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SPECIAL TOPIC

The Race for a COVID-19 Vaccine: Current Trials, Novel Technologies, and Future Directions

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Summary: The Coronavirus Disease 2019 (COVID-19) pandemic has presented a major threat to public health worldwide alongside unprecedented global economic and social implications. In the absence of a "gold standard" treatment, the rapid development of a safe and effective vaccine is considered the most promising way to control the pandemic. In recent years, traditional vaccine technologies have seemed insufficient to provide global protection against the rapid spread of emerging pandemics. Therefore, the establishment of novel approaches that are independent of whole pathogen cultivation, cost-effective, and able to be rapidly developed and produced on a large scale are of paramount importance for global health. This article summarizes the current efforts to develop a COVID-19 vaccine, including the ongoing and future anticipated clinical trials. We also provide plastic and reconstructive surgeons with insight into the novel technologies currently utilized for COVID-19 vaccine development, focusing on the very promising viral-vector-based and gene-based vaccine technologies. Each platform has its own advantages and disadvantages related to its efficacy and ability to induce certain immune responses, manufacturing capacity, and safety for human use. Once the fundamental key challenges have been addressed for viral-vector-based and gene-based vaccines, these novel technologies may become helpful in winning the fight against COVID-19 and transforming the future of health care.
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> Science knows no country, because knowledge belongs to humanity, and is the torch which illuminates the world.
>
> —Louis Pasteur

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) pandemic has presented a major threat to public health worldwide alongside unprecedented global economic and social implications. Identified in Wuhan, Hubei Province, China, in December 2019, the novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2),[1] has infected a total of 20,840,381 individuals, causing 754,566 global deaths as of August 14, 2020. An estimated 5,248,722 cases have been confirmed in the United States, and the death toll there has surpassed 160,000.[2]

COVID-19 has a relatively high degree of pre-symptomatic transmission,[3,4] high mortality rate, severe morbidity rate, and relatively long hospitalization period.[5] As a result, the fight against COVID-19 has required extensive interventions such as quarantine, social distancing, isolation of infected populations, border closures, school shutdowns, and extensive lockdowns to contain the virus, "flatten the curve," and save lives.[6] The COVID-19 pandemic has changed the landscape of plastic surgery,[7] restructured the daily experience of plastic surgery practices,[7–11] altered the way residents and fellows are trained,[12,13] substantially impacted research,[14,15] and revolutionized patient care. The implications of the current COVID-19 pandemic on plastic surgery are summarized in Table 1.

Due to the profound global implications of the COVID-19 crisis, there has been an unprecedented race to develop treatments and vaccines against SARS-CoV-2. Multiple clinical trials are underway to define potential roles for antiviral agents and specific immunomodulators[16–18] as

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Table 1. Effects of COVID-19 on Plastic Surgery

Aspect Affected	Effects
Clinical care	◦ Rescheduling/cancellation of surgeries, procedures, and in-person appointments ◦ Practice closures ◦ Telehealth for preoperative and postoperative discussions, no in-person physical examination ◦ Implementation of patient flow plans that allow for social distancing protocols ◦ Reassessment of cleaning and disinfecting protocols ◦ PPE requirements for surgeons, anesthesia, and staff ◦ Patients' screening upon entrance, "no visitors" policy, masking requirement ◦ Updated safety protocols for elective surgery ◦ New informed consent form for COVID-19 risk ◦ Relatively bear market for elective surgery
Education and training	*Residency and Fellowship Training Programs* ◦ Redeployment to ICUs and emergency rooms ◦ Utilization of virtual platforms for didactic sessions: daily team briefings, morning conferences, and grand rounds and nationally integrated didactics ◦ Case category minimum requirements by the ACGME and the ABPS might not be reached due to decreased surgical volumes *Plastic Surgery Residency Application Cycle* ◦ Cancellation of away rotations ◦ Virtual away rotations and program-applicant communication via social media ◦ Utilization of virtual platforms for didactic sessions ◦ Online residency interviews and virtual visits ◦ Rescheduling/cancellation of USMLE, subsequent changes to the ERAS application cycle and adjusted deadlines ◦ Postponement and cancellation of national and regional conferences
Research	◦ Laboratory closures ◦ Suspension of clinical trials ◦ Postponement and cancellation of national and regional conferences ◦ Utilization of virtual platforms for research and didactic sessions

ABPS, American Board of Plastic Surgery; ACGME, Accreditation Council for Graduate Medical Education; COVID-19, Coronavirus disease 2019; ERAS, Electronic Residency Application Service; ICU, intensive care unit; PPE, personal protective equipment; USMLE, United States Medical Licensing Examination.

well as passive immunization with convalescent plasma.[19] However, no "gold standard" treatment or prophylactic medication has been approved for COVID-19. Optimizing supportive care for COVID-19 positive patients remains the mainstay of therapy, including oxygen, mechanical ventilation, and treatment of the sequelae and complications.[20] With multiple waves of illness anticipated,[21] and in the absence of approved treatments, the development of a safe and effective vaccine will be a game-changing step in the global fight against COVID-19 and is considered the most promising way to eradicate the virus.[22]

This article summarizes the current efforts to develop a SARS-CoV-2 vaccine, including the ongoing and future anticipated clinical trials. We also provide plastic and reconstructive surgeons with insight into the novel technologies currently utilized for SARS-CoV-2 vaccine development, focusing on the very promising viral-vector-based and gene-based vaccine technologies (Fig. 1).

