506) (2020) 1010–1014.
[9] A Chandrashekar, J Liu, AJ Martinot, et al., SARS-CoV-2 infection protects against rechallenge in rhesus macaques, Science (2020).

[10] Y Liu, K Wang, TF Massoud, et al., SARS-CoV-2 vaccine development: an overview and perspectives, ACS Pharmacol. Transl. Sci. 3 (5) (2020) 844–858.
[11] GA Poland, IG Ovsyannikova, SN Crooke, et al., SARS-CoV-2 vaccine development: current status, Mayo Clin. Proc. 95 (10) (2020) 2172–2188.
[12] Seow J, Graham C, Merrick B, et al. Longitudinal evaluation and decline of antibody responses in SARS-CoV-2 infection. medRxiv. 2020:2020.07.09.20148429.
[13] K Wang, QX Long, HJ Deng, et al., Longitudinal dynamics of the neutralizing antibody response to SARS-CoV-2 infection, Clin. Infect. Dis. (2020).
[14] KK To, IF Hung, JD Ip, et al., COVID-19 re-infection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing, Clin. Infect. Dis. (2020).
[15] S Su, L Du, S. Jiang, Learning from the past: development of safe and effective COVID-19 vaccines, Nat. Rev. Microbiol. 16 (2020) 1–9.
[16] BF Haynes, L Corey, P Fernandes, et al., Prospects for a safe COVID-19 vaccine, Sci. Transl. Med. (2020).
[17] Q Gao, L Bao, H Mao, et al., Rapid development of an inactivated vaccine candidate for SARS-CoV-2, Science (2020) eabc1932.
[18] H Wang, Y Zhang, B Huang, et al., Development of an inactivated vaccine candidate, BBIBP-CorV, with potent protection against SARS-CoV-2, Cell 182 (3) (2020) 713–721.
[19] WH Chen, X Tao, AS Agrawal, et al., Yeast-expressed SARS-CoV recombinant receptor-binding domain (RBD219-N1) formulated with aluminum hydroxide induces protective immunity and reduces immune enhancement, Vaccine 38 (47) (2020) 7533–7541.
[20] J Yang, W Wang, Z Chen, et al., A vaccine targeting the RBD of the S protein of SARS-CoV-2 induces protective immunity, Nature (2020).
[21] Powell AE, Zhang K, Sanyal M, et al. A single immunization with spike-functionalized ferritin vaccines elicits neutralizing antibody responses against SARS-CoV-2 in mice. bioRxiv: the preprint server for biology. 2020.
[22] van Doremalen N, Lambe T, Spencer A, et al. ChAdOx1 nCoV-19 vaccination prevents SARS-CoV-2 pneumonia in rhesus macaques. bioRxiv: the preprint server for biology. 2020.
[23] Sun W, Leist SR, McCroskery S, et al. Newcastle disease virus (NDV) expressing the spike protein of SARS-CoV-2 as vaccine candidate. bioRxiv: the preprint server for biology. 2020.
[24] MA Rohaim, M. Munir, A scalable topical vectored vaccine candidate against SARS–CoV-2, Vaccines 8 (3) (2020).
[25] NB Mercado, R Zahn, F Wegmann, et al., Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques, Nature (2020).
[26] D Laczkó, MJ Hogan, SA Toulmin, et al., A single immunization with nucleoside–modified mRNA vaccines elicits strong cellular and humoral immune responses against SARS-CoV-2 in mice, Immunity (2020).
[27] KS Corbett, B Flynn, KE Foulds, et al., Evaluation of the mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primates, N. Engl. J. Med. (2020).
[28] KS Corbett, DK Edwards, SR Leist, et al., SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness, Nature 586 (7830) (2020) 567–571.
[29] W Tai, X Zhang, A Drelich, et al., A novel receptor-binding domain (RBD)-based mRNA vaccine against SARS-CoV-2, Cell Res. 5 (2020) 1–4.
