

Efficacy and safety of potential vaccine candidates against coronavirus disease 2019: A systematic review

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ABSTRACT

Search for an effective and safe vaccine to prevent transmission of current pandemic is an unmet need. This study reviews and compares the available early phase clinical data of vaccine candidates which have reached phase 3 of clinical development. The latest update of "DRAFT landscape of coronavirus (CoV) disease 2019 candidate vaccines (October 2, 2020)" released by the World Health Organization was accessed to identify the potential vaccine candidates. The full text articles (published and/or preprint) of data of early clinical trials of the selected vaccines were accessed from the links provided in the same document, PubMed and/or medRxiv.com. After extraction and synthesis, the data were critically evaluated for the study efficacy and safety outcomes. Of the total 193 candidate vaccines 10 were found to reach phase 3 of the clinical development. Nine of these were included in the evaluation process. In all of the included studies, immunogenicity and serious adverse events/local or systemic adverse events/laboratory parameters abnormality was considered as efficacy and safety outcomes respectively. Immunogenicity response with most of the vaccines was either higher than or similar to the respective controls except one (recombinant adenovirus type 26 CoV2 [Ad26.CoV2.S]) for which it was less than that in control. Overall adverse events (related and/or unrelated) were more with vaccines than those with respective control(s) in three studies, in other two, these were similar whereas in one study, the events were less in the vaccine group than in control group and in the rest, data described were descriptive only without any mention for the same for the control. In conclusion all studies showed immunogenic response to target protein of severe acute respiratory syndrome CoV-2 and which was higher than the respective control except for Ad26.CoV2.S. Many of the vaccines caused more adverse events than the controls, however most were mild and transient and/or manageable.

Key words: Coronavirus disease 2019, immunogenicity, severe acute respiratory syndrome-coronavirus-2

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INTRODUCTION

Safe and efficacious drugs and vaccines are being explored worldwide for Coronavirus disease 2019 (COVID-19), an unprecedented challenge to the humankind presently. Probably, the most effective measure to prevent and contain

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the transmission of COVID-19 remains a safe and effective vaccination. Usually, it takes over 10 years to develop a successful vaccine that is also hurdled by high failure rate (94%).^[1] However, acceleration of the process of vaccine development and distribution may be possible with global efforts by creating a platform to share knowledge and create funding opportunities. Different stake holders such as “Coalition for Epidemic Preparedness Innovations,” “World Health Organization (WHO)” and other Nongovernmental Organizations has joined in their effort for this.^[2,3] As per the draft landscape of COVID-19 candidate vaccines released by the WHO on October 02, 2020, there are 42 vaccines in clinical evaluation and of these 10 are in phase 3 of clinical development.^[4]

Recent and past studies have shown that the coronavirus (CoV) encodes four structural proteins namely spike (S), envelope (E), membrane (M), and nucleocapsid (N).^[5,6] The “S” protein plays the most critical role in fusion and entry of virus into the target cell through Angiotensin converting enzyme-2 receptor.^[7] The S1 subunit of “S” protein contains the receptor binding domain (RBD) and the S2 subunit has the necessary elements required for membrane fusion. The S1 and S2 subunits have a cleavage site recognized by host proteases and undergoes proteolytic cleavage.^[8] The “S” protein has been proposed as a target for the vaccines as well as therapeutic antibodies.^[9,10] RNA, DNA and viral vector-based vaccines have been used to transfer the genetic material encoding spike protein. The anti-“S” protein antibodies have been proposed to confer protective immunity against the virus.

The present work focuses on the potential vaccine candidates which have reached to the phase 3 of clinical development.

METHODOLOGY

Objective

Objective of the current study is to evaluate the efficacy and safety of potential vaccine candidates which have reached to phase 3 clinical trials.

