Updates in Vaccine Development for COVID-19: Evidence on Currently Available Vaccines

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Abstract

Background- COVID-19 is caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). Emergence of the worldwide outbreak in late 2019 led to a declaration of a global health emergency by the World Health Organization (WHO) and a pandemic in early March 2020. The risk of acquiring SARS-COV-2 is indiscriminatory as all individuals are at risk for infection. Nevertheless, individuals with certain underlying medical conditions such as hypertension, type 2 diabetes mellitus, and cardiovascular diseases are at increased risk for infection and severe illness indicated bysystemic inflammation primarily in the respiratory tract. To date,there are four approved or authorized COVID-19 vaccines in the United States: Pfizer-BioNTech and Moderna mRNA vaccines, Novavax protein subunit vaccine, and Johnson & Johnson's Janssen (J&J/Janssen) viral vector vaccine which is recommended only in certain situations. Both Pfizer –BioNTech and Moderna's immunization schedule includes individuals 6 months and older; Novavax and Johnson & Johnson's Janssen (J&J/Janssen) for persons at least 12 and 18 years respectively1. However, 26 candidate vaccines are currently in clinical evaluations, 6 candidate vaccines are in phase 3 trials and 139 candidate vaccines in preclinical evaluation. **Objective**- Evaluate quality, safety and immunogenicity outcomes on currently published literature related to COVID-19 candidate vaccines in phase trials. Methods- Extensive electronic database synthesis was conducted for publication selection of COVID-19 vaccine candidate trials. **Results**- Current preliminary reports of the ChAdOx1 nCoV-19 vaccine, mRNA-1273 vaccine and Ad5 vectored vaccine convey tolerable, safe, and immunogenic profiles. Further investigations are required and ongoing to evaluate efficacy of the candidate vaccines in larger population sizes that include vulnerable patients with underlying comorbidities and older age at higher risk for COVID-19 infection. **Conclusion**- Candidate vaccines for COVID-19 have rapidly been developed using platform technology and assessment of the candidate vaccine in phase 3 and 4 clinical trials should be completed stringently and conclusively despite the race against time. Cost, conflict, and vaccine hesitancy are among the other barriers to Covid-19 vaccine development.

Keywords: COVID-19; vaccines; coronavirus; immunization

Introduction

Severe acute respiratory syndrome coronavirus 2, SARS-CoV-2, belongs to class of viruses known as coronaviridae, and is a bat virus that infects animals and can cross over to cause human infection. SARS-CoV-2 has caused a global health emergency and pandemic leading to a massive unification in the science community to understand the pathogen as well as a worldwide high-speed race to develop an effective and safe vaccine using platform technologies that can tackle COVID-19, prevent secondary waves of infection and control seasonal endemic infection outbursts as seen with influenza viruses. [1,2]

SARS-CoV-2 is an enveloped virus, wrapped in an icosahedral protein shell, with crown-like spikes (S) structural proteins attached to the surface that enters the host cell by docking on the Angiotensin-Converting Enzyme 2 (ACE2) receptors. The estimated incubation period for COVID-19 is up to 14 days from the time of exposure, with severity of illness ranging from mild to severe. Patients who present with mild illness are either asymptomatic or have various symptoms such as fever and cough without shortness of breath. Patients who present with moderate to severe illness present with lower respiratory disease and can rapidly progress into multi-organ dysfunction and fatal outcomes.[3,4] Tixagevimab plus cilgavimab is the only agent authorized by the Food and Drug Administration (FDA) for use as SARS- CoV-2 Pre-Exposure Prophylaxis (PrEP) in people who are not expected to mount an adequate immune response to COVID-19 vaccination or those with contraindications for COVID-19 vaccine. This agent was originally authorized for routine PrEP of COVID-19 in the United States. However the FDA recently updated the Emergency Use Authorization (EUA) on January 26, 2023 due to the overall prevalence of non-susceptible Omicron

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subvariants now estimated to be higher than 97%. To date, the decision to administer tixagevimab plus cilgavimab should be based on the regional prevalence of the resistant subvariants as well as the individual patient's risk factor.[1] The hyperactive inflammatory response to SARS-CoV-2 infection plays a central role in the pathogenesis of COVID-19. Treatment Guidelines Panel's recommendations on the use of immunomodulators for hospitalized patients according to their disease severity currently endorses corticosteroids including dexamethasone, the interleukin-6 inhibitors tocilizumab or sarilumab, and the janus kinase (JAK) inhibitors baricitinib or tofacitinib. Remdesivir is the only antiviral drug that is currently approved by the FDA for the treatment of COVID-19. Ritonavir-boosted nirmatrelvir (Paxlovid), molnupiravir, and high-titer COVID-19 Convalescent Plasma (CCP) have received EUAs from the FDA for the treatment of COVID-19.1, 16.

Vaccine development guidelines are more stringent than those for drug development due to its complexity, specificity, affinity and isotype of the antibody to neutralize the virus.4 Eight platforms strategies have been used for the development of COVID-19 vaccines to induce adaptive immunity response, which include Live-Attenuated vaccine (LA), Inactivated vaccine (IA), DNA vaccine, RNA vaccine, Viral Vector Replicating vaccine (VVR), Viral Vector NonReplicating (VVNR), Virus-Like Particles (VLP), and subunit vaccine.[5] Once challenged with a pathogen, neutralizing antibodies will block viral docking on ACE2 in host cells by recognizing the receptor-binding domain such as the Heptad Repeat 2 (HR2) domain. On the other hand, antibodies if they have low quality and low quantity to function, it can be harmful because they can cause an Antibody-Dependent Enhancement phenomenon (ADE). During ADE, non-neutralizing antibodies bind to virus particles through the Fab domain, while the monocytes and macrophages bind to the Fc domain of the antibody, impeding the immune response pathway, thereby facilitating virus entry and host cell infection.[6]

Therefore, it's important to develop a vaccine that is safe and does not exacerbate the disease.

Vaccine development is sequentially divided into the exploratory stage where the vaccine is developed, preclinical stage where the cell is cultured and studied in animal for immunogenicity, clinical phase which constitutes of three phases, phase I which studies vaccine safety & immunity in humans, phase II which studies vaccine dose-response, schedule and route of administration, phase III which further studies vaccine safety and efficacy in a larger population, and finally the last stage where the vaccine is marketed and monitored after successful clinical trials. Notably, the average phase for a novel vaccine development process is usually 10 to 15 years as in comparison to COVID-19 where over 160 potential vaccines are already under study, including promising clinical trials in the clinical stage such as RNA vaccines, mRNA-1273 developed by Moderna and BNT162b2 dveloped by Pfizer in addition to VVNR vaccine, ChAdOx1-nCoV-19 developed at University of Oxford.[2,4]

The initial roll-out of limited quantities of vaccines that are still investigational will provide the opportunity to ethically obtain pivotal data to improve regulatory and public health decision making, thereby increasing public and professional confidence in these and other vaccines.[7-10] After relatively short follow-up in phase 3 trials, even when vaccine efficacy appears to be high, reliable information will still be needed on longer-term safety and duration of protection. Other information gaps will include more comprehensive assessments of short-term safety, knowledge of whether waning of vaccine-induced protection may lead to vaccine-enhanced disease if a vaccinee becomes infected on exposure to SARS-CoV-2, information on protection against clinically severe forms of Covid-19, and knowledge of any associations between the degree of protection and the recipient's age or coexisting conditions.[11-13]

While vaccine supplies are limited, available vaccines are either approved or authorized, it was believed that it is ethically appropriate to continue blinded follow-up of placebo recipients in existing trials and to randomly assign new participants to vaccine or placebo, and under these conditions, trial sponsors are not ethically obligated to unblind treatment assignments for participants who desire to obtain a different investigational vaccine. Conversely, there was concern that observational data obtained from nonrandomized studies after vaccine deployment could yield unreliable answers.[14-16] Observational studies are subject to substantial biases and are much less amenable to unambiguous interpretation. Their limitations are of particular concern during this public health emergency, because vaccinated and unvaccinated people will differ in their risk of exposure to infection and of serious disease, partly because of fluctuating attack rates and because during early phases of vaccine deployment, vaccinees may well be at particular risk of infection. In these circumstances, even carefully analyzed observational studies can yield misleading answers about safety and efficacy.[17,18] In addition, unrelated events that occur by chance after vaccination may be incorrectly attributed to the vaccine, and such anecdotes may be deliberately promulgated by groups opposed to vaccination. Large, placebo-controlled, phase 3 efficacy trials could provide much of the needed information if they have appropriately prolonged follow-up while random assignments are still blinded. Such continuation would yield unbiased evidence on the duration of protection and on longer-term safety, including assessment of any evidence of the vaccine eventually enhancing the risk of severe disease. Thus, early deployment of scarce doses of still-investigational vaccines (under Emergency Use Listing (EUL) or similar regulatory mechanisms) could bring additional public health benefits if accompanied by firm commitments to maintaining blinded follow-up of participants in ongoing or future placebo-controlled trials until a licensed vaccine is fully deployed in the population. In some settings, early deployment could instead use the Expanded Access/Compassionate Use (EA/CU) mechanism, under which recipients are unambiguously informed of the vaccine's investigational nature.[18] In this paper, we review currently available data from multiple efficacy trials of COVID-19 vaccine candidates under way.