VACCINES: IMMUNOLOGICAL PRINCIPLES AND VACCINE DEVELOPMENT STRATEGIES

Since the development of the first vaccine by Dr. Edward Jenner more than 200 years ago,[23] vaccinations have made an enormous contribution to global health.[24] However, the development process for conventional vaccines takes

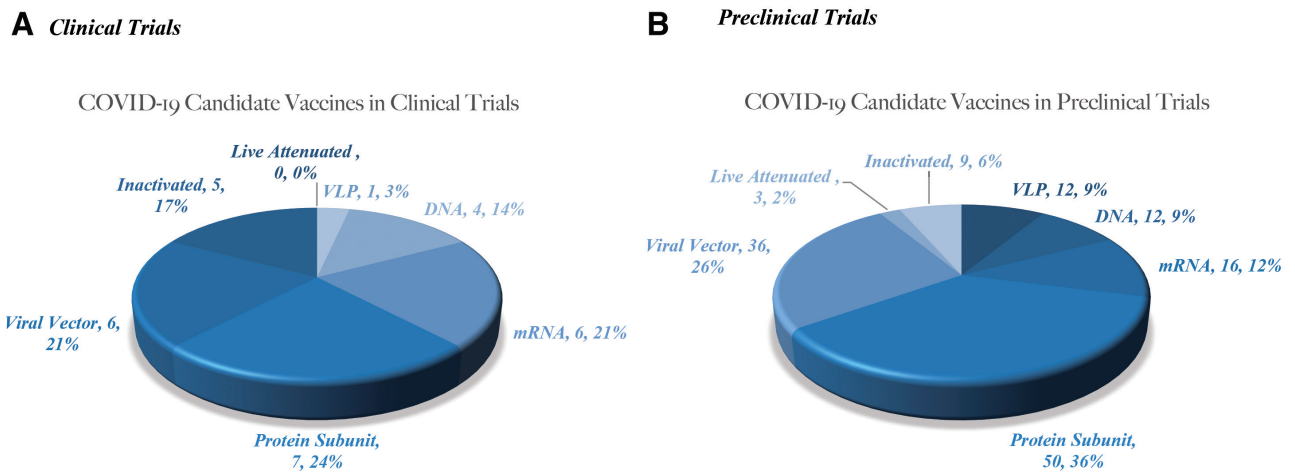

Fig. 1. Pie charts showing the development of COVID-19 candidate vaccines: (A) clinical trials and (B) preclinical trials.

more than 10 years[25] and requires 4 Phases,[26–28] as summarized in Figure 2. Therefore, the lack of time remains a major barrier for safe and effective vaccine development in outbreak situations.

Immunological Principles of Vaccination

Immunization can be derived from either passive or active immunization.[29] Passive immunization occurs with the transfer or administration of already preformed antibodies, providing temporary immunity.[29] One investigational treatment being explored for COVID-19 is the use of convalescent plasma collected from previously infected individuals, which is administered via direct transfusion to COVID-19 patients, in an attempt to confer passive immunity.[30–34]

Active immunization occurs with the exposure to an antigen and typically produces long-term immunity due to the immune system stimulation.[29] The immune system is divided into two main subsystems: the innate system, which provides an initial, non-specific response, with no memory induced, and the adaptive system, which provides a later, antigen-specific response and induces immunological memory.[35] When antigens are introduced into the bloodstream via infection or vaccination, they are captured and processed by Antigen Presenting Cells (APCs), which then display an antigen-derived peptide fragment on their surfaces. APCs then migrate to lymph nodes, and activate T helper cells through a process called "antigenic presentation." T helper cells stimulate both arms of the adaptive immunity: humoral (antibody-based) and cellular.

Humoral immunity is achieved via differentiation, proliferation, and maturation of B-lymphocytes into antibody-secreting plasma cells and memory lymphocytes of the same antigenic specificity, and cell-mediated

Fig. 2. Diagram displaying the various phases of a clinical trial.

immunity is achieved via activation of naive cytotoxic T cells to active, antigen-specific cells.[29] The stimulation of both the humoral and cell-mediated arms of the adaptive system by the production of effector cells (plasma B cells for humoral immunity and active cytotoxic T cells for cell-medicated immunity) and memory cells is required to ensure protection upon re-exposure to the same antigen.[35] Figure 3 illustrates the immune stimulation response in detail.

Conventional Vaccine Platforms

The main conventional vaccine technologies include inactivated vaccines (which utilize a killed pathogen), subunit/recombinant vaccines (which utilize specific pieces of the pathogen administered along with adjuvants), toxoid vaccines (pathogen-toxin-based), and live attenuated vaccines.[36] Each platform has its own advantages and disadvantages related to its efficacy, immunogenicity, and ability to induce certain immune responses, manufacturing capacity, and safety for human use, as summarized in Table 2.[36–42]

Novel Vaccine Platforms

In recent years, traditional vaccine technologies that consist of working with a virulent pathogen during manufacturing seem insufficient to provide global protection against the spread of emerging pandemics. Therefore, the establishment of novel approaches that are independent of pathogen cultivation (a relatively lengthy and high-risk process), are cost-effective, and could be rapidly developed and produced on a large scale, are of paramount importance for global health.[41]

Two promising novel platforms that have generated significant attention in recent years due to their potential use for a variety of applications include the viral-vector-based and gene-based vaccine technologies. Their advantages over conventional approaches highlight the role of these platforms in the new era of vaccinology, as potential game-changers in epidemics and emerging diseases.[43] The strengths and weaknesses of these platforms are summarized in Table 2 and discussed below.

