Phase III Vaccines for SARS-CoV-2: A Review of Development and Available Data

Authors
Hamid Ehsan, M.D.[1]*, Muhammad Khawar Sana, MD[2], Ayesha Sarwar M.D.[3], Nazma Hanif, M.D[4], Sana Irfan Khan, M.D.[5]

Affiliations:
[1]Graduate Student of M.S. in Biohazardous Threat Agents & Emerging Infectious Disease, Georgetown University, Washington, DC, U.S.A.

[2]Department of Internal Medicine, King Edward Medical University, Lahore, Pakistan.

[3]Department of Internal Medicine, King Edward Medical University, Lahore, Pakistan.

[4]Foundation University Medical College, Pakistan.

[5]Department of Pharmacology, All India Institute of Medical Sciences, Delhi, India.

***Corresponding author**
Name: Hamid Ehsan, MD, FACP
Postal Address: MUMH Department of Medicine, Hospitalist Department, 201 E. University Parkway, Baltimore, Maryland 21218

Phone: +9172875423
Fax: +4105542184
Email: he150@georgeotown.edu , hamid.ehsan@medstar.net

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Abstract

Background
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), has caused more than 35 million confirmed cases and more than 1 million deaths so far. This has led to global efforts to find effective treatment and vaccination to control disease transmission and decrease severity. The current efforts are focused on developing a vaccine that is safe and effective after one or two doses, provides protection for a minimum of six months, provides protection for high-risk population and reduces the risk of onward viral transmission. In this review, we summarize available information related to the development and safety profile of these phase III vaccines against SARS-CoV-2.

Methods
Literature search was performed on PubMed, Cochrane and ClinicalTrial.gov using keywords like “SARS-CoV-2”, “COVID-19”, and “Phase III vaccines”. Two individuals performed screening of the resultant library. We assessed different articles for information focusing on vaccines in phase III trials.

Results
As of September 3, 2020 update by the World Health Organization (WHO), there are currently more than 137 candidate vaccines undergoing preclinical development and of these 34 candidate vaccines are in the clinical evaluation phase, 18 are in phase I and 5 are in phase II. Currently, there are 9 vaccines in the phase III development process.
Conclusion
Multiple phase III trials of COVID-19 vaccines are in progress across the globe, highlighting the collaborative international efforts to develop a safe and effective vaccine. The available efficacy and safety data of phase I/II trials of these vaccines have shown promising results. Pharmaceutical companies are using different strategies including inactivated vaccines, RNA vaccines, recombinant viral vector vaccines and live attenuated BCG vaccine.

Key Words: SARS-CoV-2, COVID-19, Vaccine, phase III, randomized controlled trials

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative pathogen behind coronavirus disease 2019 (COVID-19), emerged from Wuhan, China in December 2019.[1] The World Health Organization (WHO) declared it a global pandemic on Mar 11, 2020.[2] This novel virus has variable infectivity varying by region with a reproductive number (R_0) reported as low as 2.2 to as high as 6.5.[3,4] There have been more than 35 million confirmed cases in 213 countries with more than 1 million deaths worldwide since the outbreak started.[5] It has led to significant health, financial, social and community burdens, with more than a third of the global population being placed on lockdown.[6]

Coronavirus is a positive-sense, single-stranded, enveloped RNA virus with surface spike proteins made of glycoprotein that help in the binding to the human cell surface and facilitate entry during infection.[7] There is currently no vaccine approved for the prevention of COVID-19 infection. According to WHO, there are currently about 137 candidate vaccines in clinical or preclinical development. As of Sept 3, 2020, 34 candidate vaccines are in clinical evaluation with 18 in phase I, 5 in phase II and 9 in phase III.[8,9] The properties of an ideal vaccine against this virus include efficacy after one or two shots with ability to confer protection for at least six months, protection of target populations such as the elderly and those with multiple comorbidities including immune-compromised individuals and healthcare workers and dampening the transmission of the virus to contacts.[10]