Materials and Methods

A comprehensive electronic research strategy was performed using NCBI, PubMed, Clinicaltrials.gov, on updates in candidate vaccine trials for COVID-19, the following keywords were used/combined in the search engines:

Indicating severe acute respiratory syndrome coronavirus 2: ("SARS-CoV-2") OR ("COVID-19") OR ("novel coronavirus") OR ("coronavirus") OR ("outbreak") Indicating COVID-19 Vaccine: ("candidate vaccine") OR ("platform technology") OR ("SARS-CoV-2 vaccines [MESH]") OR ("preliminary report") OR ("COVID-19 vaccine") OR ("clinical trials") OR ("phase I,II,III trials [MESH]") OR ("vaccine, registration") OR ("placebo") OR ("interim, report") OR ("results")

Indicating immunogenicity: ("immunity") OR ("adaptive immunity") OR ("antibodies") OR ("antigen") OR ("neutralizing") OR ("viral replication") OR ("Memory T cells, humoral [MESH]") OR ("B cell, lymphocytes") OR ("receptor binding domain, RBD") OR ("protection") OR ("serologic") OR ("seroconvert")

Eligibility Criteria

The search strategy was based on the selected keywords to extract published articles from the databases. The search publication was limited to one year since recent onset of SARS-COV-2 many publications have been released thereafter. All the published literature that was accessed was in English and studied in humans only. The selection of the articles was limited to studies that included preliminary reports, peer-reviewed articles if available and clinical trials sorted as the following: clinical trial phase I, phase II, phase I-II parallel study which is currently adopted by developers of COVID-19 candidate vaccines to shorten time for approval, open label, randomized or non-randomized, control trials.

Criteria for inclusion included: 1) clinical evidence 2) safety 3) efficacy 4) quality outcomes 5) clinical trials in phase I, II, III 6) prophylaxis vaccine 7) All ages (child, adult, and older adult)

Criteria for exclusion: 1) vaccines in preclinical evaluation 2) candidate vaccines not registered according to regulatory standards 3) Literature not studied in humans 4) any treatment regimen beyond the scope of the review objective 5) clinical trial not yet recruiting 6) post exposure prophylaxis.

Results

Shown in Tables 1-5 is a summary of the major COVID-19 vaccines that are either approved/authorized or under development. This list is not exhaustive but instead reflects some of the major vaccines highlighted in company materials or publicly available literature and public databases. [7-10,15,19-31]

1. [a]Based on live virus 80% plaque-reduction neutralization testing (PRNT80) assay
2. [b]Based on wild-type virus microneutralization assay (MNA) with an inhibitory concentration of 50%, with relative light units as readout
3. [c]Based on wild-type virus MNA with an inhibitory concentration of 80%
4. [d]Based on wild-type virus MNA with a 50% tissue culture infective dose of 100 (100TCID50)
5. [e]Based on wild-type virus MNA with an inhibitory concentration of 50%, with Cytopathic effect (CPE) as readout
6. [f]Based on wild-type virus MNA with an inhibitory concentration of 50%
7. [g]Based on wild-type virus MNA with Cytopathic effect (CPE) as readout
8. [h]Based on live virus 50% plaque-reduction neutralization

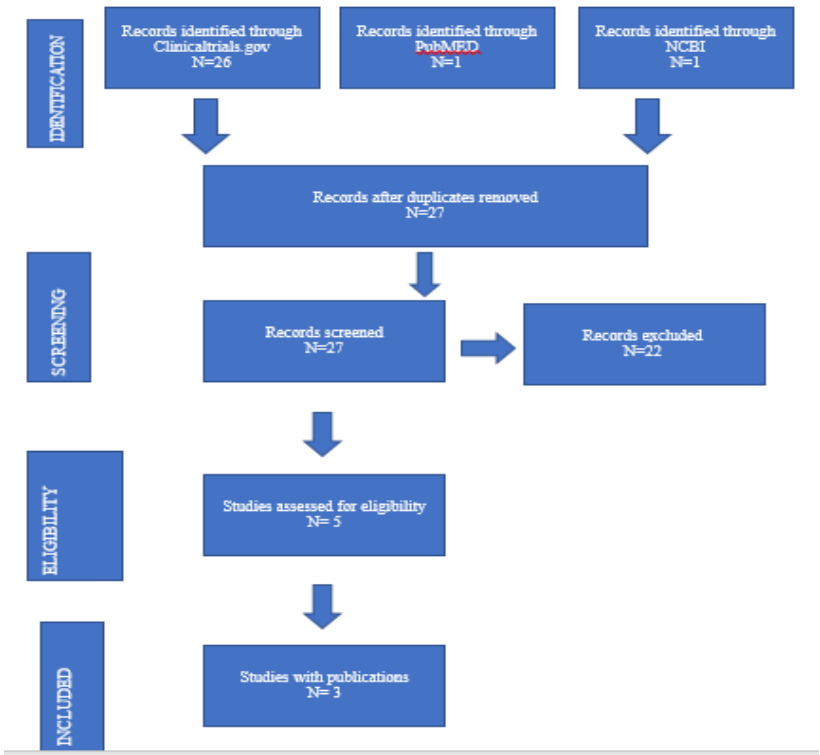

Figure 1: Eligibility Criteria

Table 1: List of top vaccines with Approval or Authorized

Name	Vaccine Type	Primary Developers	Country of Origin	Authorization/Approval
Pfizer BioNTech Comirnaty (BNT162b2)	mRNA-based vaccine	Pfizer, BioNTech; Fosun Pharma	Multinational	UK, Bahrain, Canada, Mexico, US, Singapore, Costa Rica, Ecuador, Jordan, Panama, Chile, Oman, Saudi Arabia, Argentina, Switzerland, Kuwait, EU, WHO (emergency use validation)
Moderna COVID-19 Vaccine (mRNA-1273)	mRNA-based vaccine	Moderna, BARDA, NIAID	US	US, Canada, EU, Israel, UK, France, Switzerland
CoronaVac	Inactivated vaccine (formalin with alum adjuvant)	Sinovac	China	China, Turkey
COVID-19 Vaccine AstraZeneca (AZD1222) ChAdOx1-nCoV-19	Adenovirus vaccine	BARDA, OWS	UK	UK, India, Argentina, Dominican Republic, El Salvador, Mexico, Morocco
Sputnik V	Non-replicating viral vector	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Russia	Russia, Palestine
BBIBP-CorV	Inactivated vaccine	Beijing Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	China	China, United Arab Emirates, Bahrain, Egypt
JNJ-78436735 (formerly Ad26.COV2.S)	Non-replicating viral vector	Johnson & Johnson	US	US, EU
NVX-CoV2373	Nanoparticle vaccine	Novavax	US	US, EU

Table 2: Vaccine candidates in development

Candidate	Mechanism	Sponsor	Trial Phase	Institution
Convidicea (Ad5-nCoV)	Recombinant vaccine (adenovirus type 5 vector)	CanSino Biologics	Phase 3	Tongji Hospital; Wuhan, China
Bacillus Calmette-Guerin (BCG) vaccine	Live-attenuated vaccine	University of Melbourne and Murdoch Children's Research Institute; Radboud University Medical Center; Faustman Lab at Massachusetts General Hospital	Phase 2/3	University of Melbourne and Murdoch Children's Research Institute; Radboud University Medical Center; Faustman Lab at Massachusetts General Hospital
INO-4800	DNA vaccine (plasmid)	Inovio Pharmaceuticals	Phase 2/3	Massachusetts General Hospital Center for Pharmaceutical Research, Kansas City. Mo.; University of Pennsylvania, Philadelphia
VIR-7831	Plant-based adjuvant vaccine	Medicago; GSK; Dynavax	Phase 2/3	Medicago
No name announced	Adenovirus-based vaccine	ImmunityBio; NantKwest	Phase 2/3	
CVnCoV	mRNA-based vaccine	CureVac	Phase 2b/3	CureVac
No name announced	Recombinant vaccine	Anhui Zhifei Longcom Biopharmaceutical, Institute of Microbiology of the Chinese Academy of Sciences	Phase 2	Various
ZyCoV-D	DNA vaccine (plasmid)	Zydus Cadila	Phase 2	Zydus Cadila

testing (PRNT50) assay

9. [i]Based on wild-type virus MNA with an inhibitory concentration of 99%

10. ND not determined

Discussion

In response to the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic, over 200 vaccine candidates against coronavirus disease 2019 (COVID-2019) are under development and currently moving forward at an unparalleled speed.[1] Among of them, preliminary results from phase 3 efficacy trials are encouraging, with more than 90% efficacy against COVID-19 diseases for the two mRNA vaccines (BNT162b2 and mRNA-1273), and 70.4% and 91.4% efficacy for ChAdOx1 and rAd26/rAd5 COVID-2019 vaccine,