Literature search

The latest update of “DRAFT landscape of COVID-19 candidate vaccines (October 2, 2020)” released by the WHO^[4] was accessed to identify the potential vaccine candidates. All the vaccines which have entered phase 3 of the clinical development only were selected for inclusion in this study. The full text articles (published and/or preprint) of data of early clinical trials of the selected vaccines were accessed from the links provided in the same document. Vaccines, for which the link(s) for the full text articles of early clinical trials were not provided there, were searched in the “PubMed,” “Google Scholar” and “medRxiv” using the search terms “BNT162b2 vaccine for COVID-19

phase 2,” “Ad26COVs vaccine for COVID-19 phase 2” and “Inactivated novel CoV (2019-CoV) vaccine phase 1/2 trial.” Data from the full text articles were extracted, synthesized, entered into the Microsoft Excel. The data were critically evaluated for the study outcomes.

RESULTS

A total of 193 vaccine candidates were found to be in the development pipeline of which 42 were in the clinical whereas the rest were in the preclinical stage of development. Of the vaccines in the clinical stage of development, only 10 have reached to Phase 3. Of these 10 vaccines, the efficacy and/or safety data of one vaccine candidate could not be accessed and therefore finally early phase data of nine candidate vaccines were used for evaluation [Figure 1].

Early clinical phases and their data for each included candidate vaccine followed by their critical evaluation is described [Supplementary Material 1].

ChAdOx1-nCoV-19

ChAdOx1-nCoV-19/AZD1222 is nonreplicating chimpanzee adenovirus vaccine vector vaccine used to express the spike glycoprotein of severe acute respiratory syndrome CoV 2 (SARS-CoV-2).^[11] It was proposed to prevent the SARS-CoV-2 infection based on studies on rhesus macaques.^[12] The study presents preliminary result of Phase 1/2 randomized clinical trial [Supplementary Material 1]. Local and systemic adverse reactions were more common in the ChAdOx1 nCoV-19 group. Fatigue and headache were the most commonly reported systemic reactions. There were no serious adverse events (SAE) in this group. Anti-spike protein IgG responses peaked by day 28 (157 enzyme-linked immunosorbent assay [ELISA] units, 96–317) and had not

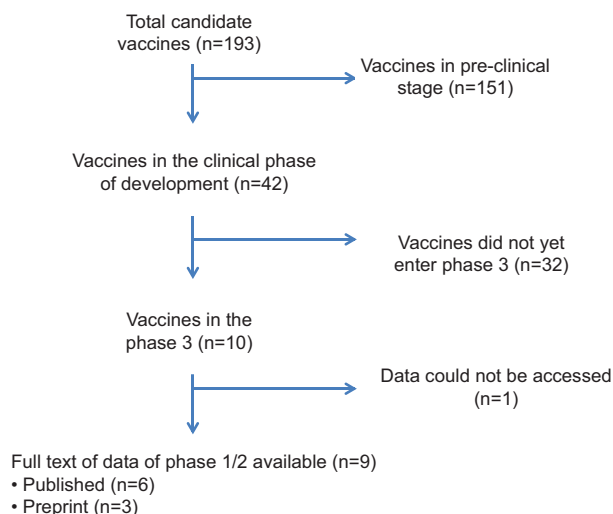


Figure 1: Flow diagram showing the process of inclusion of the studies

declined significantly by day 56. Neutralizing assay against SARS-CoV-2 were detected in 32 (91%) of 35 participants after a single dose when measured in micro-neutralization assay 80 and in 35 (100%) participants when measured in plaque reduction neutralization test (PRNT50). After a booster dose, all participants had neutralizing activity. The total IgG response and virus neutralization assay as measured by Marburg virus neutralization and a pseudo-virus neutralization assay was comparable to convalescent plasma. For cellular response, specific T-cell peaked on day 14 (median 856 spot-forming cells per million peripheral blood mononuclear cells, interquartile range 493–1802, $n = 43$).^[11]

BNT162b1/BNT162b2

BNT162b1/BNT162b2 is modified RNA with lipid nanoparticle envelope which encodes a SARS-CoV-2 receptor-binding domain (BNT162b1) or full-length spike protein (BNT162b2). For this study, 195 healthy volunteers were divided into 13 groups depending upon age of participant vaccine candidate, and dose (10–30 µg). The safety and efficacy outcomes are as mentioned in supplementary material. Similar pattern of local adverse events was observed after both candidate vaccine but systemic adverse events were milder and less frequent with BNT162b2. Both vaccines elicited similar IgG and neutralizing response and immunogenicity was more marked in younger age group (18–55) compared to older age group (65–85). The neutralizing titer as measured on day 7 after second dose was 1.1–1.6 times greater than convalescent serum GMT in 65–85 years old and from 2.8 to 3.8 times the convalescent serum panel GMT in 18–55 years. Cellular response was not measured.^[13]