The mechanism used for developing most of the COVID-19 vaccines focuses on inducing antibody responses to prevent it from entering human cells and multiplying. In other cases, the destruction and elimination of already infected cells by the vaccines might also be achieved by the induction of antibody and cellular immune responses thereby limiting the virus's replication within a transiently infected host.[11] However, SARS-CoV-2 spike (S) protein is becoming a popular target for vaccines as it induces the formation of

neutralizing antibodies by immune cells.[12] DNA or mRNA constructs can be used for the expression of S-proteins and similarly recombinant virus vectors such as adenovirus or vaccinia virus can also be used.[13] Alternatively, the delivery of vaccines may also be achieved via either a recombinant with or without an accompanying adjuvant or as a killed/attenuated vaccine.[14] The methods mentioned above, and many more, are currently being employed in numerous vaccine programs globally. This review discusses the phase III vaccines for SARS-CoV-2 in terms of development and available data on efficacy and safety.

Table 1 Platforms of vaccines against COVID-19 and their developmental stages*granted Fast

Platform		Example	Development stage
Conventional	Inactivated virus	Polio vaccine	Phase III (PiCoVacc)
	Live attenuated virus	M.M.R. vaccine	Preclinical
	Protein sub-unit	Influenza vaccine	Phase I/II
	Virus-like particles	HPV vaccine	Preclinical
Novel	Viral vector	Ebola vaccine	Phase III (AZD1222)
	D.N.A.	Unlicensed	Phase I
	RNA	Unlicensed*	Phase III (mRNA-1273, BNT162)
	A.P.C.	Unlicensed	Phase I/II

Track designation by the United States Food and Drug Administration (F.D.A.) on May 12, 2020

Abbreviations: COVID-19: coronavirus disease 2019; A.P.C.: antigen presenting cells

2. Results and Discussion

There are several types of vaccines for generating immunity against pathogens (Table 1). The factors that contribute to considering one particular type of vaccine for development include the immune system's response, available technology, resources and the affected population.[15]

The live-attenuated vaccines are produced by modification of disease-producing pathogen that is weakened but remains viable and capable of inducing an immune response. These vaccines are usually beneficial and tend

to create strong immunity. One or two doses of most live-attenuated vaccines can generate lifelong immunity in most cases.[15] However, the need for extensive safety testing makes them a less attractive option in the current pandemic situation.[16] There is no live attenuated vaccine in clinical trials for SARS-CoV-2 yet, but some are in the preclinical evaluation phase in India and Turkey.[9]

The inactivated vaccines are generated by the killed version of the pathogen but they retain their immunogenicity. The level of immunity provided is not as strong as live-attenuated vaccines and a series of booster shots are required.[15] However, they are easy to produce and have a better safety and stability profile than live attenuated vaccines.[17] There are several inactivated SARS-CoV-2 vaccines currently in phase III trials in China (ChiCTR2000034780), U.A.E. (ChiCTR2000034780), Brazil (NCT04456595) and Indonesia (669/UN6.KEP/EC/2020).[9]

The subunit (recombinant, polysaccharide and conjugate) vaccines use specific pathogen components to stimulate the immune system. Using a subunit makes these vaccines safer and relatively easy to produce. These vaccines also require adjuvants to increase immunogenicity.[15]

No vaccine from this category is in phase III trial, but multiple subunit vaccine candidates are in phase I/II and preclinical evaluation.[9]

The recombinant vector vaccines contain live-attenuated viruses that are genetically engineered to carry D.N.A. that encodes for viral antigens.[18] These vaccines can elicit a robust immune response and do not require an adjuvant. Recombinant adenoviruses are commonly used as vectors because they are highly efficient in transferring genetic material to the cells and have a broad ability to infect both dividing and non-dividing cells.[19] Three SARS-CoV-2 recombinant vector vaccines are currently in phase III trials. The University of Oxford along with AstraZeneca has a phase III trial running in Brazil (ISRCTN89951424) and a multi-center phase III trial in the U.S. (NCT04516746). CanSino and Beijing Institute of Biotechnology are also running a global multi-center phase III trial for their vaccine (NCT04526990). Gamaleya Research Institute of Epidemiology and Microbiology has a viral vector vaccine based on weakened human adenovirus in a phase III trial (NCT04530396) in Russia.[9]