Viral-vector-based Vaccines

Viral vector vaccines use separate, genetically engineered, viruses to carry DNA of target antigens into human cells. The DNA contained in the viral vector encodes antigens that, once expressed in the infected human cells, elicit antigen-specific humoral and cell-mediated immune responses via antigen presentation (Fig. 3).[44] A variety of viruses have been employed as viral vectors,[45] with Adenovirus (Ad) vectors being the most commonly utilized due to their various advantages. Ad vectors' advantages over other viral vectors include their ability to enter a broad range of target cells in humans,[46] deliver various target antigens and large DNA insertions,[47] and induce potent humoral and cellular responses.[48] However, utilizing an unrelated virus for delivery poses several challenges in terms of manufacturing, safety, and immunogenicity, as summarized in Table 2.

Gene-based Vaccines

Gene-based vaccine platforms consist of genetic sequences in the form of plasmid DNA[49] and mRNA.[50] Once injected intramuscularly (IM), the genetic sequence enters the myocytes[51] to achieve encoding of the desired antigen.[52] The endogenously synthesized antigens are then secreted from myocytes for cross presentation and consecutive stimulation of humoral and cellular responses,

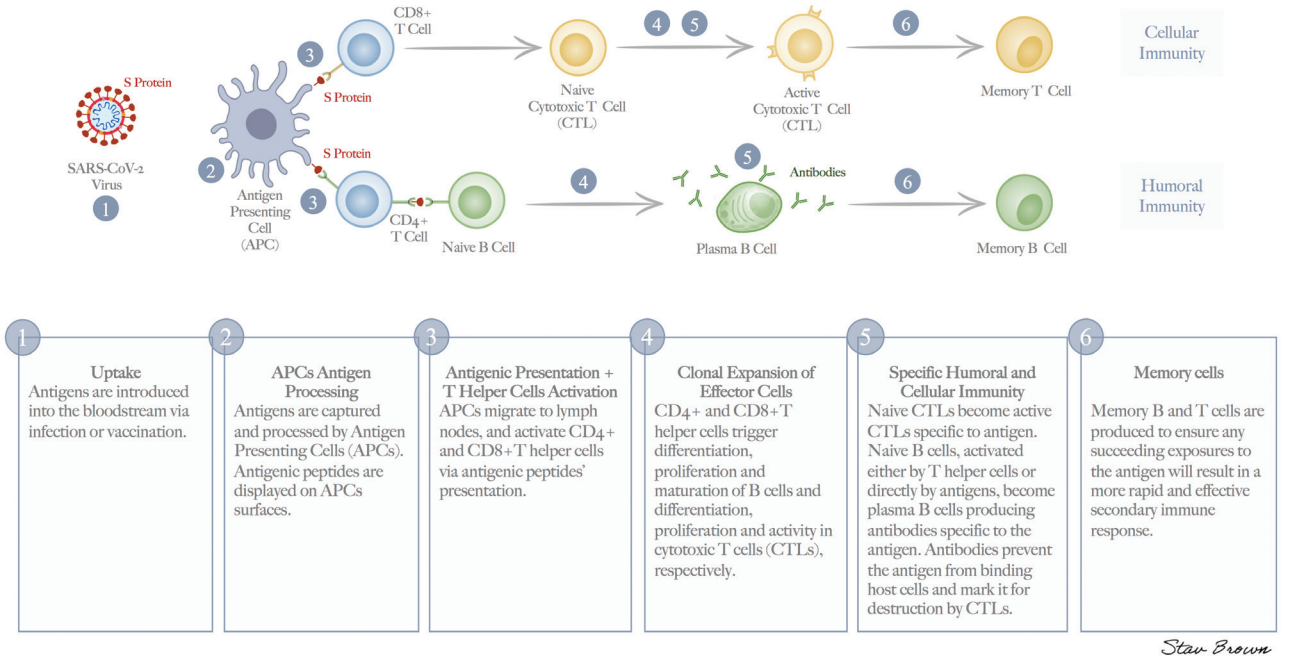

Fig. 3. Illustration depicting the stimulation of humoral and cellular immune responses.