Recombinant adenovirus type 26 and recombinant adenovirus type 5

Recombinant adenovirus type 26 (rAd26) and recombinant adenovirus type 5 (rAd5) are nonreplicating adenovirus vectored vaccine which is comprised of two components, rAd26 and rAd5, both of which carry the gene which encodes for SARS-CoV-2 full-length spike glycoprotein. The vaccine was used as two formulations namely frozen (Gam-COVID-Vac) and lyophilized (Gam-COVID-Vac-Lyo). It was a phase 1/2 open label nonrandomized study [Supplementary Material 1].

The most common systemic and local adverse events were pain at injection site (58%), hyperthermia (50%), headache (42%), asthenia (28%), and muscle and joint pain (24%). There was no SAE. RBD-specific IgG reciprocal titer and neutralizing antibody reciprocal titer peaked at day 42 for both frozen and lyophilized formulations and were significantly higher than the those in the convalescent plasma from COVID-19 patients at day 28 and 42. Cell-mediated responses were detected in all participants at day 28 with both formulations as shown by median cell proliferation of CD4+ and CD8+ cells.^[14]

mRNA-1273

mRNA-1273 is a mRNA based vaccine with lipid nanoparticle capsule which encodes the S-2P antigen consisting of the SARS-CoV-2 glycoprotein with a transmembrane anchor and an intact S1–S2 cleavage site. It was a phase 1, dose-escalation, open label clinical trial designed to determine the safety, reactogenicity, and immunogenicity [Supplementary Material 1].

The common systemic and local adverse events (>50%) were fatigue, chills, headache, myalgia, and pain at the injection site. There was no SAE but one patient in 25 µg group developed urticaria due to which he was not given the 2nd dose of vaccine. There was dose-dependent increase in antibody titer against both S2 protein and RBD. The median titers after second vaccination were in the upper quartile of the values in convalescent plasma samples from COVID-19 patients as measured on day 36, 43, and 57 after the first injection. Similarly, PsVNA and PRNT assay were found increased after second injection and were either at or above the values of convalescent serum. Intracellular cytokine assay showed Th1-specific response (tumor necrosis factor- α , interleukin-2, and interferon- γ) after vaccination.^[15]

Whole inactivated virus vaccine (Sinopharm)

This vaccine was tested in phase 1 and 2 clinical trials and the study included presents interim analysis results of randomized, double-blind, placebo-controlled trial in 96 (Phase 1) and 224 (Phase 2) healthy adults aged between 18 and 59 years. Details of trials and outcomes measured are mentioned [Supplementary Material 1]. The most common adverse events were injection site pain and fever which were mild, transient, and self-limiting. No SAE was reported. Humoral immunogenicity was measured as neutralizing antibody titers against live SARS-COV-2 and specific IgG-binding antibody titers against whole SARS-CoV-2 antigen. In phase 1 trial, increasing antibody titer was observed after 2nd and 3rd dose but the final measured titer at day 14 after 3rd injection was found to be highest in low dose group compared to middle and high dose group in both neutralization antibody test and IgG specific antibody test. In phase 2 trial, which compared two dosing schedules of middle dose (5 µg), showed that day 0 and 21 has higher antibody titer compared to those receiving day 0 and 14 schedule for both neutralization antibody test and IgG-specific antibody test.^[16,17]

Whole inactivated virus vaccine (Sinovac)