The mRNA vaccines are formulated using an mRNA sequence that encodes the antigen of interest.[18] These have the potential to simulate natural infection and elicit a potent immune response. Other advantages include incorporation of multiple mRNAs into one vaccine, elimination of the need to handle the infectious virus and rapid production.[20,21] The mRNA vaccines have shown promising results in animal models infected with influenza, Zika and rabies viruses.[22] Pfizer, in collaboration with BioNTech and Fosun Pharma, is evaluating four mRNA vaccine candidates. Two of the four vaccines (BNT162b1, BNT162b2) have been in phase III trials since July in the U.S., Argentina, Brazil and Germany (NCT04368728).[9] These vaccines are lipid nanoparticle formulated and target the SARS-CoV2 full-length spike glycoprotein. Modernatx, Inc. started phase III trials of their vaccine mRNA-1273 in July 2020 at different centers in the U.S. (NCT04470427). This is also a lipid nanoparticle formulated vaccine which encodes the stabilized prefusion SARS-CoV-2 spike protein.[9]

3. Characteristics of Current Phase III COVID-19 Vaccines

The characteristics of individual vaccine currently phase III trials are listed in Table 2 and study characteristics are enlisted in Table 3. Table 4 discusses the outcome data of the included trials so far.

3.1 AZD1222 Vaccine

AZD1222 is based on the replication-defective simian adenovirus vector ChAdOx1. It contains the genes for a spike protein of SARS-CoV-2 (GenBank accession number MN908947).

In a phase I/II study, 1077 participants were enrolled and randomized to two groups receiving either vaccination with AZD1222 (n=543) or MenACWY (meningococcal Vaccine for A, C, W and Y strain) (n=534). Antibodies against spike protein peaked by day 28 in the AZD1222 group and remained elevated until day 56. Greater than 90% of participants achieved neutralizing antibody titers after a single intramuscular injection. Interferon-gamma (IFN-γ) levels peaked at day 14 and were on the downtrend at day 56. Successful vaccination with AZD1222 is likely to protect for about a year.[10]

Headache, malaise, chills, fatigue and mild to moderate pain were more frequent in the AZD1222 arm (60-70%) when compared to MenACWY (40-50%).[10] However, no serious adverse events have been reported with the new vaccine. Researchers also used prophylactic paracetamol to address local and systemic adverse reactions. Adverse events reported in the paracetamol subgroup were less frequent than the placebo group. Muscle ache occurred in 60% of participants in the placebo group versus 48% in the paracetamol group. Similarly, malaise occurred in 61% versus 48%, chills in 56% versus 27% and fever in 51% versus 36% in placebo versus paracetamol group, respectively. Laboratory adverse events included neutropenia as expected, however it was predominantly self-limiting and mild/moderate in intensity.[10]

AstraZeneca, the company behind AZD1222, has announced the expected price as a few dollars per dose. Latin America is expected to produce it for under $4. Serum Institute in India declared they would keep the price under $3 for India and other developing nations. Likewise, Italy announced that a single shot would be kept at $2.80 in Europe. The manufacturers have vowed that production will remain not-for-profit. The expected cost in the remaining regions is yet to be disclosed.[23,24]

3.2 CoronaVac Vaccine

CoronaVac is an inactivated whole-virus vaccine. The WIV04 strain from the National Genomic Data Center of the Chinese Academy of Science is being used in the development of this vaccine. This strain is isolated from a patient in Wuhan. National Institutes for Food and Drug Control of China approved the vaccine, placebo (alum) and the trial.[25]