[30] GD Sempowski, KO Saunders, P Acharya, et al., Pandemic preparedness: developing vaccines and therapeutic antibodies for COVID-19, Cell 181 (7) (2020) 1458–1463.
[31] TRF Smith, A Patel, S Ramos, et al., Immunogenicity of a DNA vaccine candidate for COVID-19, Nat. Commun. 11 (1) (2020) 2601.
[32] J Yu, LH Tostanoski, L Peter, et al., DNA vaccine protection against SARS-CoV-2 in rhesus macaques, Science (2020).
[33] S Xia, Y Zhang, Y Wang, et al., Safety and immunogenicity of an inactivated SARS–CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial, Lancet Infect. Dis. (2020).
[34] S Xia, K Duan, Y Zhang, et al., Effect of an inactivated vaccine against SARS-CoV-2 on safety and immunogenicity outcomes: interim analysis of 2 randomized clinical trials, JAMA 324 (10) (2020) 1–10.
[35] C Keech, G Albert, I Cho, et al., Phase 1-2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine, N. Engl. J. Med. (2020).
[36] FC Zhu, YH Li, XH Guan, et al., Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial, Lancet 395 (10240) (2020) 1845–1854.
[37] FC Zhu, XH Guan, YH Li, et al., Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial, Lancet 396 (10249) (2020) 479–488.
[38] SP Graham, RK McLean, AJ Spencer, et al., Evaluation of the immunogenicity of prime-boost vaccination with the replication-deficient viral vectored COVID-19 vaccine candidate ChAdOx1 nCoV-19, NPJ Vaccines 5 (2020) 69.
[39] DY Logunov, IV Dolzhikova, OV Zubkova, et al., Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia, Lancet 396 (10255) (2020) 887–897.
[40] LA Jackson, EJ Anderson, NG Rouphael, et al., An mRNA Vaccine against SARS–CoV-2 – preliminary report, N. Engl. J. Med. (2020).
[41] MJ Mulligan, KE Lyke, N Kitchin, et al., Phase 1/2 study of COVID-19 RNA vaccine BNT162b1 in adults, Nature (2020).
[42] Walsh EE, Frenck R, Falsey AR, et al. RNA-Based COVID-19 Vaccine BNT162b2 Selected for a Pivotal Efficacy Study. medRxiv. 2020.
[43] NN Zhang, XF Li, YQ Deng, et al., A thermostable mRNA Vaccine against COVID-19, Cell (2020).
[44] Y Wu, F Wang, C Shen, et al., A noncompeting pair of human neutralizing antibodies block COVID-19 virus binding to its receptor ACE2, Science (2020).
[45] A Baum, BO Fulton, E Wloga, et al., Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies, Science 369 (6506) (2020) 1014–1018.
[46] D Wrapp, D De Vlieger, KS Corbett, et al., Structural basis for potent neutralization of betacoronaviruses by single-domain Camelid antibodies, Cell 181 (5) (2020) 1004–1015.
[47] Y Wu, C Li, S Xia, et al., Identification of human single-domain antibodies against SARS-CoV-2, Cell Host Microbe 27 (6) (2020) 891–898.
[48] V Monteil, H Kwon, P Prado, et al., Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2, Cell 181 (4) (2020) 905–913.
[49] S Xia, M Liu, C Wang, et al., Inhibition of SARS-CoV-2 (previously 2019-nCoV) infection by a highly potent pan-coronavirus fusion inhibitor targeting its spike protein that harbors a high capacity to mediate membrane fusion, Cell Res. 30 (4) (2020) 343–355.
[50] Y Cao, B Su, X Guo, et al., Potent neutralizing antibodies against SARS-CoV-2 identified by high-throughput single-cell sequencing of convalescent patients' B cells, Cell 182 (1) (2020) 73–84.
[51] S Du, Y Cao, Q Zhu, et al., Structurally resolved SARS-CoV-2 antibody shows high efficacy in severely infected hamsters and provides a potent cocktail pairing strategy, Cell (2020).