CoronaVac/Sinovac was tested in a double-blind randomized controlled trial involving 600 healthy volunteers. The participants were randomized into six groups to receive two doses of either 3 µg or 6 µg vaccine or placebo on days 0 and 14 or days 0 and 28 schedule. The primary outcome for safety was local and systemic adverse events within 7 days of each injection, unsolicited symptoms recorded

during a 28-day follow-up. The primary immunogenicity outcome was geometric mean titer (GMT) of IgG antibodies against RBD of SARS-CoV-2 and neutralizing antibody titer using cytopathogenic effect assay. There was no significant difference between two-dose groups within days 0/14 and days 0/28 groups. However, participants in day 0/28 group were found to have higher titers for both IgG-specific antibody against RBD and neutralizing antibodies. Further the titers were higher in younger population than the older.^[17]

Adenovirus type-5-vectored vaccine

This vaccine contained a replication defective adenovirus-5 vector and was tested in a randomized double-blind placebo-controlled phase 2 trial in China. In this study, healthy adult HIV negative and previous SARS-CoV-2-free volunteers were randomized into three arms to receive either vaccine in a dose of 1×10^{11} ($n = 253$), 5×10^{10} viral particles per mL ($n = 129$) or placebo ($n = 126$). Other characteristics of the study can be accessed through supplementary material. The geometric means titers of RBD ELISA antibody responses were 94.5 and 85.1 for the two vaccine dose groups, respectively. At day 28 postvaccination, the RBD ELISA antibody titer peaked at 656.5 and 571.0 in the two-dose groups, respectively. In the two dose groups, 96 and 97% participants showed seroconversion of RBD-specific ELISA antibodies at day 28. GMT of neutralizing antibody responses to live SARS-CoV-2 in the two dose groups were 19.5 and 18.3, respectively. Seroconversion for neutralizing antibodies against live SARS-CoV-2 in two-dose groups occurred in 59 and 47% of the participants in these groups respectively at day 28 postvaccination. Increasing age was found to be independent negative factor for RBD-specific ELISA antibodies and neutralizing antibodies against live SARS-CoV-2 and pseudo-virus. Both of the dose groups had similar incidence of solicited adverse events but significantly higher than placebo group. The incidence of severe (Grade 3) ADR (e.g., fever) was significantly higher in first dose group than the second-dose group and placebo. No SAE was reported during 28 days' postvaccination.^[18]

Adenovirus type 26 coronavirus 2.S vaccine

Ad26.COV2.S is a nonreplicating adenovirus vector-based vaccine utilizing the spike (S) protein of SARS-CoV-2. It was administered at two-dose level of 5×10^{10} (low dose) or 1×10^{11} (high dose) viral particles per vaccination, either as a single dose or as a two-dose schedule, 8 weeks apart in healthy adults [Supplementary Material 1]. Interim safety data indicated that most of the adverse events were mild to moderate (Grade 1 and Grade 2) in severity and resolved on the same day or the following day. Two SAEs were also reported, the first for hypotension which later was not found to be vaccine related by the investigator and the second was a case with fever who needed hospitalization and was found to be vaccine related. The increased incidence of adverse events was seen with higher dose and in younger age group.

The immunogenicity data reported is obtained in the first 4 weeks after the first vaccination in unblinded manner and includes only limited number of participants from cohort group 3 ($n = 15$). Humoral immunity as measured on day 29 after vaccination by ELISA for anti-spike antibody and neutralization assays were comparable in both dose groups. GMTs of antibody against S protein in low dose as well as in higher dose group were lower than GMT of 899 obtained from human convalescent serum.

Neutralization assay using a wild type virus at day 29 after immunization in cohort 1a had GMTs of 214 and 243 for the low and high dose levels, respectively. A similar immunogenicity profile was observed in the 15 participants in cohort 3 with GMTs of 196 and 127 in low and high dose levels, respectively. Thus, higher antibody titers were found in low dose group for both ELISA and neutralization antibody test in cohort 3. There was increased expression of Th1 cytokine producing CD4+ and CD8+ T cell in both cohort 1a and 3 for both dose levels.^[19]

NVX-CoV2373

This is a recombinant SARS-CoV-2 (rSARS-CoV-2) nanoparticle vaccine made from full length spike protein and matrix-M1 (adjuvant). Vaccine was planned to be tested in a phase 1–2 trial. Phase 1 trial has been completed. In this trial, 134 participants were randomized to five study groups to receive various combinations of vaccine 5 µg, 25 µg, adjuvant 50 µg and placebo. Outcome measures are mentioned in Supplementary Material 1.^[20]

Reactogenicity was absent or mild in all the participants across all five study groups following both the vaccinations. Reactogenicity events extended 2 days beyond the day 7 postfirst vaccination and it did not extend beyond day 7 postsecond vaccination.