Table 3: Summary of Clinical Trials with Interim Reports

Source/Study Design	Treatment arms	Intervention	Inclusion and Exclusion Criteria	Primary and Secondary outcomes	Results
ChAdOx1 nCoV-19 (AZD1222) Astra Zeneca and University of Oxford. Folegatti and Pollard et al.20206 Phase I/II, single blind, RCT conducted between April 23 and May 21,2020	Random assignment (1:1) ratio of ChAdOx1 nCoV-19 vaccine (experimental) compared with a licensed MenACWY conjugate vaccine (placebo) at five trial sites. 2 of the 5 trial sites allowed prophylactic administration of paracetamol to alleviate vaccine-associated reactions. ChAdOx1 nCoV-19 vaccine was administered intramuscularly into deltoid at a dose of 5x1010 viral particles. MenACWY vaccine was administered intramuscularly into deltoid at dose of 0.5 mL	1077 participants were recruited into 4 groups: Group 1: (n=88) N=44 were vaccinated with ChAdOx1 nCoV-19 vaccine N=44 were vaccinated with MenACWY vaccine. Group 2/4: (n=979) n=489 were vaccinated with ChAdOx1 nCoV-19 vaccinen=490 were randomized to MenACWY conjugate vaccine with n=1 receiving ChAdOx1 nCoV-19 vaccine. Group 3(non-randomized): N=10 were vaccinated with ChAdOx1 nCoV-19 vaccine and booster ChAdOx1 nCoV-19 vaccine 28 days after first dose N=56 received prophylactic paracetamol with ChAdOx1 nCoV-19 vaccine. N=57 received prophylactic paracetamol with MenACWY vaccine.	Inclusion: Healthy adults ages 18-59 years old with ability to provide written informed consent. Exclusion: History of confirmed SARS-CoV-2 infection, high risk individuals such as frontline healthcare workers, new onset of fever, cough, SOB, anosmia, or ageusia.	Primary outcomes: efficacy, safety of vaccine measured by occurrence of adverse events which is still ongoing and will be followed up on days 184 and 364. Secondary outcomes: Adverse events occurring 7 or 28 days after vaccination, cellular and humoral response of ChAdOx1 nCoV-19, efficacy in terms of death, seroconversion rates, and COVID-19 hospital admissions.	Pain associated with ChAdOx1 nCoV-19 vaccine was reduced with the use of prophylactic paracetamol (50%) versus patients who did not (67%). Fatigue and headache were the most commonly reported reaction after ChAdOx1 nCoV-19 vaccination, 70% and 68% respectively in patients in the non-paracetamol prophylactic group and 71% and 46% respectively in patients receiving ChAdOx1 nCoV-19 vaccine only. Antibodies against SARS-CoV-2 spike protein peaked by day 28, remained elevated to day 56 in patients who received one dose of ChAdOx1 nCoV-19. While patients with the booster dose, an increase in ntibodies against SARS-CoV-2 spike protein was observed at day 56. Similar increase in serum antibody levels to both spike protein and receptor binding domain was also observed at day 28 with and without booster dose. Interferon-gamma ELISpot responses against SARS-CoV-2 spike proteins were elevated at day 14 and were decreased by day 56 after vaccination. 4 out of 98 participants had neutralizing antibody titers >8 against SARS-CoV-2 spike proteins and 11 out of 270 participants had high ELISA titers prior to vaccination which may indicate underlying asymptomatic infection.
mRNA-1273 Moderna LA Jackson et al. 2020 Phase I, dose-escalation, open label, non-randomized trial conducted between March 16 and April 14,2020	Participants received mRNA-1273 at three different dose ranges, 25,100,250 mcg diluted with normal saline to 0.5 mL injection administered on days 1 and 29 into the deltoid muscle	45 participants were recruited into three groups in a dose-escalation, sentinel manner Group 1: n=15 received mRNA-1273 25 mcg beginning with n=4 sentinel participants followed by Group 2: n=15 received mRNA-1273 100 mcg, beginning with n=4 sentinel participants followed by Group 3: n=15 received mRNA-1273 250 mcg, beginning with n=4 sentinel participants no specified instructions to pre medicate or post medicate with antipyretics or analgesics such as acetaminophen	Inclusion: Healthy adults ages 18 to 55 years old able to provide written informed consent Exclusion: Pregnant, breastfeeding females, known or suspected SARS-CoV-2 infection, presence of significantly uncontrolled medical or psychiatric conditions	Primary outcome: Safety measured by adverse events reported using a standard toxicity grading scale Secondary outcomes: Immunogenicity including SARS-CoV-2 binding antibody, neutralization and T-cell response	One participant in the 25-mcg group was withdrawn due to urticaria on both legs that was observed 5 days after first dose of vaccination. Higher systemic adverse events were reported after the 2nd dose of vaccine than the first dose, all were mild or moderate in severity except for the 250 mcg group where 3 participants reported one or more severe event. Fever was not reported after first dose schedule but was reported in all three arms after second dose administration. Antibody responses win the 25 and 100 mcg group was notably similar to the convalescent serum specimen but was exceeded in the 250 mcg arm. Neutralizing activity using PsVNA and PRNT was detected in sample serum in all participants after second vaccination. CD4 T-cell responses were observed and especially Th1 cytokines over Th2 cytokine expression in the 25 and 100 mcg groups. Morever, CD8 T-cell response was elicited at low level in the 100 mcg dose group after second vaccine schedule

BNT162b1 & BNT162b2 BioNTech Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate-selection, and efficacy study in healthy individuals. NCT04368728	The study consists of 2 parts: Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part.	195 participants underwent randomization. In each of 13 groups of 15 participants, 12 participants received vaccine and 3 received placebo.		Inclusion: Male or female participants between the ages of 18 and 55 years, inclusive, 65 and 85 years, inclusive, or ≥12 years, inclusive, at randomization (dependent upon study phase). In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55 or >55 years of age]). Healthy participants who are determined by medical history, physical examination, and clinical judgment of the investigator to be eligible for inclusion in the study. • Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures. Participants who, in the judgment of the investigator, are at risk for acquiring COVID-19. Exclusion: Phases 1 and 2 only: Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV). Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study. History of severe adverse reaction associated with a vaccine and/ or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s). Receipt of medications intended to prevent COVID 19. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/ or laboratory/ physical examination. Women who are pregnant or breastfeeding. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.	Primary outcomes: Local and systemic adverse events abnormal hematology and chemistry laboratory values grading shifts in hematology and chemistry laboratory assessments Secondary outcomes: Immunogenicity SARS-CoV-2 serum neutralizing antibody levels, expressed as GMTs Achieving a greater than or equal to 4-fold rise from before vaccination in SARS-CoV-2 serum neutralizing antibody levels SARS-CoV-2 anti-S1 binding antibody levels and anti-RBD binding antibody levels, expressed as GMCs
Moderna, NIAID (mRNA-1273) SARS-CoV-2 Vaccine Phase 3 randomized, observer-blinded, placebo-controlled trial DOI: 10.1056/ NEJMoa2035389	The trial enrolled 30,420 volunteers who were randomly assigned in a 1:1 ratio to receive either vaccine or placebo (15,210 participants in each group). A two-dose regimen in a volume of 0.5 ml containing 100 μg of mRNA-1273 or saline placebo.	A total of 30,420 participants underwent randomization, and the 15,210 participants in each group were assigned to receive two doses of either placebo or mRNA-1273 (100 μg). Of the participants who received a first injection, 14,073 of those in the placebo group and 14,134 in the mRNA-1273 group were included in the primary efficacy analysis;	Inclusion: Participants (males and females 18 years of age or older, who are at risk of SARS-CoV-2 infection with no known history of SARS-CoV-2 infection, are a subset of the planned target population. Participants ≥ 65 years of age	Primary: To demonstrate the efficacy of mRNA-1273 to prevent Covid-19. To evaluate the safety and reactogenicity of 2 injections of the mRNA-1273 vaccine given 28 days apart. Secondary: To evaluate the efficacy of mRNA-1273 to prevent severe Covid-19. To evaluate the efficacy of mRNA-1273 to prevent serologically confirmed SARS-CoV-2 infection or Covid-19 regardless of symptomatology or severity.	Safety vaccine recipients had higher rates of local reactions (e.g., pain, erythema, swelling) and systemic reactions (e.g., Headache, fatigue, myalgia) than placebo recipients. Most reactions were mild to moderate and resolved over 1-3 days. Efficacy: The incidence of Covid-19 was lower among vaccine recipients than among placebo recipients as early as 14 days after the first dose. Protection in the vaccine group persisted for the period of follow-up.