[52] M Yuan, NC Wu, X Zhu, et al., A highly conserved cryptic epitope in the receptor-binding domains of SARS-CoV-2 and SARS-CoV, Science (2020).
[53] Z Lv, YQ Deng, Q Ye, et al., Structural basis for neutralization of SARS-CoV-2 and SARS-CoV by a potent therapeutic antibody, Science (2020).
[54] F Amanat, D Stadlbauer, S Strohmeier, et al., A serological assay to detect SARS–CoV-2 seroconversion in humans, Nat. Med. 26 (7) (2020) 1033–1036.
[55] L Dai, T Zheng, K Xu, et al., A universal design of betacoronavirus Vaccines against COVID-19, MERS, and SARS, Cell 182 (3) (2020) 722–733.
[56] J Lu, G Lu, S Tan, et al., A COVID-19 mRNA vaccine encoding SARS-CoV-2 virus-like particles induces a strong antiviral-like immune response in mice, Cell Res. 30 (10) (2020) 936–939.
[57] AC Walls, YJ Park, MA Tortorici, et al., Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein, Cell 181 (2) (2020) 281–292.
[58] Q Wang, Y Zhang, L Wu, et al., Structural and functional basis of SARS-CoV-2 entry by using human ACE2, Cell (2020).
[59] M Hoffmann, H Kleine-Weber, S Schroeder, et al., SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically proven protease inhibitor, Cell 181 (2) (2020) 271–280.
[60] D Wrapp, N Wang, KS Corbett, et al., Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation, Science 367 (6483) (2020) 1260–1263.
[61] Hsieh CL, Goldsmith JA, Schaub JM, et al. Structure-based Design of Prefusion-stabilized SARS-CoV-2 Spikes. bioRxiv: the preprint server for biology. 2020.
[62] E Margolin, WA Burgers, ED Sturrock, et al., Prospects for SARS-CoV-2 diagnostics, therapeutics and vaccines in Africa, Nat. Rev. Microbiol. 10 (2020) 1–15.
[63] Y Watanabe, JD Allen, D Wrapp, et al., Site-specific glycan analysis of the SARS–CoV-2 spike, Science 369 (6501) (2020) 330–333.
[64] J Talon, M Salvatore, RE O'Neill, et al., Influenza A and B viruses expressing altered NS1 proteins: a vaccine approach, Proc. Natl. Acad. Sci. USA 97 (8) (2000) 4309–4314.
[65] AJ Broadbent, CP Santos, A Anafu, et al., Evaluation of the attenuation, immunogenicity, and efficacy of a live virus vaccine generated by codon-pair bias de-optimization of the 2009 pandemic H1N1 influenza virus, in ferrets, Vaccine 34 (4) (2016) 563–570.
[66] B Pulendran, J Oh, H Nakaya, et al., Immunity to viruses: learning from successful human vaccines, Immunol. Rev. 255 (1) (2013) 243–255.
[67] MS Diamond, JE Ledgerwood, TC. Pierson, Zika Virus Vaccine development: progress in the face of new challenges, Annu. Rev. Med. 70 (2019) 121–135.
[68] P Dormitzer, G Galli, F Castellino, et al., Influenza vaccine immunology, Immunol. Rev. 239 (1) (2011) 167–177.
[69] H Weingartl, M Czub, S Czub, et al., Immunization with modified vaccinia virus Ankara-based recombinant vaccine against severe acute respiratory syndrome is associated with enhanced hepatitis in ferrets, J. Virol. 78 (22) (2004) 12672–12676.
[70] CT Tseng, E Sbrana, N Iwata-Yoshikawa, et al., Immunization with SARS coronavirus vaccines leads to pulmonary immunopathology on challenge with the SARS virus, PLoS One 7 (4) (2012) e35421.