Geometric mean fold rise of anti-spike IgG ELISA unit response with adjuvanted regimens exceeded to those without adjuvant by a factor of at least 10 at day 21 postfirst vaccination and by a factor of at least 100 at day 28 following second vaccination. The antibody titers following single vaccination with adjuvant was similar to that of convalescent plasma of asymptomatic COVID-19 patient. The titers after second vaccination with adjuvant exceeded to the values in the convalescent plasma of symptomatic COVID-19 outpatients whereas it was similar to that of convalescent plasma of symptomatic hospitalized COVID-19 patients.

Critical evaluation of early phase results

In all of the included studies of the candidate vaccines, immunogenicity (humoral [anti-spike protein/specific site-antibodies and/or neutralizing antibodies titer] and/or cellular) and SAEs/local or systemic adverse events/laboratory parameters abnormality were considered as efficacy and safety outcomes. Because in different studies

the immunogenicity was assessed by different methods and expressed in different terms therefore head-to-head comparison among the data could not be possible. Similarly for the safety outcomes where the depiction of data is not uniform across the studies including comparing with the control and therefore data could only qualitatively be compared.

Immunogenicity response with most of the vaccines was either higher than or similar to the respective controls except one where the elicited antibody titer was less than that in the control convalescent serum/plasma [Table 1]. Overall adverse events (related and/or unrelated) were more with vaccines than the those with respective control(s) in

three studies, in other two, these were found to be similar whereas in one study, the events were less in the vaccine group than the control group and in the rest of the studies data described was descriptive only without any mention for the same for the control [Table 1].

DISCUSSION

Search for an effective and safe medical product for prophylaxis as well as the management of COVID-19 is an unmet need in today's time. A number of products are being investigated for the same purpose. Vaccines have played a vital role to improve the human health

Table 1: Metadata of various coronavirus disease 2019 vaccine trials for comparison

Name of first author of studies included	Candidate vaccine	Developer	Study design	Control	Immunogenicity for vaccine versus control	Safety of vaccine versus control
Folegatti PM <i>et al.</i>	ChAdOx1 nCoV-19	Astra Zeneca/Oxford	Single blind RCT	MenACWY	GMT of anti-spike IgG antibodies and neutralizing Abs > control	SAE in ChAdOx1 nCoV-19 < control
Walsh EE <i>et al.</i>	BNT162b1 BNT162b2	BNT/Pfizer	Single blind RCT	Placebo	GMT of Nab > convalescent plasma	Systemic reactogenicity in vaccine ~ placebo, adverse events in vaccine > placebo
Logunov DY <i>et al.</i>	rAd26 and rAd5	Gamaleya Research Institute	Open, nonrandomized trial	None	Anti-spike Ab responses > convalescent plasma, Nab response ~ convalescent plasma	No serious adverse events, mild local and systemic adverse events, mild and transient deviation in laboratory parameters (no control)
Xia S <i>et al.</i>	Inactivated vaccine	Sinopharm/wuhan	Double-blind RCT	Alum-based placebo	GMT of neutralizing and specific IgG antibody > placebo	Overall percentage of participants experiencing AE > placebo
Zhang Y <i>et al.</i>	CoronaVac	Sinovac	Double-blind RCT	Placebo	RBD antibody and neutralizing Ab titer > placebo	AEs with vaccine ~ placebo
Zhu FC <i>et al.</i>	Adenovirus type-5 (Ad5)-vectored vaccine	CanSino Biologics/Beijing Institute of Biotechnology	Double-blind (RCT)	Placebo	GMT of IgG Antibodies and neutralizing Abs > placebo	Solicited ADR > placebo ($P<0.0001$)
Jackson LA <i>et al.</i>	mRNA-1273	Moderna/NIAID	Open label clinical trial	None	GMT for Anti-S 2P and RBD antibody > convalescent plasma	No SAE, mild local ADRs
Sadof J <i>et al.</i>	Ad26.COV2.S		Double blind RCT (interim results)	Placebo	GMT of antispike and neutralizing antibodies < convalescent plasma	Two SAE, No grade 4 AE (no comparison with control)
Keech C <i>et al.</i>	NVX-CoV2373 (recombinant full length SARS-CoV-2 spike protein nanoparticle based)	Novavax	Double blind RCT	Placebo, adjuvant, nonadjuvanted vaccine, Convalescent serum of COVID-19 patients	GMT of anti-spike Antibody with Vaccine > Convalescent serum of COVID-19 outpatients vaccine ~ convalescent serum of COVID-19 hospitalized patients	Reactogenicity in vaccine ~ placebo