It is a dual shot vaccine administered intramuscularly in a 2 - 4 week period. In the phase II trial, 600 healthy adults were randomly assigned to receive two vaccine shots either at day 0 and 14 (n=297) or day 0 and 28 (n=294). The medium (5-μg) dose was chosen after a successful phase I trial. Antibody titers remained elevated two weeks post vaccine completion. Results in more time points were not available for the phase II trial at the time of preparing this review.[25]

All participants seroconverted in the phase I trial and the phase II group received injections on days 1 and 21. However, the phase II group who received the vaccine on days 0 and 14 positively seroconverted in only 85.7% of the participants.[25]

Fourteen participants in the phase I trial and 21 participants in the phase II trial reported injection site pain. Fever was reported by two participants in the phase I trial and eight participants in the phase II trial. Most adverse events were mild (below grade 3), self-resolving and did not require any particular treatment. Grade 3 or above adverse events were reported in four participants in the phase II trial however, they were all deemed unrelated to the vaccine.[25]

The data on the expected cost incurred to the public has not yet been revealed.

3.3 mRNA-1273 Vaccine

This novel lipid nanoparticle (LNP)-encapsulated mRNA encoded for the spike protein's prefusion-stabilized form is being pursued against SARS-CoV-2. It is administered as two shots via intramuscular route four weeks apart at a dose of 25-µg, 100-µg or 250-µg.[26]

A pseudo-typed lentivirus is being used which can infect human cells on only a single-round to develop a virus neutralization assay (PsVNA). Another plaque-reduction neutralization testing (PRNT) assay using live wild-type SARS-CoV-2 is being used to assess neutralization.[26] In the clinical trial performed to assess efficacy, neutralization activity was found in all participants that reduced SARS-CoV-2 infectivity by at least 80% at six weeks post-inoculation. The geometric mean titers (GMTs) with $PRNT_{80}$ was 340 (95% CI 184 - 627) in the low dose (25-µg) group and 654 (95% CI 460-930) in the medium dose (100-µg) group.[26] Hence, the expected duration of protection with this response rate is six weeks.[26]

Systemic adverse events were reported in 33% of the low dose (25-µg) group as compared to 67% in the medium dose (100-µg) group. However, only 53% reported adverse events in the high dose (250-µg) group. All adverse events were manageable. Fever was reported only after the second injection.[26]

The cost incurred to the public is expected to be around $32 to $37 per-dose.[26] Another primary concern regarding mRNA-based vaccines is the extremely low temperature required to maintain efficacy during distribution and storage. The cost, along with the temperature requirement, makes this vaccine option less suitable for lower-income countries along the equator.

3.4 BNT162b1 Vaccine

Another mRNA-based vaccine is under development using the same principles as that of the previous discussed vaccine.[27] The vaccine is administered via two intramuscular injections given four weeks apart.

In order to evaluate the maximum tolerable dose of BNT162b1, the dose-escalation study used 10-µg, 30-µg or 100-µg of BNT162b1. A total of 45 healthy adults were randomized to receive the two doses of either low (10-µg), medium (30-µg) or high (100-µg) at day 0 and 21. A week after the second dose the average GMTs raised from 168 to 267, showing efficacy.[27]

Pain at the injection site, mild to moderate fatigue and headache were more commonly reported in all BNT162b1 groups compared to the placebo group. Systemic adverse events were reported by 50 % of participants in low and medium dose groups as compared to 58.3% in the high dose group. Grade 3 adverse events were reported in two participants from BNT162b1 groups. Grade 3 lymphopenia was seen in 8.3%, 9.1 % and 33.3% participants of the low, medium and high dose groups, respectively. The lymphopenia resolved spontaneously within a week.[27]

Pfizer and BioNTech have reached an agreement with the U.S. government to keep the price as low as $19.50 per-dose.[23]

3.5 Ad5-nCoV Vaccine

The Ad5-vectored COVID-19 vaccine is genetically engineered and based on adenovirus type-5 with a vector that expresses the SARS-CoV-2 spike protein on its surface.[25] The vaccine is administered as a single intramuscular injection.