Table 2. SARS-CoV-2 Vaccine Development Platforms

Platform (Refs)	No. Clinical Trials	No. Pre-clinical Studies	Platform Status	Advantages	Disadvantages	Existing Licensed Vaccines
Inactivated	5	9	Licensed	Safety: ◦ Cannot replicate ◦ No adjuvants required Efficacy: ◦ High potency ◦ Multivalent	Safety: ◦ Infection risk Efficacy: ◦ Often induces weaker immune responses than other methods Production and Manufacturing: ◦ Complex manufacturing—lengthy, relatively small quantities produced ◦ Requires vigorous quality control	HAV, influenza (shot only), Polio (shot only), rabies
Live attenuated virus	0	3	Licensed	Safety: ◦ No adjuvants required Efficacy: ◦ High potency ◦ Multivalent ◦ Induction of long-lived responses	Safety: ◦ Reversion risk ◦ Inactivation may lead to undesired effects and exacerbated disease ◦ Adverse effects in immune-compromised Efficacy: ◦ Inactivation may hamper protective immune responses Production and Manufacturing: ◦ Requires whole pathogen cultivation, high biosafety level, and specialized laboratories ◦ Relatively high production costs requires dedicated production processes and facilities for each vaccine ◦ Insufficient production capacities for global vaccination	Measles, mumps, rubella (MMR combined vaccine), rotavirus, smallpox, chickenpox, yellow fever
Viral vector	Non-replicating: 5 Replicating: 1	Non-replicating: 19 Replicating: 17	Experimental	Safety: ◦ Favorable safety profile—whole pathogen cultivation not required ◦ No adjuvants required Efficacy: ◦ Able to induce potent, antigen-specific cellular and humoral immune responses ◦ Strong innate immune response Production and manufacturing: ◦ High producibility—independent of whole pathogen cultivation ◦ High specificity and accuracy—can be engineered easily to accurately express any antigen of choice, specific targeting, and processing in the cell due to antigen delivery as genetic information ◦ High versatility—allows large insertions in genome and therefore the development of a large variety of vaccines ◦ Sufficient production capacities for global vaccination due to established high yield production processes with means of upscaling	Safety: ◦ Potential induction of anti-vector immunity ◦ Potential environmental risks associated with the release of genetically modified organisms ◦ Potential integration into the host genome and persistent replication of attenuated vaccines ◦ Potential risk for infection Efficacy: ◦ Previous infection/pre-existing immunity to the viral vector may hamper immune responses ◦ Inability to administer multiple times Production and Manufacturing: ◦ Cell-based and antigen-dependent manufacturing ◦ Requires vigorous monitoring ◦ Complex manufacturing	Non-replicating: none Replicating: dengue fever

(*Continued*)

Table 2. (*Continued*)

Platform (Refs)	No. Clinical Trials	No. Pre-clinical Studies	Platform Status	Advantages	Disadvantages	Existing Licensed Vaccines
Protein Subunit	7	50	Licensed	Safety: ◦ Non-infectious Efficacy: ◦ Strong humoral response	Safety: ◦ Requires additional adjuvants Efficacy: ◦ Multiple doses are usually required Production and Manufacturing: ◦ Requires dedicated production processes, facilities and stability assays for each vaccine ◦ Multivalent formulation can be challenging	Hib, HBV, HPV, Whooping cough (part of the DTaP combined vaccine), Pneumococcal disease, Meningococcal disease, Shingles
RNA	6	16	Experimental	Safety: ◦ Favorable safety profile—whole pathogen cultivation not required, non-infectious ◦ No interaction with the host-cell DNA, avoiding the potential risk of genomic integration ◦ Natural degradation and lack of persistence in cells Efficacy: ◦ Generation of potent humoral and cellular immune responses ◦ Very potent innate immune response ◦ Can be administered multiple times (boosting) Administration: ◦ Can be administered by different routes, do not require additional administration devices Production and Manufacturing: ◦ High specificity—able to encode any antigen of choice ◦ High versatility—able to produce different vaccines using the same established production process and facility. ◦ Safe, rapid, and scalable production—based on in vitro systems that are simple to monitor, production free of animal-derived products ◦ Small amounts of expressed protein required due to amplification by the immune system	Safety: ◦ Potential risk for severe adverse reactions ◦ Production and Manufacturing: ◦ Relatively high production costs	None
DNA	4	12	Experimental	Safety: ◦ Favorable safety profile— whole pathogen cultivation not required, non-infectious Efficacy: ◦ Generation of potent humoral and cellular immune responses ◦ High stability Production and Manufacturing: ◦ High specificity—able to encode any antigen of choice ◦ Safe, rapid and scalable production—based on in vitro systems that are simple to monitor, production free of animal-derived products	Safety: ◦ Potential long-term persistence, risk of genomic integration, potentially leading to mutagenesis and oncogenesis. ◦ Potential generation of autoantibodies ◦ Potential adverse effects due to cytokines/co-stimulatory molecules expression used to enhance DNA immunogenicity Efficacy: ◦ Low immunogenicity in humans Production and Manufacturing: ◦ Requires additional methods to enhance DNA uptake, expression, and immunogenicity: delivery devices such as gene gun, needle, jet injection, and in vivo electroporation and molecular adjuvants	None
Other platforms	1	12	N/A	N/A	N/A	N/A

DNA, Deoxyribonucleic acid; DTaP, diphtheria, tetanus, and acellular pertussis; HAV, Hepatitis A virus; Hib, *Haemophilus influenzae* type b; HBV, Hepatitis B virus; HPV, human papillomavirus; RNA, ribonucleic acid.

as illustrated in Figure 3.[53] The main advantages of the gene-based platform include the construction of antigens directly from the genetic sequence of the desired protein and a generic manufacturing process, which allows for efficient production of different vaccines using the same established processes and facilities, given the genetic sequence is available.[54]