~: Similar to, ADR: Adverse drug reaction, AEs: Adverse events, COVID-19: Coronavirus disease 2019, GMT: Geometric mean titer, MenACWY: Meningococcal conjugate vaccine, RBD: Receptor binding domain, RCT: Randomized controlled trial, SAE: Serious adverse reaction, COVID-19: Coronavirus disease 2019, Nab: Neutralizing antibody, NIAID: National Institute of Allergy and Infectious Diseases

by reducing the morbidity and/or mortality from both the infectious and noninfectious diseases. Today's pandemic is another challenge for research society to develop an effective and safe vaccine against it. There are a number of vaccine candidates at various preclinical or clinical stages of development. This piece of work presents a summary of data of early clinical phases of the vaccines against SARS-CoV-2 which have reached to phase 3 clinical trial.

The Phase 1/2 randomized clinical trial of ChAdOx1 nCoV-19/AZD1222 showed development of higher humoral immunity compared to that with convalescent plasma from recovered patients of COVID-19. Cellular immunity was induced as evident from increased expression of interferon- γ producing T-cell. Currently, it is in phase 3 trial in the US, the UK, and India (NCT04516746). The trial was halted temporarily following review of the safety data after report of a SAE in one patient but was resumed shortly after it was declared safe by Medicines Health Regulatory Authority in the UK.^[21]

BNT162b1/BNT162b2 are modified RNA with lipid nanoparticle envelope. Phase 1 trial performed to evaluate different doses of two vaccines has shown a greater humoral response than that with convalescent plasma for both vaccines. However, cellular response was not evaluated in this study. Since the systemic reactions after BNT162b2 were milder and less frequent it was selected for further Phase 2/3 clinical studies.

The findings for rAd26 and rAd5 vaccine showed again a significantly greater humoral immunity response than that with convalescent plasma. Cellular immunity was also induced as shown by proliferation of T-cells. It also showed the adequate safety and tolerability of the vaccine. This vaccine is registered by the Russian Ministry of Health in August and became the first registered COVID-19 vaccine.^[22] Currently, phase 3 trial is underway for this vaccine in Russia (NCT04530396) and Belarus (NCT04530396).

In the study of inactivated Vaccine/Sinopharm, immunogenicity, unlike other COVID-19 vaccine trials, was not compared with that in the convalescent plasma of recovered patients. It also did not evaluate cellular immunity. Currently, the vaccine is in phase 3 clinical trial in UAE and Abu Dhabi (ChiCTR2000034780).

The CoronaVac/sinovac vaccine has shown to be effective against protection of SARS-CoV-2 in rhesus macaques.^[23] In human trial, the two different doses of vaccine were well tolerated and induced humoral immunity in healthy adults aged 18–59 years. The incidence of adverse reactions in the 6 μ g and 3 μ g group were also comparable. Currently, the vaccine is in phase 3 clinical trial in Brazil (NCT04456595) and Indonesia (INA-WXFM0YX). It is already given emergency use authorization for high risk people.^[24]

The mRNA-1273 vaccine has shown to induce protective immunity against SARS-CoV-2 viral infection in nonhuman primate.^[25] The Phase 1 dose escalating study has also shown that it is generally safe and induces humoral and cellular immunity in participant of age 18–59 years. The humoral immunity induced is comparable to that of convalescent plasma. It has also been stated to have induce strong immunity in older adults.^[26] According to the statement of MODERNA the vaccine has completed recruitment for phase 2 trial^[27] and currently the vaccine is recruiting for Phase 3 clinical trial in US (NCT04470427). Participants will receive intramuscular injection of 100 μ g mRNA-1273 on Day 1 and on Day 29.