[71] M Bolles, D Deming, K Long, et al., A double-inactivated severe acute respiratory syndrome coronavirus vaccine provides incomplete protection in mice and induces increased eosinophilic proinflammatory pulmonary response upon challenge, J. Virol. 85 (23) (2011) 12201–12215.
[72] F Yasui, C Kai, M Kitabatake, et al., Prior immunization with severe acute respiratory syndrome (SARS)-associated coronavirus (SARS-CoV) nucleocapsid protein causes severe pneumonia in mice infected with SARS-CoV, J. Immunol. 181 (9) (2008) 6337–6348.
[73] F. Krammer, SARS-CoV-2 vaccines in development, Nature 586 (7830) (2020) 516–527.
[74] J Pallesen, N Wang, KS Corbett, et al., Immunogenicity and structures of a rationally designed prefusion MERS-CoV spike antigen, Proc. Natl. Acad. Sci. USA 114 (35) (2017) E7348-e7357.
[75] K Xu, Y Song, L Dai, et al., Recombinant chimpanzee adenovirus vaccine AdC7-M/E protects against Zika virus infection and testis damage, J. Virol. 92 (6) (2018).
[76] PM Folegatti, KJ Ewer, PK Aley, et al., Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial, Lancet 396 (10249) (2020) 467–478.
[77] G Maruggi, C Zhang, J Li, et al., mRNA as a transformative technology for vaccine development to control infectious diseases, Mol. Ther. 27 (4) (2019) 757–772.

[78] N Pardi, MJ Hogan, FW Porter, et al., mRNA vaccines – a new era in vaccinology, Nat. Rev. Drug Discov. 17 (4) (2018) 261–279.
[79] N Pardi, MJ Hogan, RS Pelc, et al., Zika virus protection by a single low-dose nucleoside-modified mRNA vaccination, Nature 543 (7644) (2017) 248–251.
[80] JM Richner, S Himansu, KA Dowd, et al., Modified mRNA vaccines protect against Zika virus infection, Cell 169 (1) (2017) 176.
[81] WM Bogers, H Oostermeijer, P Mooij, et al., Potent immune responses in rhesus macaques induced by nonviral delivery of a self-amplifying RNA vaccine expressing HIV type 1 envelope with a cationic nanoemulsion, J. Infect. Dis. 211 (6) (2015) 947–955.
[82] U Sahin, K Kariko, O. Tureci, mRNA-based therapeutics-developing a new class of drugs, Nat. Rev. Drug Discov. 13 (10) (2014) 759–780.
[83] N Pardi, MJ Hogan, MS Naradikian, et al., Nucleoside-modified mRNA vaccines induce potent T follicular helper and germinal center B cell responses, J. Exp. Med. 215 (6) (2018) 1571–1588.
[84] D Laczkó, MJ Hogan, SA Toulmin, et al., A single immunization with nucleoside–modified mRNA vaccines elicits strong cellular and humoral immune responses against SARS-CoV-2 in mice, Immunity 53 (4) (2020) 724-732.e7.
[85] H Lin, B Yip, L Huang, et al., Zika virus structural biology and progress in vaccine development, Biotechnol. Adv. 36 (1) (2018) 47–53.
[86] AO Hassan, NM Kafai, IP Dmitriev, et al., A single-dose intranasal ChAd vaccine protects upper and lower respiratory tracts against SARS-CoV-2, Cell 183 (1) (2020) 169-184.e13.

**Dr. Qingrui Huang**, an associate professor in Institute of Microbiology, Chinese Academy of Sciences, China. He received Ph.D from Institute of Process Engeering, Chinese Academy of Sciences. He has been focusing on the development of vaccines against bacterium and viruses, especially mRNA vaccines and protein subunit vaccines.

**Dr. Jinghua Yan**, a professor and Principle Investigator in Institute of Microbiology, Chinese Academy of Sciences, China. She obtained Ph.D from Institute of Bioengineering, Academy of Military Medical Sciences. Her reserach interest mainly focuses on the development of vaccines and therapeutic antibodies against emerging viruses.