Unlike conventional vaccine technologies, which consist of a lengthy process of inactivating or attenuating a live pathogen or making a recombinant protein, making a gene-based vaccine is relatively rapid and potentially low-risk, eliminating the need to work with a virulent pathogen during manufacturing.[38] In addition, plasmid DNA and mRNA vaccine constructs encode only the antigen of interest, avoiding other redundant, potentially detrimental proteins and the replication of infectious viral particles.[55]

However, since their initial presentation in 1990,[56] there has never been a commercial vaccine utilizing gene-based technologies approved for use. There have been many technical challenges to overcome to enable the promise of the gene-based platform,[57] including optimizing the delivery of these foreign nucleic acids into human cells[58,59] and increasing the potency, stability, and expression of the encoded protein.[38,55] These goals have been achieved by new formulations, including lipids, polymers, and novel delivery devices for improved intracellular delivery and stability, and strong molecular adjuvants for improved potency.[60,61]

DNA-based Vaccines consist of antigen-encoding plasmids. While allowing a relatively simple, safe, and time-saving production process, the DNA-based platform poses several challenges related to administration, safety, and immunogenicity, as summarized in Table 2. Unlike DNA vaccines, *mRNA-based vaccines* translate directly into the cytoplasm, undergo natural degradation,[50] and cannot integrate into the host genome.[41] These advantages in terms of safety, efficacy, and manufacturing make the mRNA technology a promising avenue for a rapid response to the emerging COVID-19 pandemic, and are summarized, alongside the disadvantages, in Table 2.

COVID-19 VACCINE DEVELOPMENT: CURRENT CLINICAL TRIALS

Finding the most suitable target site for SARS-COV-2 vaccine development is extremely important. The SARS-CoV-2 coronavirus belongs to the subfamily of *Coronavirinae*, with a genomic structure of (+) ss-RNA.[62] Hoffman et al.[63] described the SARS-CoV-2 cell entry and replication mechanisms in detail and Bouhaddou et al.[64] recently demonstrated the role of virus-containing filopodia induced in host cells by SARS-CoV-2 in viral replication. Cell entry of SARS-CoV-2 is orchestrated by the viral spike (S) proteins, which give the virus its characteristic corona-like morphology, via binding the host cellular receptors.[63,65] Due to its pivotal role, a vaccine against S protein can prevent SARS-CoV-2's proliferation and spread.[66]

As of August 14, 2020, there have been 29 vaccine candidates in clinical trials, as summarized in Table 3 and Figure 1. In total, 13 trials are currently in Phase 1, 8 in joint Phase 1/2, 2 in Phase 2 and 6 in Phase 3. An estimated 138 vaccine candidates are currently in preclinical studies.[67] While 12 clinical trials are based on traditional techniques utilizing inactivated viruses (5 trials),[68–73] and protein subunits (7 trials),[74–77] 16 trials utilize novel platforms including the viral vector-based platform (6 trials),[78–84] and gene-based platform (10 trials: 6 mRNA-based, 4 DNA-based).[85–94] Current viral-vector-based and gene-based vaccines under development target the S protein of SARS-CoV-2.[86,88]

Viral-vector-based Clinical Trials

Three viral-vector-based vaccines are currently under clinical trials (Table 3). The Adenovirus Type 5 Vector (Ad5-nCoV) and ChAdOx1 nCoV-19 trials are the furthest along in development and will be discussed below.

Adenoviral Vectors of Human Origin: Ad5-nCoV

Ad5-nCoV is a recombinant adenovirus type-5 (Ad5) vectored COVID-19 vaccine expressing the S protein of SARS-CoV-2.[95] Ad5 is a non-replicating vector of human origin, and one of the most widely used adenoviral vectors.[96] However, the widespread pre-existing immunity to Ad5 among the human population might hinder its immunogenicity and hamper its clinical use.[97] Phase 1 results have recently been published,[80,95] demonstrating that the Ad5 vectored COVID-19 vaccine was tolerable and immunogenic at 28 days post-vaccination. Most adverse reactions were mild or moderate in severity, with the most common adverse reactions being fever, fatigue, headache, and muscle pain. No serious adverse events were noted within 28 days post-vaccination. Neutralizing antibodies increased significantly at day 14, and peaked 28 days post-vaccination, while specific T-cell response peaked at day 14 after one administration of the vaccine. However, in patients with pre-existing anti-Ad5 immunity, both the specific antibody response and T-cell response induced by vaccination were diminished.[95] The recently published Phase II results[81,98] have confirmed Phase I results, demonstrating that the Ad5-vectored COVID-19 vaccine was safe, and induced significant immune responses in the majority of recipients after a single immunization. Phase III results are expected before the end of 2020.