			will be eligible for enrollment with or without underlying medical conditions further increasing their risk of severe COVID-19. Exclusion: • Acutely ill or febrile 72 hours prior to or at screening. • Pregnant or breastfeeding. • Prior administration of an investigational coronavirus (SARS-CoV, MERS-CoV) vaccine • Demonstrated inability to comply with the study procedures. • An immediate family member or household member of this study's personnel. • Known or suspected allergy or history of anaphylaxis, urticaria, or other significant adverse reaction to the vaccine or its excipients. • Bleeding disorder • Received or plans to receive a non-study vaccine within 28 days prior to or after • Has participated in an interventional clinical study within 28 days prior to the day of enrollment. • Immunodeficient state, asplenia, recurrent severe infections. • Has received systemic immunosuppressants		
	Were given 28 days apart, into the deltoid muscle of the same arm.				

			or immune-modifying drugs for >14 days in total within 6 months prior to screening • Has received systemic immuno-globulins or blood products within 3 months prior to the day of screening. • Has donated ≥ 450 mL of blood products within 28 days prior to screening			
Johnson & Johnson (ENSEMBLE) Ad26.COV2.S Covid-19 Vaccine Randomized, Double-blind, Placebo-controlled Phase 1/2a Study to Evaluate the Safety, Reactogenicity, and Immunogenicity NCT04436276. DOI: 10.1056/NEJMoa2034201	Cohort 1a Group 1-5 • (Adults ≥18 to ≤55 years) Cohort 1b Group 1-5 • (Adults ≥18 to ≤55 years) Cohort 2 Group 1-2 • (Adults ≥18 to ≤55 years) Cohort 3 Group 1-5 (Adults ≥65 years)	Vaccinations/ Injections • Ad26COVS1 5×1010 vp • Ad26COVS1 1×1011 vp • Placebo	Inclusion: • Signed an ICF • Adhere to the prohibitions and restrictions specified in this protocol. • Cohorts 1 and 2 only healthy, male, or female, 18 to 55 years of age, and contraceptive (women of childbearing potential). • Cohorts 1 and 3 only: Participant must have a body mass index (BMI) <40 kg/m2 • Cohort 3 only: participant must be either in good or stable health. Exclusion: • Clinically significant acute illness. • History of malignancy within 5 years. • Known allergy or history of anaphylaxis or other serious adverse reactions to vaccines or their excipients.	Primary: To assess the safety and reactogenicity of Ad26COVS1 at 2 dose levels, 5×1010 vp and 1×1011 vp, administered intramuscularly (IM) as a single-dose or 2-dose schedule in healthy adults aged ≥18 to ≤55 years and in adults aged ≥65 years in good health with or without stable underlying conditions. Secondary: To assess the humoral and cellular immune response to Ad26COVS1	All participants in Cohorts 1, 2, and 3: • Solicited local and systemic adverse events (AEs) for 7 days after each vaccination. • Unsolicited AEs for 28 days after each vaccination • Serious adverse events (SAEs) throughout the study (from first vaccination until end of the study; SAEs occurring before the first vaccination will be summarized separately)

			• Abnormal function of the immune system. • A history of acute poly-neuropathy. • Chronic urti-caria (recur-rent hives), eczema or adult atopic dermatitis. • Received treatment with immunoglob-ulins (Ig) in the 2 months or blood prod-ucts in the 4 months.		
Zhu et al. 202013 Phase I, dose-escalating, single center, non-randomized trial conducted between March 16 and March 27,2020	Participants received Ad5 vectored vac-cine at three dose ranges. 5 x 1010, 1 x 1010 and 1.5 x 1011 viral par-ticles adminis-tered intramus-cularly	108 participants were recruited into three groups in a dose-escalating manner. Group 1: N=36 received lose dose Ad5 vectored vaccine followed by Group 2: N=36 received medium dose Ad5 vectored vaccine Followed by Group 3: N=36 received high dose Ad5 vectored vaccine (meningococcal group A, C, W, and Y conjugate vaccine or saline). Participants in the ChAdOx1 nCoV-19 group received two doses containing 5 × 1010 viral particles (standard dose; SD/SD cohort); a subset in the UK trial received a half dose as their first dose (low dose) and a dose as their first dose (low dose) and a standard dose as their second dose (LD/ SD cohort).	Inclusion: Healthy adults ages 18 to 60 years old able to provide written informed consent. Exclusion: • Pregnant, breastfeeding females • Known or suspected SARS-CoV-2 infection • Presence of significantly uncontrolled medical or psychiatric conditions.	Primary outcome: Adverse events in the 7-day time frame after vaccination Secondary outcomes: Safety in 28-day time frame post vaccination and immunogenicity	The most commonly reported systemic adverse event was fever and muscle pain within the 7-day time frame and no severe adverse event reported within 28 days T cell response and neutralizing antibody activity was observed at day 14 and peaked at day 28.
ChAdOx1 nCoV-19 (AZD1222) Evaluated the safety and efficacy of the ChAdOx1 nCoV-19 vaccine in a pooled interim analysis of four trials. Voysey et al 202124	23 848 participants were enrolled. Participants aged 18 years and older were randomly assigned (1:1) to ChAdOx1 nCoV-19 vaccine or control	The primary efficacy analysis included symptomatic COVID-19 in seronegative participants with a nucleic acid amplification test-positive swab more than 14 days after a second dose of vaccine. Participants were analysed according to treatment received, with data cutoff on Nov 4, 2020.			Overall vaccine efficacy across both groups was 70·4% (95·8% CI 54·8-80·6; 30 [0·5%] of 5807 vs 101 [1·7%] of 5829). From 21 days after the first dose, there were ten cases hospitalised for COVID-19, all in the control arm; two were classified as severe COVID-19, including one death. There were 74 341 person-months of safety follow-up (median 3·4 months, IQR 1·3-4·8): 175 severe adverse events occurred in 168 participants, 84 events in the ChAdOx1 nCoV-19 group and 91 in the control group.