Ad26.COV2.S has been shown to provide protective immunity in animal models of rhesus macaques and Syrian golden hamster and upon challenge with SARS-CoV-2.^[28,29] In the phase 1/2a study the vaccine has been found to be safe. It was found to elicit humoral immune response as detected on day 29 after single injection which was quantitatively less than those in convalescent serum samples.

NVX-CoV2373 has used novel recombinant nano-technology to generate antigen derived from the CoV spike protein. The phase 1 study has shown it to be safe and to induce immunity that is more than the levels in COVID-19 patient's convalescent serum. The vaccine had also induced CD4⁺ T-cell responses that were biased toward a Th1 phenotype. Phase 2 has started on the basis of the safety results and phase 3 is in preparatory stages.

Thus for now, there are few vaccines available which have shown positive safety and efficacy results in early phases of clinical development, however, the evidence obtained from phase 3 trials will actually contribute in conclusive decision making. To shorten the duration of phase 3 trials, one of the way outs that is proposed is, the human challenge trials, where the participants are deliberately exposed to optimum viral-load to prove efficacy of vaccine in disease prevention. The WHO has already released key criteria for the ethical acceptability of COVID-19 human challenge studies.^[30]

CONCLUSION AND RECOMMENDATIONS

All of the studies have shown immunogenic response to some or other protein of SARS-CoV-2. The studies showed higher desirable immunogenicity as compared to the respective control except for one, i.e., Ad26.CoV2.S vaccine which showed immunogenicity less than the convalescent plasma. Many of the vaccines caused more SAE/adverse events/ADRs than the controls, however most were mild and transient and/or manageable.

As mentioned previously, because of hurdles in the direct quantitative comparison of safety and efficacy outcomes of various vaccines, a head-to-head comparison trial may

require to choose the most suitable vaccine candidate among all, but it can further delay the vaccine development process. Another issue with these data is short duration of follow-up. It ranges from a maximum of 56 days to as little as 28 days following a dose of a vaccine. Therefore, long-term data are required from these studies to understand the duration of protection conferred.

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Conflicts of interest

There are no conflicts of interest.

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SUPPLEMENTARY MATERIAL

Supplementary Material 1: General characteristics of vaccines included in the study

Author	Candidate vaccine	Type of vector	Developer	Site	Design	Control	Phase
Follegati PM <i>et al.</i>	ChAdOx1 nCoV-19	Nonreplicating viral vectored vaccine	Astra Zeneca/ Oxford	UK	Single blind RCT	MenACWY	Phase 1/2
Walsh EE <i>et al.</i>	BNT162b1 BNT162b2	Lipid nanoparticle formulated, modified RNA vaccine	BNT/Pfizer	US	Single blind RCT	Placebo	Phase 1
Logunov DY <i>et al.</i>	rAd26 and rAd5	Nonreplicating recombinant adenovirus	Gamaleya Research Institute	Russia	Open, nonrandomized trial	None	Phase 1/2
Xia S <i>et al.</i>	Inactivated vaccine	Inactivated SARS-CoV-2 vaccine	Sinopharm/ wuhan	China	Double blind RCT	Alum based placebo	Phase1/2
Zhang Y <i>et al.</i>	CoronaVac	Inactivated SARS-CoV-2 vaccine	Sinovac	China	Double-blind RCT	Placebo	Phase 2
Zhu FC <i>et al.</i>	Ad5-vectored vaccine	Nonreplicating viral vector	CanSino Biologics/ Beijing Institute of Biotechnology	China	Double-blind RCT	Placebo	Phase 2
Jackson LA <i>et al.</i>	mRNA-1273	RNA vaccine with lipid nanoparticle capsule	Moderna/ NIAID	US	Open label clinical trial	None	Phase 1, dose-escalation,
Sadof J <i>et al.</i>	Ad26.COV2.S	Non replicating recombinant adenovirus		US, Belgium	Double-blind RCT	Placebo	Phase 1/2a
Keech C <i>et al.</i>	NVX-CoV2373 (recombinant full length SARS-CoV-2 spike protein nanoparticle based)	Baculovirus Sf9 insect cell expression system	Novavax	Australia	Double blind RCT	Placebo	Phase 1-2