Adenoviral Vectors of Non-human Origin: ChAdOx1 nCoV-19 (AZD1222)

Adenoviral vectors of non-human origin induce enhanced memory and more poly-functional $CD8^+$ T cells compared with Ad5 and are less likely to be hampered by pre-existing immunity.[48,99] ChAdOx1 nCoV-19 is a replication-deficient chimpanzee adenovirus expressing the S protein of SARS-CoV-2. Phase I/II results have recently been published,[79,100] demonstrating an acceptable safety profile of *ChAdOx1 nCoV-19* with no serious adverse events. The vaccine induced both humoral and cellular immune responses and all participants had neutralizing activity after a booster dose. Phase III is currently ongoing

Table 3. Candidate Vaccines against SARS-CoV-2 Currently in Clinical Trials

S. No.	Vaccine Name	Developer (Country)	Platform	Phase 1 Start Date (mm/dd/yyyy)	Current Phase	Participants' Age and Sample Size (N)*	Mode of Administration	Vaccination Schedule*	Same Platform for Other Viral Candidates
1	N/A	Beijing Institute of Biological Products and Sinopharm (China)	Inactivated	04/28/2020	Phase 3 (ChiCTR2000034780) Phase 1/2 (ChiCTR2000032459)	◦ Ages: 18 and over ◦ N = 15,000	IM	Day 0, 14 or 0, 21	
2	N/A	Wuhan Institute of Biological Products and Sinopharm (China)	Inactivated	04/11/2020	Phase 3 (ChiCTR2000034780) Phase 1/2 (ChiCTR2000031809)	◦ Ages: 18 and over ◦ N = 15,000	IM	Day 0, 14 or 0, 21	
3	PiCoVacc/ PROFISCOV	Sinovac (China)	Inactivated	04/16/2020	Phase 3 (NCT04456595) Phase 1/2 (NCT04383574) (NCT04352608)	◦ Ages: 18 and over ◦ N = 8870	IM	Day 0, 14	SARS
4	N/A	Institute of Medical Biology, Chinese Academy of Medical Sciences (China)	Inactivated	05/15/2020	Phase 1/2 (NCT04470609) Phase 1 (NCT04412538)	◦ Ages: 18–59, 60 and over ◦ N = 942, 471	IM	Day 0, 28	
5	BBV152	Bharat Biotech (India)	Inactivated	07/13/2020	Phase 1/2 (NCT04471519)	◦ Ages: 16–65 ◦ N = 1125	IM	Day 0, 14	
6	ChAdOx1 nCoV-19 (AZD1222)	University of Oxford and AstraZeneca (UK)	Viral vector (non-replicating)	03/19/2020	Phase 3 (ISRCTN89951424) Phase 2b/3 (2020-001228-32) Phase 1/2 (2020-001072-15)	◦ Ages: 18–55 ◦ N = 10,260; 30,000; 2000	IM	Day 0	MERS, influenza, TB, Chikungunya, Zika, MenB, plague
7	Adenovirus Type 5 Vector (Ad5-nCoV)	CanSino Biological and Beijing Institute of Biotechnology (China)	Viral vector (non-replicating)	03/16/2020	Phase 2 (ChiCTR2000031781) Phase 1 (ChiCTR2000030906)	◦ Ages: 18 and over ◦ N = 500	IM	Day 0	EBOV
8	Gam-COVID-Vac	Gamaleya Research Institute (Russia)	Viral vector (non-replicating)	06/17/2020	Phase 1 (NCT04436471) (NCT04437875)	◦ Ages: 18–60 ◦ N = 38	IM	Day 0	
9	Ad26COVS1	Janssen Pharmaceutical Companies (USA, Belgium)	Viral vector (non-replicating)	07/15/2020	Phase 1/2 (NCT04436276)	◦ Ages: 18-55 ◦ N = 1045	IM	Day 0, 56	
10	N/A	ReiThera/LEUKOCARE/ Univercells (Italy, Germany, Belgium)	Viral vector (non-replicating)	N/A	Phase 1)2020-002835-31(	N/A	IM	N/A	
11	COVID-19-101	Institute Pasteur/Themis/Univ. of Pittsburg CVR/Merck Sharp & Dohme (Belgium, France)	Viral vector (replicating)	08/10/2020	Phase 1 (NCT04497298)	◦ Ages: 18–55 ◦ N = 90	IM	Day 0, 28	
12	NVX-CoV2373	Novavax (USA, Australia)	Protein subunit	05/25/2020	Phase 1/2 (NCT04368988)	◦ Ages: 18–59 ◦ N = 131	IM	Day 0, 21	RSV; CCHF, HPV, VZV, EBOV
13	SCB-201	Clover Biopharmaceuticals Inc./ GSK/Dynavax (Australia)	Protein subunit	06/19/2020	Phase 1 (NCT04405908)	◦ Ages: 18–75	IM	Day 0, 21	HIV, REV Influenza
14	N/A	Anhui Zhifei Longcom Biopharmaceutical/ Institute of Microbiology, Chinese Academy of Sciences (China)	Protein subunit	06/22/2020	Phase 2 (NCT04466085) Phase 1 (NCT04445194)	◦ Ages: 18–59 ◦ N = 900	IM	Day 0, 28 or 0, 28, 56	MERS

(*Continued*)

Table 3. (*Continued*)