ChAdOx1 nCoV-19 (AZD1222) Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomized, controlled, phase 2/3 trial. Ramasamy et al 202025	560 participants were enrolled: 160 aged 18–55 years (100 assigned to ChAdOx1 nCoV-19, 60 assigned to MenACWY), 160 aged 56–69 years (120 assigned to ChAdOx1 nCoV-19: 40 assigned to MenACWY), and 240 aged 70 years and older (200 assigned to ChAdOx1 nCoV-19: 40 assigned to MenACWY).	18–55 years group, 1:1 to either two doses of ChAdOx1 nCoV-19 or two doses of MenACWY; in the 56–69 years group, 3:1:3:1 to one dose of ChAdOx1 nCoV-19, one dose of MenACWY, two doses of ChAdOx1 nCoV-19, or two doses of MenACWY; and in the 70 years and older, 5:1:5:1 to one dose of ChAdOx1 nCoV-19, one dose of MenACWY, two doses of ChAdOx1 nCoV-19, or two doses of MenACWY. Prime-booster regimens were given 28 days apart. Participants were then recruited to the standard-dose cohort (3·5–6·5 × 1010 virus particles of ChAdOx1 nCoV-19) and the same randomisation procedures were followed, except the 18–55 years group was assigned in a 5:1 ratio to two doses of ChAdOx1 nCoV-19 or two doses of MenACWY.	Inclusion: Participants were eligible if they did not have severe or uncontrolled medical comorbidities or a high frailty score (if aged ≥65 years).	The coprimary outcomes of the trial were efficacy, as measured by the number of cases of symptomatic, virologically confirmed COVID-19, and safety, as measured by the occurrence of serious adverse events.	Local and systemic reactions were more common in participants given ChAdOx1 nCoV-19 than in those given the control vaccine, and similar in nature to those previously reported (injection-site pain, feeling feverish, muscle ache, headache), but were less common in older adults (aged ≥56 years) than younger adults. In those receiving two standard doses of ChAdOx1 nCoV-19, after the prime vaccination local reactions were reported in 43 (88%) of 49 participants in the 18–55 years group, 22 (73%) of 30 in the 56–69 years group, and 30 (61%) of 49 in the 70 years and older group, and systemic reactions in 42 (86%) participants in the 18–55 years group, 23 (77%) in the 56–69 years group, and 32 (65%) in the 70 years and older group In participants who received two doses of vaccine, median anti-spike SARS-CoV-2 IgG responses 28 days after the boost dose were similar across the three age cohorts
Thomas et al. 2022 Study of safety and efficacy of BNT162b2 vaccine in subgroup of individuals with pre-existing stabilized neoplasm Randomized, placebo-controlled, observer-blinded global phase 3 clinical trial.	The total study comprised of 46,429 participants (≥ 12 years) randomized at 152 sites in 6 countries. Subgroup participants were isolated based on eligibility parameters.	Subgroup particpants (n= 3813) divided in two groups Group 1: n=1902 received 2-dose BNT162b2 mRNA vaccine 21 days apart.. Group 2: n=1911 received two doses saline placebo 21 days apart.	Inclusion: • History of past/active neoplasm (including benign/unknown etiology) • ≥ 12 years of age Exclusion: • Prior SARS-CoV-2 infection • Prior COVID-19 vaccination • Immunodeficiency diagnosis and related hospitalization 6 weeks prior to enrollment • Active therapy involving: - Cytotoxic agents - Systemic corticosteroids for ≥ 14 days - Radiotherapy - Blood plasma products - Immunoglobulin	Primary outcome: To demonstrate the efficacy of BNT162b2 vaccination against COVID-19 for people with underlying malignancy. Secondary: To assess safety, adverse events and, immune-genicity of BNT162b2 vaccine in subgroup of individuals with a history of neoplasm.	Overall BNT162b2 vaccine has a similar efficacy and safety profile regardless of neoplasm diagnosis. Efficacy for Subgroup was 94.4% (95% CI: 85.2, 98.5) 6 months post-dose 2 administration. Comparatively to total study population, efficacy was 91.1%. There were reports of COVID-19 infection for 4 BNT162b2 recipients and 71 placebo recipients. Adverse events (AE) were reported at incidence rates of 95.4 (BNT162b2) and 48.3 (placebo) per 100 person-years, the most prevalent reports being reactogenicity linked (i.e. injection-site pain, fatigue, pyrexia). No distinctions in AE presented within subgroup and total study participants. 3 BNT162b2 and 1 placebo recipients withdrew due to vaccine-related AEs. No vaccine-related deaths were reported.

Chalkias et al. 2022 Study of immunogenicity and safety of bivalent omicron-containing mRNA-1273.214 booster versus the monovalent mRNA-1273 booster against the omicron variant (B.1.1.529) Open-label, ongoing, 6-part, phase 2/3 study	819 total adult participants, with prior immunization of two-dose primary series (100 µg) and one-dose mRNA-1273 booster (50 µg) were enrolled. Divided into two cohorts: Part F cohort were administered a second booster injection of 50 µg mRNA-1273. Part G cohort were administered a second booster injection of 50 µg mRNA-1273.214.	Part F: n=377 Secondary booster mRNA-1273 is single stranded mRNA encoding soley the spike glycoprotein of ancestral SARS-CoV-2 (Wuhan-Hu-1)) (administered between February 18 and March 8, 2022). Part G: n=437 Secondary booster mRNA-1273.214 contained two mRNAs (1:1 ratio, 25 µg each), encoding the prefusion-stabilized spike glycoproteins of ancestral SARS-CoV-2 (Wuhan-Hu-1) and the omicron variant (BA.1)) (administered between March 8 and March 23, 2022).	Inclusion: • Healthy adults (≥ 18 years) with proof of vaccination present on day • Female participants with childbearing potential must: - Provide an initial negative pregnancy test prior to vaccination (day 1) - Consent to preventing pregnancy for 3 months following day 1 - Cease breastfeeding • Previous or current enrollment in Phase 3 of mRNA 1273 COVE trial: • Received 2 doses of mRNA 1273 (with second dose ≥6 months prior to enrollment). • Received primary booster of mRNA-1273 ≥3 months prior to enrollment. Exclusion: • Pregnant/ breastfeeding females • Known or suspected SARS-CoV-2 infection (within 14 days) • Presence of significantly uncontrolled/ acute medical or psychiatric conditions • Acutely ill or febrile 72 hours prior to or at screening. • Immunodeficiency • Myocarditis or pericarditis within 2 months prior	Primary: To demonstrate non-inferiority neutralizing antibody response of mRNA-1273.214 as compared with mRNA-1273 against omicron and SARSCoV-2 (D614G) on the basis of geometric mean titer ratio and percent difference in of participant response To evaluate the safety and reactogenicity of mRNA-1273.214 To demonstrate superiority of the antibody response after administration of mRNA-1273.214 against the omicron Secondary: To evaluate the mRNA-1273.214 immunogenicity compared to mRNA-1273 at all timepoints post-administration Seroresponse testing at 28 days (two-sided alpha level, 0.025) to verify if primary objectives were met	Most frequent solicitated adverse reaction after administration of both second boosters was injection-site painwere fatigue, headache, myalgia, and arthralgia in both groups. Majority of AR were mild to moderate (grades 1 and 2) occurred within 7 days for both groups. No grade 4 events occurred in either group. Overall incidences of AE was 5.7% (mRNA-1273.214) and 5.8% (mRNA-1273), with not discontinuations as result. Percentages of participants with seroresponse against SARS-CoV-2 were 100% for both boosters, estimate difference (ED) of 0 confirming noninferiority. For response against omicron, 0.8% less for the monovalent noninferiority criterion (ED 1.5%). Geometric mean titer (GMT) of neutralizing antibodies (all with 95% CI) was greater for mRNA-1273.214 than mRNA-1273 for all comparisons, regardless of previous SARS-2-CoV-2 infection. GMT findings supported that mRNA-1273.214 has a safety and reactogenicity profile analogous to mRNA-1273. Bivalent booster elicited superior neutralizing antibody responses against omicron at 28 days after immunization. GMT were also higher against omicron subvariants BA.4/5 SARS-CoV-2.

					• Bleeding disorder contraindicated for intramuscular injection • Previous AR to Covid vaccination (allergy, anaphylaxis, urticaria, etc.) • Donation of ≥450 mL of blood products within 28 days prior day 0 and/or during study • Received prior or day 0/plans to receive: - Any licensed vaccine within 28 days prior/ after day 1 (excluding influenza) - Immune-modifying drugs or corticosteroids (≥10 mg/ day) for >14 days within 6 months - Immunoglobulins/blood products within 3 months

*RCT- Randomized Controlled Trial *MenACWY- meningococcal group A, C, W-135, and Y * SOB- shortness of breath COVE- Coronavirus Efficacy, EUA- Emergency Use Authorization, SRR- Seroresponse Rate, GMT- Geometric Mean Titers (neutralizing antibody responses), ED- Estimate Difference of Percentage Point, AR- Adverse Response, CI- Confidence Interval

Table 4: Clinical trials results of COVID-19 vaccine candidates ongoing in phase III efficacy trials

Vaccine developer	Platform	Target dose and schedule in phase III trial	Preliminary vaccine efficacy against COVID-19	Immunogenicity of target dose and schedule in phase I/II trial	
				Neutralizing antibody titers	T cell response
Moderna (mRNA-1273)7,8,22,23	mRNA expressing spike protein	100 µg (Day 0, 28)	94.10%	1:654 (18-55 years)[a] 1:878 (56-70 years[a] 1:317 (≥71 years)[a]	CD4 Th1 cell responses and low CD8 T cell responses
Pfizer/BioNTech (BNT162b2)12, 19, 20, 21	mRNA expressing spike protein	30 µg (Day 0, 21)	95.00%	1:163 (18-55 years)[b] 1:206 (65-85 years)[b]	ND
AstraZeneca/University of Oxford (ChAdOx1/ AZD1222) 6,24,25	Non-replicating chimpanzee adenoviral vector expressing spike protein	Low dose (2.55 × 1010VP)/ Standard dose (5 × 1010VP) (Day 0, 28)	70.4% (Low-standard dose: 90.0%; Standard-standard dose: 62.1%)	1:143/1:144 (56-69 years)[c] Low-low dose/ Standard- Standard dose 1:161/1:193 (18-55 years)[c] 1:150/1:161 (≥70 years)[c]	IFNγ-ELISpot T-cell responses
Gamaleya Center (rAd26/ rAd5)27,31	Non-replicating recombinant adenoviral type26 and type5 expressing spike protein	10×10^{10}VP (Day 0, 21)	91.40%	1:46-1:49 (18-60 yeas)[d]	CD4 Th1 and CD8 T cell resposes