In a phase II trial, 508 eligible participants were assigned randomly to either receive a low dose (1×10^{11} viral particles) (n=253) or high dose (5×10^{10} viral particles) (n=129) or placebo shot (n=126). There was a significant induction of neutralizing antibodies with GMTs as 19.5 (95% CI 16.8-22.7) versus 18.3 (14.4-23.3) in low dose versus high dose groups, respectively, four weeks after vaccination. Seroconversion of the neutralizing antibody against SARS-CoV-2

appeared in 59% of participants receiving the low dose vaccine.[25]

Within 14 days following vaccination at least one adverse event was reported by 72%, 74% and 37% of participants in the low dose group, high dose group and placebo, respectively ($p<0.0001$). The most common adverse events, regardless of dose, were pain at site of injection, fatigue, fever and headache. These adverse events mostly resolved spontaneously in 3 to 4 days. No serious adverse event was reported until 4 weeks post-vaccination.[25]

3.6 Gam-COVID-Vac Vaccine

This vaccine contains two adenoviruses (rAd26 and rAd5) carrying the genetic code for SARS-CoV-2 spike protein in their vectors.[10,28] A receptor-binding domain (RBD) is found on one of the two subunits of the spike protein. This RBD interacts with the ACE2 receptor present on the human cell surface. S2 subunit is involved in the mediation of the fusion of viral membrane with cell membranes.

In phase I/II trials, 76 participants were enrolled. In phase I, nine volunteers were given rAd26-S and another nine received rAd5-S. In phase II, 20 participants were given rAd26-S and rAd5-S each. Regarding efficacy, SARS-CoV-2 RBD-specific immunoglobulins were detectable in 88.9% of rAd26-S group 14 days after administration and in 84.2% of rAd5-S group 14 days after administration.100% of participants developed the antibodies 3 weeks after administration. In phase II, the detection of SARS-CoV-2 RBD-specific IgGs was observed in the majority of participants on the 14th day while all participants had SARS-CoV-2 RBD-specific IgGs beginning on day 21. An increase in RBD-specific IgG titers was observed following a booster with rAd5-S. One week after rAd5-S booster, there was a significant increase in GMT with Gam-COVID-Vac vaccine ($p<0.0001$ at day 28 versus day 21) as well as with Gam-COVID-Vac-Lyo vaccine ($p<0.0001$ at day 28 versus day 21). Four weeks post rAd26-S vaccination, SARS-CoV-2 RBD-specific GMTs were significantly higher in volunteers who had the booster than in those who did not receive the booster, amounting to a GMT of 1866 after Gam-COVID-Vac ($p=0.0047$) and 1372 after Gam-COVID-Vac-Lyo ($p=0.0042$). Upon analysis of the neutralizing antibodies to SARS-CoV-2 it became evident that only the administration of both rAd26-S and rAd5-2 produced neutralizing antibodies in 100% of participants. In contrast, with rAd26-S, 61.1% of participants seroconverted (lyophilized frozen). In summary, all participants produced neutralizing antibodies to SARS-CoV-2 spike protein with a seroconversion rate of 100%. Furthermore, there was 100% detection of cell-mediated immunological responses in the participants on day 28. The median cell proliferation of 2.5% in CD4+ cells and 1.3% in CD8+ cells were noted with frozen formulation while the lyophilized formulation induced a median cell proliferation of 1.3% in CD4+ cells and 1.1% in CD8+ cells.[29]

The safety data reported pain at the injection site in 58%, hyperthermia in 50%, headache in 42%, asthenia in 28% and muscle and joint pain in 24% of participants. Most adverse events were mild. No serious adverse events were reported.[29]

3.7 Bacillus Calmette-Guérin (BCG) Vaccine

The Bacillus Calmette-Guérin (BCG) vaccine is a live attenuated vaccine and stimulates a strong immune response in healthy individuals. It should not be given to individuals with a weak immune system in the setting of medications or underlying illness.[30]