S. No.	Vaccine Name	Developer (Country)	Platform	Phase 1 Start Date (mm/dd/yyyy)	Current Phase	Participants' Age and Sample Size (N)*	Mode of Administration	Vaccination Schedule*	Same Platform for Other Viral Candidates
15	COVAX19	Vaxine Pty Ltd/Medytox (Australia)	Protein subunit	06/30/2020	Phase 1 (NCT04453852)	◦ Ages: 18–65 ◦ N = 40	IM	N/A	
16	KBP 201	Kentucky Bioprocessing, Inc (USA)	Protein subunit	09/14/2020	Phase 1/2 (NCT04453852)	◦ Ages: 18–70 ◦ N = 180	IM	Day 0, 21	
17	N/A	University of Queensland/CSL/ Seqirus (Australia)	Protein subunit	07/13/2020	Phase 1 (ACTRN12620000674932p)	◦ Ages: 18–55 ◦ N = 120	IM	Day 0, 28	
18	MVC-COV1901	Medigen Vaccine Biologics Corporation/NIAID/Dynavax (Taiwan)	Protein subunit	09/01/2020	Phase 1 (NCT04487210)	◦ Ages: 20–50 ◦ N = 45	IM	Day 0, 28	
19	mRNA-1273	Moderna and NIAID (USA)	mRNA	03/16/2020	Phase 3 (NCT04470427) Phase 2 (NCT04405076) Phase 1 (NCT04283461)	◦ Ages: 18 and over ◦ N = 30,000	IM	Day 0, 28	Multiple candidates
20	BNT162	BioNTech and Pfizer (Germany and USA)	mRNA	04/29/2020	Phase 3 (NCT04368728) Phase 1/2 (2020–001038–36) (NCT04368728)	◦ Ages: 18–85 ◦ N = 29,481	IM	Day 0, 28	
21	COVAC1	Imperial College London (UK)	mRNA	04/01/2020	Phase 1 (ISRCTN17072692)	◦ Ages: 18–45 ◦ N = 320	IM	N/A	EBOV; LASV, MARV, Inf (H7N9), Rabies
22	CVnCoV	Curevac (Germany, Belgium)	mRNA	06/18/2020	Phase 1 (NCT04449276)	◦ Ages: 18–60 ◦ N = 168	IM	Day 0, 28	Rabies, LASV, YFV; MERS, InfA, Zika, dengue, NPV
23	N/A	People's Liberation Army (PLA) Academy of Military Sciences/ Walvax Biotech (China)	mRNA	06/25/2020	Phase 1 (ChiCTR2000034112)	◦ Ages: 18–80 ◦ N = 168	IM	N/A	
24	ARCT-021	Arcturus/Duke-NUS (Singapore)	mRNA	08/10/2020	Phase 1/2 (NCT04480957)	◦ Ages: 21–80 ◦ N = 92	IM	Day 0,14 or 0,28	
25	INO-4800	Inovio Pharmaceuticals (USA)	DNA	04/03/2020	Phase 1/2 (NCT04336410)	◦ Ages: 18 and over ◦ N = 120	ID	Day 0, 28	Multiple candidates
26	nCov	Cadila Healthcare Limited (India)	DNA	07/04/2020	Phase 1/2 (CTRI/2020/07/026352)	◦ Ages: 18–55 ◦ N = 1084	ID	Day 0, 28, 56	
27	GX-19	Genexine Consortium (Korea)	DNA	06/17/2020	Phase 1 (NCT04445389)	◦ Ages: 18–50 ◦ N = 190	IM	Day 0, 28	
28	N/A	Osaka University/AnGes/Takara Bio (Japan)	DNA	N/A	Phase 1 (NCT04463472)	◦ Ages: 20–65 ◦ N = 30	IM	Day 0, 14	
29	N/A	Medicago Inc. (Quebec, Canada)	VLP	07/10/2020	Phase 1 (NCT04450004)	◦ Ages: 18–55 ◦ N = 180	IM	Day 0, 21	

*Data reflect the most advanced clinical phase available.

No, number; N/A, not available; CCHF, Crimean-Congo Hemorrhagic Fever; DNA, Deoxyribonucleic acid; EBOV, Ebola virus; GMFR, Geometric mean fold rise; GMI, Geometric Mean Increase; GMR, Geometric Mean Ratio; GMT, Geometric Mean Titer; HPV, Human Papillomavirus; IFN-γ, Interferon gamma; IgG, Immunoglobulin G; IgM, Immunoglobulin M; LASV, Lassa virus; LNP, Lipid nanoparticles; MARV, Marburg virus; Inf, influenza; MenB, Serogroup B Meningococcal; MERS, Middle East Respiratory Syndrome; mRNA, messenger ribonucleic acid; NIAID, National Institute of Allergy and Infectious Diseases; NPV, nuclear polyhedrosis virus; RNA, Ribonucleic acid; RSV, Respiratory syncytial virus; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; TB, Tuberculosis; VZV, Varicella-zoster virus; YFV, yellow fever virus.

in the UK, the USA, Brazil, and South Africa, and results are expected in the Fall of 2020.[83,101]

Gene-based Vaccines Clinical Trials

Totally, 4 DNA-based and 5 mRNA-based vaccines are currently in clinical trials (see Table 3). The *m-RNA-1273 trial* is the furthest along in development and will be discussed below.

m-RNA-1273

mRNA-1273 developed in collaboration with the National Institute of Allergy and Infectious Disease (NIAID) of the National Institute of Health (NIH) is considered one of the frontrunners in vaccine development. The mRNA-1273 vaccine consists of mRNA of the S protein synthesized in vitro, and coated with lipid nanoparticles for effective delivery.