CanSino Biological Inc./Beijing Institute of Biotechnology Convidicea (Ad5-nCoV)[14,18]	Non-replicating recombinant adenoviral type5 expressing spike protein	5×10^{10}VP (Day 0)	ND	1:21.2 (18-44 years)[e] 1:17.8 (45-54 years)[e] 1:9.6 (≥55 years)[e]	IFNγ-ELISpot T-cell responses
Janssen (Ad26. COV2.S)[26,31]	Non-replicating recombinant adenoviral type26 expressing spike protein	5×10^{10}VP (Day 0)	ND	1:214 (18-55 years)[f] 1;196 (≥65 years)[f]	CD4 Th1 and CD8 T cell responses
Sinovac (CoronaVac) [28,31]	Inactivated	3ug (Day 0, 14)	ND	1:27.6 (18-59 yeas)[g]	ND
Beijing Institute of Biological Products (BBIBP-CorV)[29,31]	Inactivated	4ug (Day 0, 21)	ND	1:218.9 (18-59 yeas)[h]	ND
Novavax (NVX-Cov2373) [30,31]	Recombinant SARS-CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix-M	5 µg SARS-CoV-2 rS + 50 µg Matrix-M1 adjuvant (Day 0, 21)	ND	1:3906.3 (18-79 years)[i]	CD4 Th1 cell responses

Table 5: Summary of Active Clinical trial Protocols without Interim Reports

Source/Study Design	Treatment arms	Intervention	Inclusion and Exclusion Criteria	Primary and Secondary outcomes
PiCoVacc- Sinovac Biotech Parallel phase I/II randomized double-blind single center placebo-controlled trial NCT: NCT0435260811	Arm 1: two doses of medium dosage inactivated SARS-CoV-2 vaccine at the emergency vaccination schedule (0,14 days) Arm 2: two doses of high dosage inactivated SARS-CoV-2 vaccine at the emergency vaccination schedule Arm 3: two doses of placebo at the emergency vaccination schedule (0,14 days) Arm 4: two doses of medium dosage inactivated SARS-CoV-2 vaccine at the routine vaccination schedule (0,28 days) Arm 5: two doses of high dosage inactivated SARS-CoV-2 vaccine at the routine vaccination schedule (0,28 days) Arm 6: two doses of placebo at the routine vaccination schedule (0,28days)	744 participants were randomized to experimental and placebo arm. 144 participants are allocated at phase 1 and 600 participants allocated at phase II.	Inclusion: Healthy adults ages 18 to 59 years old able to provide written informed consent. Exclusion: known or suspected SARS infection, presence of significantly uncontrolled medical or psychiatric conditions, abnormal laboratory results in physical examination	Primary: safety after completion of whole vaccine schedule and immunogenicity on days 14 and 28 in the emergency and routine schedule respectively. Secondary: Safety outcomes within first seven days of each injection and up to 6 months after completion of dose schedule. Immunogenicity profile on days 42 and 56 in the emergency and routine schedule respectively.
BNT162 (a1,b1,b2,c2)- BioNTech Parallel Phase I/ II nonrandomized, multicenter dose escalation trial investigating 4 prophylactic SARS-CoV-2 RNA vaccines. NCT0438070112	Arm 1: BNT162a1 Arm 2: BNT162b1 Arm 3: BNT162b2 Arm 4: BNT162b2	200 participants are non-randomized into the 4 treatment arms	Inclusion: Healthy adults ages 18 to 55 years old able to provide written informed consent. Exclusion: Pregnant, breastfeeding females, known or suspected SARS-CoV-2 infection, presence of significantly uncontrolled medical or psychiatric conditions	Primary outcomes: Local and systemic adverse events Secondary outcomes: Immunogenicity
mRNA-1273 vaccine Moderna COVE Phase III, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older to prevent COVID-19 for up to 2 years after the second dose of mRNA-1273. NCT04470427	Arm 1: Experimental: Arm 1: Experimental: mRNA-1273 Participants will receive 1 intramuscular (IM) injection of 100 microgram (ug) mRNA-1273 on Day 1 and on Day 29. Arm 2: Placebo Comparator: Placebo 0.9% sodium chloride (normal saline) Participants will receive 1 IM injection of mRNA-1273-matching placebo on Day 1 and on Day 29.	30,420 volunteers who were randomly assigned in a 1:1 ratio to receive either vaccine or placebo (15,210 participants in each group). More than 96% of participants received both injections, and 2.2% had evidence (serologic, virologic, or both) of SARS-CoV-2	Inclusion: Participants who are at high risk of SARS-CoV-2 infection, defined as adults whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19. Healthy adults or adults with pre-existing medical conditions who are in stable condition. Exclusion:	Primary outcomes: Local and systemic adverse events Prevention of Covid-19 illness with onset at least 14 days after the second injection in participants who had not previously been infected with SARS-CoV-2. [Time Frame: Day 29 (second dose) up to Day 759 (2 years after second dose)] Secondary outcomes:

				Immunogenicity Efficacy of mRNA-1273 in the prevention of severe Covid-19 as indicated by clinical signs as predefined [Time Frame: Day 29 (second dose) up to Day 759 (2 Primary outcomes: Local and systemic adverse events Prevention of Covid-19 illness with onset at least 14 days after the second injection in participants who had not previously been infected with SARS-CoV-2. [Time Frame: Day 29 (second dose) up to Day 759 (2 years after second dose)] Secondary outcomes: Immunogenicity Efficacy of mRNA-1273 in the prevention of severe Covid-19 as indicated by clinical signs as predefined [Time Frame: Day 29 (second dose) up to Day 759 (2 years after second dose)] Geometric Mean Titer (GMT) of SARS-CoV-2 Specific Neutralizing Antibody (nAb) [Time Frame: Day 1, Day 29, Day 57, Day 209, Day 394, and Day 759] Geometric Mean Fold Rise (GMFR) of SARS-CoV-2 Specific nAb [Time Frame: Day 1, Day 29, Day 57, Day 209, Day 394, and Day 759]
			infection at baseline.	Presenting as acutely ill or febrile 72 hours prior to or at Screening. Fever is defined as a body temperature ≥38.0°C/100.4°F. pregnant or breastfeeding. History of anaphylaxis, urticaria, or other significant adverse reaction requiring medical intervention after receipt of a vaccine. Bleeding disorder considered a contraindication to intramuscular injection or phlebotomy. Known history of SARS-CoV-2 infection. Prior administration of an investigational coronavirus (SARS-CoV, Middle East Respiratory Syndrome [MERS]-CoV) vaccine Immunosuppressive or immunodeficient state, including human immunodeficiency virus (HIV) infection, asplenia, and recurrent severe infections. Has received systemic immunosuppressants or immune-modifying drugs for >14 days in total within 6 months prior to Screening

Table 6: Summary of Safety and Efficacy Data obtained in Clinical Trials for Vaccines developed for Children and Adolescents

Company	Stage	Description	Safety & Efficacy Results
BioNTech Pfizer Childrens Vaccine (BNT-1262)	Phase 3	Researchers at BioNTech and Pfizer have done testing of their vaccine containing nucleoside-modified mRNA of the SARS-CoV-2 spike glycoprotein in adolescents. The vaccine was proved safe and effective in preventing transmission and serious illness in adults. Despite generally having milder symptoms, children and adolescents who have underlying medical conditions are still at risk for severe symptoms of Covid-19.	Safety- The safety profile of the vaccine in adolescents (12-15 years old) is very similar to that of adults. Local events were reported more than systemic events with severity ranging from mild to moderate. Injection-site pain was the most commonly reported side effect with an incidence of 1.5% (compared to 0 in the placebo group). The most common systemic events reported were headache and fatigue. Fever was reported in 20% of the 12-to-15-year-olds after receiving the second dose. One possibly significant event was a 14-year-old boy who had a fever of 40.4°. The participant did not receive the second dose. Efficacy- In this limited trial, the vaccine was 100% successful in preventing incidence of Covid-19. There were no reported cases of Covid-19 in the trial group 7 days after receiving dose 2 as compared to 16 in the placebo group. Immunologically, the response of adolescents to the vaccine was noninferior to the immune response produced by BNT-1262 in young adults (16-25 years old).
Moderna Childrens Vaccine (mRNA-1273). Moderna Childrens Vaccine (mRNA-1273) (cont'd)	Phase 2-3	In the Coronavirus Efficacy trial, the vaccine was proved safe and effective in adults and is now being evaluated in use for adolescents age 12-17.	Safety- Safety- Solicited local reactions were very common after both the first and the second injection (94.2% and 93.4%, respectively) compared to the placebo group. The most common solicited local reaction was injection-site pain. Grade 3 reactions occurred in 6.8% of patients after the first injection and in 8.9% after the second injection. Systemic reactions were reported in 68.5% of the participants after the first injection and in 86.1% after the second injection. Grade 3 reactions were reported in 4.4% and 13.7% of participants. No cases of myocarditis were reported during this trial as was expected because the rate is estimated to be in the range of 13 per million. Efficacy- The efficacy of the vaccine is difficult to assess based on this trial because of the low incidence of Covid-19 in the trial population. Using the less stringent CDC definition for case incidence, the vaccine