The effect of the B.C.G. vaccination on prevention of COVID-19 is still unknown. Though there is evidence from *in vivo* studies that B.C.G. has non-specific effects on the immune system, these effects lack clinical relevance and have not been elaborated well.[31,32] There are currently two registered trials that aim to study the effects of the B.C.G. vaccination on COVID-19. One of them is in

health care workers and the other is in the elderly. The objective of these trials is to reduce the absenteeism rate of health care workers and to reduce the hospital admission rate among the elderly.[33,34] The BRACE trial is investigating whether the B.C.G. vaccination provides protection against or reduces the severity of COVID-19 among healthcare workers in Australia. This randomized controlled trial will be testing 10,000 healthcare workers across Australia and other countries including the Netherlands and Spain. The participants will receive either a B.C.G. vaccine or a placebo and will be monitored over 12 weeks to observe if they contract COVID-19 and, if so, the severity of their symptoms will be recorded.[33] The trial involving the elderly is being carried out in the Netherlands where senior citizen organizations are facilitating recruitment of participants. In both of these trials participants will be randomized to either receive 0.1 ml of the licensed B.C.G. vaccine (Danish strain 1331) or placebo. The primary outcome of the BRACE trial is the number of days lost due to unplanned absenteeism in healthcare workers measured every two weeks. The primary outcome of the trial in the elderly is the total number of hospital admissions due COVID-19.[35]

4. Conclusion

The current COVID-19 pandemic has disrupted all aspects of human life. However, the future offers hope as COVID-19 vaccine development is showing promising results in terms of efficacy and safety. Current phase III vaccines are in different categories including inactivated (3), RNA (2), recombinant viral vector (3) and long-standing live attenuated B.C.G. vaccine. The use of different vaccine platforms can help overcome some important challenges pertaining to vaccine development such as safety, duration of protection, immunity for high-risk populations and disease transmission. Most of these vaccine trials are being conducted simultaneously on different parts of the globe and many of the trials involve more than one nation. This highlights the collaborative international efforts to develop a vaccine against this common enemy.

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Table 2 Characteristics of vaccines against COVID-19 currently in phase III trials

Vaccine	Developer/Manufacturer	Platform	Type	Route	Doses	Timings
AZD1222	University of Oxford/AstraZeneca	Non-Replicating Viral Vector (Adenovirus)	ChAdOx1-S	IM	1	Day 0
PiCoVacc	Sinovac Life Sciences Co., Ltd	Inactivated	Inactivated plus adjuvant	I.M.	2	Day 0, 14
Unnamed	Wuhan Institute of Biological Products/Sinopharm	Inactivated	Inactivated	I.M.	2	Day 0, 14 or 0, 21
Unnamed	Beijing Institute of Biological Products/Sinopharm	Inactivated	Inactivated	I.M.	2	Day 0, 14 or 0, 21
mRNA-1273	NIAID/ModernaTX, Inc.	R.N.A.	LNP-encapsulated mRNA	I.M.	2	Day 0, 28
BNT162	BioNTech SE/Pfizer	R.N.A.	3 LNP-mRNAs	IM	2	Day 0, 28
Ad5-nCoV	Beijing Institute of Biotechnology/ CanSino Biologics Inc.	Recombinant viral vector	Adenovirus type 5	I.M.	1	Day 0
Gam-COVID-Vac	Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation	Combined Viral vector	rAd26, rAd5	I.M.	2	Day 0, 21
B.C.G. Vaccine	Royal Children's Hospital/Murdoch Childrens Research Institute	Live attenuated bacteria	Danish strain 1331	ID	1	Day 0

Abbreviations: NIAID: National Institute of Allergy and Infectious Diseases; L.N.P.: lipid nanoparticle; I.M.: intramuscular; ID: intradermal