Phase I results have recently been published,[86,102] demonstrating that mRNA-1273 was generally safe and well tolerated, with 1 incidence of a grade 3 adverse event (erythema around the injection site), and 3 incidences of grade 3 systemic symptoms (including fever, muscle pain and headache) seen at the highest dose group, only following the 2nd dose. All adverse events have been transient and self-resolving. No grade 4 adverse events or serious adverse events have been reported. Phase II is currently ongoing,[85] and Phase III is expected to commence before the end of July 2020 in collaboration with the NIAID. Phase III results are expected before the end of 2020.[102]

LOOMING CHALLENGES OF COVID-19 VACCINE DEVELOPMENT

While the preliminary results of the discussed trials are encouraging, whether a vaccine generates the needed types of immune responses to result in protective efficacy is unknown and cannot be predicted by Phase I studies. There still remain significant questions and uncertainties as to clinical efficacy and effects of potential mutations on the vaccine's immunogenicity and long-term efficacy, safety, and potential benefit for specific target populations.

Clinical Efficacy and Long-term Immunity

One of the main questions that arise is whether a COVID-19 vaccine would be able to provide immunity, when it is still uncertain whether previously infected patients are protected from reinfection.[103–107] Research in other coronavirus species has shown that immunity may not be long-lasting, with 2–3 years of protection estimated from work with SARS and MERS.[102,108,109]

To date, there is no evidence for cases of SARS-CoV-2 reinfections, [103] and preliminary evidence in humans[110] and rhesus macaques[111] suggests that acquired immunity may protect from future reinfection, at least temporarily[104,111–113] with most patients who recovered from COVID-19 producing sufficient amounts of neutralizing antibodies to protect against reinfection. A recently reported case series also indicated sufficient neutralizing antibody titers in convalescent plasma to neutralize SARS-CoV-2 in 5 COVID-19 patients, who all recovered after treatment.[114] While further research is needed to assess the benefits and risks of convalescent plasma therapy for people with COVID-19,[33,34] these preliminary findings provide hope for the development of an effective vaccine against SARS-CoV-2.[32] However, there have been few reports of post-recovery positive PCR tests performed in asymptomatic or mildly symptomatic patients, which could be explained as either false-negative results, prolonged viral clearance, and shedding or reinfection.[106,107,115–117]

Further points that need to be addressed to better understand the immune responses to SARS-CoV-2 and the optimal vaccine profile and administration regimens include the lack of correlation between antibody titer rates and clinical improvement, the durability of neutralizing antibodies, and their correlation with durable immunity.[118,119] The current gaps in knowledge highlight the importance of inducing potent humoral and cellular immune responses as potentially generated by viral-vector-based and gene-based vaccines.

Potential mutations in the S protein may also affect the long-term efficacy of a vaccine. There has been direct evidence of functionally meaningful S protein mutations that appear to mediate a higher binding affinity when compared with previous SARS viruses.[120] Therefore, it is difficult to ensure that the current novel vaccines targeting SARS-CoV-2 protein S could be used for a long term. This highlights the importance of a cost-effective platform that is able to produce different vaccines rapidly and safely using existing production processes and already established manufacturing infrastructure. This is one of the main potential strengths of the gene-based technology over the conventional vaccine development platforms.

Clinical Safety and Adverse Events

There have been previous reports of systemic reactions to mRNA, DNA, and viral-vectored vaccines, including adverse reactions identified in the Ad5-nCoV[95] and mRNA-1273 Phase 1 trials.[89] These outcomes have raised concerns about the safety of these novel platforms. As previously discussed, one of the main concerns of utilizing mRNA-based platforms is the potential toxicity of synthetically formulated mRNA due to its inherent inflammatory nature.[55] The use of DNA-based vaccines and viral-vector-based vaccines raises safety concerns due to their potential long-term persistence,[121,122] genome integration,[123,124] autoantibody generation, potential induction of anti-vector immunity,[124] and adverse effects due to co-stimulatory molecule expression.[125]

These safety concerns cannot be fully investigated by pre-clinical studies because humans may respond differently than the animal models used in the pre-clinical safety testing.[126] Therefore, it is of vital importance to fully characterize the potential risks of these novel platforms and adjust dosing schemes accordingly. This holds true especially for mRNA-based vaccines, where repeated administration (boosting) is needed for generating the desired neutralizing antibody titer levels.[127]

Clinical Benefit for Specific Target Populations

A major question that requires further investigation is whether the elderly and immunocompromised populations,

who experience higher clinical attack rates and a more severe clinical course,[128] would be able to mount a sufficiently robust antibody response to provide immunity in response to the vaccine. Most current trials are designed to include healthy elderly participants as part of advanced clinical phases; however, safety and potential efficacy should be established to include immunocompromised patients.

CONCLUSIONS

In conclusion, the rapid development of an effective and safe vaccine has become the most promising way to control the COVID-19 pandemic. Over 20 candidate vaccines are in clinical trials and over 100 are in preclinical trials, utilizing both conventional and novel technologies. The viral-vector-based and gene-based vaccine technologies are promising novel platforms that have generated significant attention in recent years due to their potential use for a variety of applications. Their various advantages over conventional approaches highlight their role in the new era of vaccinology as potential game-changers in epidemics and emerging diseases. Once the fundamental key challenges have been addressed for viral-vector-based and gene-based vaccines, these novel technologies may become helpful in winning the fight against COVID-19 and in transforming the future of health care.

In the words of Louis Pasteur: *In the field of observation, chance favors only the prepared mind.*

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