			efficacy in this trial was 93.3% with an onset of 14 days after the second injection. Based on serological testing, this vaccine produces a similar immune response to that of adults.
Sinovac Biotech (CoronaVac)	Phase 1/2	The whole inactivated virus vaccine developed by the Chinese company Sinovac Biotech was previously found to be effective and well-tolerated in adult populations aged 18-59. Children aged 3-17 were given either a half dose (1.5 µg) or a full dose (3.0 µg) depending on weight. Note: A Phase 3 study conducted on CoronaVac has not yet been published	Safety- Of the 550 participants, 146 reported an adverse reaction within 28 days of either dose. Most adverse reactions were mild and moderate in severity. In 2 or 550 participants, a severe adverse reaction was reported. The most common reactions were injection site pain (13%) and fever (5%). Broken down by age, the prevalence of adverse reactions was highest in the 12-17 age group (35%). Efficacy- CoronaVac was found to be immunogenic in children 3-17 years-old. The seroconversion rates of neutralizing antibodies were over 96% after the two dose regimen. The 3.0 µg groups showed a higher geometric mean titer (GMT) than the 1.5 µg groups. Overall, both groups showed a higher GMT than the 18-59 age group which corresponds to the immune responses shown in other vaccines.
Cadila Healthcare (ZyCov-D)	Phase 3	This three-dose needle-free DNA Plasmid Vector vaccine developed by Cadila Healthcare was previously found to be safe and effective in Phase 1 and 2 trials in India. This Phase 3 trial was done on a larger adult population as well as an adolescent population.	Safety- 924 people reported 1243 adverse events over the course of 84 days and three doses. The most common reported local adverse events were pain at the injection site, redness, and swelling. The most common systemic reactions were headache, fever, and muscle pain. Overall, there were no severe vaccine-related events and the vaccine was well-tolerated. Efficacy- The seroconversion rate at day 84 of the trial was higher in the 12-17 ge group than the general population (100% for the 12-17 age group and 93.3% for the general population). Overall, ZyCov-D was found to be 64.9% effective against mild Covid-19 cases and 100% effective against severe and moderate Covid-19 cases. Additionally, during the time at which this trial was being conducted, the main variant in India was the Delta variant. Therefore, researchers concluded that the vaccine is effective against the Delta variant.
NovaVax (NVX CoV2373)	Phase 2/3	October 2022: This study aims to prove the safety and immunogenicity of 2 primary doses and a booster dose given 21 days apart to pediatric patients.	October 2022: This study is expected to be completed in 2025.

respectively.[3-6]

ChAdOx1 nCoV-19 (AZD1222)

A parallel phase I/II, single blind, randomized controlled trial was conducted between April 23 and May 21,2020 to assess the safety, reactogenicity, and immunogenicity profile of recombinant ChAdOx1 nCoV-19 vaccine in a single or two-dose schedule. ChAdOx1 nCOV-19 is a nonreplicating adenoviral vectored vaccine genetically engineered using platform technology to encode the spike peptides that are expressed on the surface of SARS-CoV-2. [3] Also, 1,077 participants were enrolled in the study with 543 participants allocated in the ChAdOx1 nCov-19 arm and 534 participants in the MenACWY vaccine with similar baseline characteristics such as median age of 35 years old, approximately 49.8% females and 50.2% males with majority being white (90.9%). Participants were administered MenACWY vaccine rather than saline to minimize the risk of unblinding since viral vectored vaccines are known to cause systemic reactions.[7]

The primary outcomes of the study were to assess efficacy and safety. However primary endpoints are not addressed in this preliminary report until the follow up period of 6 and 12 months which is still ongoing. Secondary outcomes included safety and reactogenicity at day 7 and 28 days and cellular and humoral. Overall, the study was able to conclude that ChAdOx1 nCOV-19 had a safe, tolerable and immunogenic profile. Safety was measured by adverse reaction outcomes categorized as mild, moderate and severe, and requiring hospitalization. Pain and fatigue were the most reported outcome. 39% of patients reported mild pain in the paracetamol group versus 53% in the non-paracetamol group after first dose of ChAdOx1 nCOV-19. 41% of patients reported mild fatigue in the paracetamol group versus 36% in the non-paracetamol group after first dose of ChAdOx1 nCOV-19. Patients who received the booster dose did not report any moderate pain and fatigue.[9] Two of the ten patients and one of the ten patients enrolled in the booster arm experienced fatigue and pain respectively.[10] One assay called ELISA, analyzed antibodies (ELISA units, EU) against SARS-CoV-2 spike protein peaked by day 28 (157.1 EU [96.2,316.9] and remained elevated until day 56 28 (119 [70.3,203.4], while in the booster arm there was an increase from day 2828 (210.7 [149.4,321.6] to day 56 28 (639.2 [360,792.2] indicating an immune host response that may be correlated with protection against infection.[10]

A later study evaluated the safety and efficacy of the ChAdOx1 nCoV-19 vaccine in a pooled interim analysis of four ongoing blinded, randomized, controlled trials done across the UK, Brazil, and South Africa.[25] Participants aged 18 years and older were randomly assigned (1:1) to ChAdOx1 nCoV-19 vaccine or control (meningococcal group A, C, W, and Y conjugate vaccine or saline). Participants in the ChAdOx1 nCoV-19 group received two doses containing 5 × 1010 viral particles (standard dose; SD/SD cohort); a subset in the UK trial received a half dose as their first dose (low dose) and a standard dose as their second dose (LD/SD cohort). The primary efficacy analysis included symptomatic COVID-19 in seronegative participants with a nucleic acid amplification test-positive swab more than 14 days after a second dose of vaccine. Participants were

analyzed according to treatment received, with data cutoff on Nov 4, 2020.[25] Vaccine efficacy was calculated as 1 - relative risk derived from a robust Poisson regression model adjusted for age.

Overall vaccine efficacy across both groups was 70·4% (95·8% CI 54·8–80·6; 30 [0·5%] of 5807 vs 101 [1·7%] of 5829). From 21 days after the first dose, there were ten cases hospitalised for COVID-19, all in the control arm; two were classified as severe COVID-19, including one death. There were 74 341 person-months of safety follow-up (median 3·4 months, IQR 1·3–4·8): 175 severe adverse events occurred in 168 participants, 84 events in the ChAdOx1 nCoV-19 group and 91 in the control group. ChAdOx1 nCoV-19 has an acceptable safety profile and has been found to be efficacious against symptomatic COVID-19.24 ChAdOx1 nCoV-19 appears to be better tolerated in older adults than in younger adults and has similar immunogenicity across all age groups after a boost dose.[26]

Some limitations of these data [7,10, 25, 26] include the shortened time period of the parallel phase which typically take years to monitor, single-blind design of the trial where investigators are not masked to the treatment intervention, the lack of variability in the patient characteristics. Further trials are now being investigated and assessing the efficacy of the vaccine in older patients who are high risk for infection and individuals with underlying co-morbidities and various ethnic backgrounds. Further assessment of the efficacy of this vaccine is warranted in all age groups and individuals with comorbidities.[25,26]

mRNA-1273

A Phase I, dose-escalation, open label, non-randomized trial8,9 was conducted between March 16 and April 14,2020 to assess the safety and immunogenicity profile of a candidate vaccine, mRNA-1273, that is lipid coated and allows for stabilization of the spike proteins on the coronavirus surface. 45 healthy adults were allocated to three dose groups (n=15): 25 mcg, 100 mcg, and 250 mcg in a dose escalation manner. If a dose limiting safety concern was observed, the dose escalation intervention was halted in the sentinel participants who receive intervention before the rest of the enrollees to reduce risk associated with vaccine.[11] However, no severe adverse event was met according to the trial design prespecified criteria in the sentinel participants and remainder of the cohorts.[10] Baseline characteristics were similar among the three groups, median age was 33 years old, equal female and male distribution, and higher white enrollment compared to other race and ethnic groups.