Author	Efficacy outcome	Safety outcome	Total sample size	Route	Schedule
Follegati PM <i>et al.</i>	Humoral responses Total IgG ELISA against trimeric SARS-CoV-2 spike protein Multiplexed immunoassay Neutralization assays Cellular responses as assessed using an <i>ex-vivo</i> interferon- γ enzyme-linked immunospot assay	Occurrence of any adverse events by 28 days of vaccination	1077	IM	Single injection (10 patients received booster dose)
Walsh EE <i>et al.</i>	Humoral Immunogenicity SARS-CoV-2 serum neutralization assay RBD-binding or S1-binding IgG immunoassays	Solicited local Reactions, systemic events, and use of antipyretic and/or pain medication within 7 days after vaccination unsolicited AEs and SAEs from Dose 1 through 1 month after Dose 2	195	IM	Two 0.5-mL injections BNT162b1 BNT162b2or placebo, 21 days apart
Logunov DY <i>et al.</i>	Humoral immunity IgG antibody against receptor binding domain Virus neutralizing antibody titers Cellular immunity Interferon- γ production CD8+/CD4+lymphoproliferation after vaccination	Number of participants with adverse events after vaccination	76	IM	0, 21 days

Contd...

Xia S <i>et al.</i>	Humoral immunity Nab titers Specific IgG-binding antibody titers	Local and systemic adverse events on diary cards within 7 days of each injection unsolicited symptoms recorded during a 28 days follow-up	320	IM	Phase 1 - Three injections at days 0, 28, and 56 Phase 2 - Two injections on days 0 and 14 and days 0 and 21
Zhang Y <i>et al.</i>	Humoral immunity IgG antibodies against RBD of SARS-CoV-2 Nab titer	local and systemic adverse events on diary cards within 7 days of each injection unsolicited symptoms recorded during a 28 days follow-up	600	IM	Day 0, 14 or Day 0, 28
Zhu FC <i>et al.</i>	Humoral response GMTs of specific ELISA antibody responses to the RBD Neutralizing antibody responses at day 28	Incidence of adverse reactions within 14 days	508	IM	Single injection
Jackson LA <i>et al.</i>	Humoral immunity ELISA based antibody test for S-2P and RBD Nab test (PsVNA) and by live wild-type, PRNT Cellular immunity by cytokine- staining assay for T cell response	Systemic and local adverse events for 7 days after each vaccination	45	IM	0.5-ml injection in the deltoid muscle on days 1 and 29
Sadof J <i>et al.</i>	Humoral immunity ELISA based antibody test against spike protein Nab test Cellular immune by ICS after stimulation with Serum peptide pools	local and systemic adverse events on within 7 days of each injection Any adverse event during a 28 days' follow-up after each injection	810	IM	Single dose and two-dose, 8 weeks apart
Keech C <i>et al.</i>	Humoral immunity by ELISA based IgG antibody test against spike protien	Number and percentage of participants with solicited local and systemic reactogenicity, their duration and peak intensity for 7 days postvaccination and laboratory values at day seven post-vaccinations (i.e., day 7 and day 28)	131 for phase 1	IM	Two doses, 0.6 mL at days 0 and 21

MenACWY: Meningococcal conjugate vaccine, ELISA: Enzyme-linked immunosorbent assay, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, RCT: Randomized controlled trial, RBD: Receptor binding domain, AEs: Adverse events, SAE: Serious adverse reaction, Nab: Neutralizing antibody, Ad5: Adenovirus type-5, GMTs: Geometric mean titers, PRNT: Plaque-reduction neutralization testing, ICS: Intracellular cytokine staining, IM: Intramuscular, NIAID: National Institute of Allergy and Infectious Diseases'