Table 3 Ongoing phase III trials of vaccines against COVID-19

Trial ID	Phase	N	Intervention	Comparator	Primary Outcome measure	Start date	Estimated primary completion date
ISRCTN89951424, NCT04516746	III	30000	AZD1222	Placebo	Efficacy, safety, reactogenicity	Aug 17, 2020	Dec 2, 2020
NCT04456595, 669/UN6.KEP/EC/2020	III	9000	Adsorbed COVID-19 (inactivated) vaccine	Placebo	Efficacy, safety	Jul 21, 2020	Sep 2021
ChiCTR2000034780 (United Arab Emirates)	III	5000	Inactivated SARS-CoV-2 vaccine	Placebo	Efficacy	Jul 16, 2020	Jul 15, 2021
ChiCTR2000034780 (China)	III	5000	Inactivated SARS-CoV-2 vaccine	Placebo	Efficacy	Jul 16, 2020	Jul 15, 2021
NCT04470427	III	30000	mRNA-1273	Placebo	Efficacy, safety	Jul 27, 2020	Oct 27, 2022
NCT04368728	III	30000	BNT162b1, BNT162b2	Placebo	Efficacy, safety	Apr 29, 2020	Apr 16, 2021
NCT04526990	III	40000	Ad5-nCoV	Placebo	Efficacy, safety	Aug 30, 2020	Dec 30, 2021
NCT04530396	III	40000	Gam-COVID-Vac	Placebo	Efficacy	Aug 31, 2020	May 1, 2021
NCT04327206	III	10000	BCG Vaccine	Placebo	Efficacy	Mar 30, 2020	Jun 30, 2021

Table 4 Results of phase I/II trials of vaccines that are currently in phase III against COVID-19

Study	Trial ID	Phase	N	Median age (range)	Intervention	Control	Dose	Timing	Outcome measures (at 4 weeks)	Common adverse events
Folegatti et al.	NCT04324606	I/II	1077	35	ChAdOx1 (n=543)	MenACWY (n=534)	Single dose	Day 0	Anti-spike protein titers: median 157 EU	Fatigue, myalgia, malaise, chills, fever, headache
Zhang et al. (preprint)	NCT04352608	II	600	NA (18-59)	CoronaVac	Placebo	Two doses	Day 0, 14 *vs.* Day 0, 28	92.4% SC (Day 0, 14) 97.4% SC (Day 0, 28) Neutralizing antibody range: 23.8-65.4	Pain at injection site
Xia et al.	ChiCTR2000031809	II	224	44	Inactivated Vaccine	Aluminum hydroxide	Two doses	Day 0, 14 *vs.* Day 0, 21	97.6% SC (Day 0, 14) 97.6% SC (Day 0, 21)*	Pain at injection site, fever
Jackson et al.	NCT04283461	I	45	33 (18-55)	mRNA-1273	N.A.	25-μg *vs.* 100-μg *vs.* 250-μg	Day 0, 29	ELISA anti–S-2P: 40,227 (25-μg), 109,209 (100-μg), 213,526 (250-μg)	Fever, fatigue, headache, chills, myalgia, pain at injection site
Mulligan et al.	NCT04368728	I/II	45	NA (18-55)	BNT162b1	NA	10-μg *vs.* 30-μg *vs.* 100-μg	Day 0, 21	Neutralizing titers: 1.9 to 4.6-fold	NA
Zhu et al.	NCT04341389	II	508	39	Ad5-nCoV (382)	Placebo (n=126)	1×10^{11} vp (n=253) *vs.* 5×10^{10} vp (n=129)	Day 0	59% SC (1×10^{11} vp) 61% SC (5×10^{10} vp) Neutralizing titers: 19.5 (1×10^{11} vp) 18.3 (5×10^{10} vp)	Pain at injection site, fever, headache, fatigue

*neutralizing antibodies to live SARS-CoV-2
Abbreviation: MenACWY: meningococcal group A, C, W-135, and Y conjugate vaccine; E.U.: ELISA units; SC: seroconversion; vp: viral particles

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