Primary outcome of the study was safety analysis and secondary outcome was immunogenicity. Safety analyses was measured by local and systemic adverse events graded as mild, moderate or severe. Participants experienced more solicited adverse events that were mainly mild and moderate during the second vaccination compared the first vaccination in all three arms. In the first 25 mcg dose group, 20% and 13.3% of the participants experienced mild and moderate systemic symptoms, respectively. In the first 100 mcg dose group 53.3% and 13.3% of the participants experienced mild and moderate systemic symptoms, respectively. In the first 250 mcg dose group 26.7% and 26.7% of the participants experienced mild and moderate systemic symptoms, respectively.[12] In the second 25 mcg dose group, 30.8% and 23.1% of the participants experienced mild and moderate systemic symptoms, respectively. In the second 100 mcg dose group 20% and 80% of the participants experienced mild and moderate systemic symptoms, respectively. In the second 250 mcg dose group 14.3%, 64.3% and 21.4% of the participants experienced mild, moderate, severe systemic symptoms, respectively. Participants in the highest 250 mcg dose group reported severe symptoms such as fatigue, chills, syncope, and erythema. PsVNA and PRNT assays used to detect vaccine induced neutralizing activity was revealed in all group arms. Participants in the 25 and 100 mcg group had neutralizing activity similar to that of convalescent serum samples but higher neutralizing activity in the 250 mcg group. CD4 T-cell responses were observed and especially Th1 cytokines over Th2 cytokine expression in the 25 and 100 mcg groups. Moreover, CD8 T-cell response was elicited at low level in the 100 mcg dose group after second vaccine schedule. Testing of the humoral response elicited by mRNA-1273 is currently being investigated and phase II and III trials are ongoing to further evaluate efficacy, safety and dosing noted in this preliminary report.[8-12]

Limitations of the study include an open label intervention, small sample size and the unvarying baseline characteristics of the participants. Risk of bias include the contribution to the manuscript drafting by Moderna which is also the codeveloper and provider of the vaccine.

The later studies consist of phase 3 randomized, observer-blinded, placebo-controlled trial was conducted at 99 centers across the United States. [23-24] Persons at high risk for SARS-CoV-2 infection or its complications were randomly assigned in a 1:1 ratio to receive two intramuscular injections of mRNA-1273 (100 μg) or placebo 28 days apart. The primary end point was prevention of Covid-19 illness with onset at least 14 days after the second injection in participants who had not previously been infected with SARS-CoV-2.

The trial enrolled 30,420 volunteers who were randomly assigned in a 1:1 ratio to receive either vaccine or placebo (15,210 participants in each group). More than 96% of participants received both injections, and 2.2% had evidence (serologic, virologic, or both) of SARS-CoV-2 infection at baseline. Symptomatic Covid-19 illness was confirmed in 185 participants in the placebo group (56.5 per 1000 person-years; 95% Confidence Interval (CI), 48.7 to 65.3) and in 11 participants in the mRNA-1273 group (3.3 per 1000 person-years; 95% CI, 1.7 to 6.0); vaccine efficacy was 94.1% (95% CI, 89.3 to 96.8%; P<0.001). Efficacy was similar across key secondary analyses, including assessment 14 days after the first dose, analyses that included participants who had evidence of SARS-CoV-2 infection at baseline, and analyses in participants 65 years of age or older. Severe Covid-19 occurred in 30 participants, with one fatality; all 30 were in the placebo group. Moderate, transient reactogenicity after vaccination occurred more frequently in the mRNA-1273 group. Serious adverse events were rare, and the incidence was similar in the two groups.[23-24]

Key limitations of the data are the short duration of safety and efficacy follow-up. The trial is ongoing, and a follow-up duration of 2 years is planned, with possible changes to the trial design to

allow participant retention and ongoing data collection. Another limitation is the lack of an identified correlate of protection, a critical tool for future bridging studies. As of the data cutoff, 11 cases of Covid-19 had occurred in the mRNA-1273 group, a finding that limits the study's ability to detect a correlate of protection.[23-24,32] However, this may be addressed in the future as cases accrue and immunity wanes, when it may become possible to determine such a correlate.

BNT162b2

Initially, the studies were started with four arms for four different vaccines BNT162a1, BNT162b1, BNT162b2, and BNT162c2 administered using a Prime/Boost (P/B) regimen for determining dose ranging of these vaccines undertaken with dose escalation and de-escalation plus the evaluation of interim dose levels. It also included dose ranging in older participants. The vaccine BNT162c2 was to be administered using a Single Dose (SD) regimen. Three additional cohorts aged from 18 to 85 years was to receive BNT162b2 only.[13]

Later on, based on most promising data obtained for BNT162b2, a multinational, placebo-controlled, observer-blinded, pivotal efficacy trial, where trial participants 16 years of age or older were randomly assigned in a 1:1 ratio to receive two doses, 21 days apart, of either placebo or the BNT162b2 vaccine candidate (30 µg per dose). BNT162b2 is a lipid nanoparticle–formulated, nucleoside-modified RNA vaccine that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein.[14] The primary end points were efficacy of the vaccine against laboratory-confirmed Covid-19 and safety.[20]

A total of 43,548 participants underwent randomization, of whom 43,448 received injections: 21,720 with BNT162b2 and 21,728 with placebo. There were 8 cases of Covid-19 with onset at least 7 days after the second dose among participants assigned to receive BNT162b2 and 162 cases among those assigned to placebo; BNT162b2 was 95% effective in preventing Covid-19 (95% credible interval, 90.3 to 97.6). Similar vaccine efficacy (generally 90 to 100%) was observed across subgroups defined by age, sex, race, ethnicity, baseline body-mass index, and the presence of coexisting conditions. Among 10 cases of severe Covid-19 with onset after the first dose, 9 occurred in placebo recipients and 1 in a BNT162b2 recipient. The safety profile of BNT162b2 was characterized by short-term, mild-to-moderate pain at the injection site, fatigue, and headache. The incidence of serious adverse events was low and was similar in the vaccine and placebo groups.[20,32]

A subgroup of 3813 individuals that had a coexisting condition or history of neoplasm was analyzed within the overall group in order to assess safety and efficacy of the vaccine. Out of the total number of the subgroup, 1902 participants received two doses of BNT162b2, while the rest of 1911 participants received two doses of placebo saline solution. A total of 4 COVID-19 cases was reported among the BNT162b2 recipients and 71 COVID-19 cases among the placebo recipients. Within the subset of individuals with a malignant neoplasm (n=2222), 3 COVID-19 cases were reported in BNT162b2 recipients and 40 COVID-19 cases among placebo recipients, regardless of SARS-CoV-2 infection history. Efficacy in the subgroup was 94.4% (95% CI: 85.2, 98.5) and proved to be consistent with the efficacy reported in the overall group. Adverse events were similar to the overall group and vaccine-related AEs were more frequent among BNT162b2 (IR: 95.4 and 69.4 per 100 person-years exposure, respectively) than placebo recipients (IR: 48.3 and 16.7, respectively). A low number of participants of the subgroup reported severe AEs (IR: 5.6, BNT162b2; 3.6, placebo; per 100 person-years) or serious AEs (IR: 6.7, BNT162b2; 3.6, placebo). One participant reported ventricular arrhythmia on the day of the second dose administration and another experienced lymphadenopathy on day 13 after first dose administration. The participant has also experienced non-serious vaccine-related AEs of chills, injection-site erythema, injection-site pain, and injection-site warmth, and withdrew from the study due to AEs. The case was eventually resolved. A total of 6 BNT162b2 recipients and 4 placebo recipients were withdrawn from the study due to AEs. One death was reported among the BNT162b2 recipients and two among the placebo recipients, but none of the deaths were related to the vaccine. The most common AEs were fatigue, injection-site pain, and pyrexia. AEs were similar in characteristics and magnitude within individuals with all types of neoplasms. Limitations of the study of the subgroup are represented by individuals with a current condition or history of neoplasm undergoing treatment such as systemic immunosuppressants or immune-modifying drugs for >14 days in total within 6 months prior to selection (for corticosteroids ≥10 mg/day of prednisone equivalent) or is expecting the need for immunosuppressive therapy at any time during participation in the study.[42]

Limitations include the fact that with approximately 19,000 participants per group in the subset of participants with a median follow-up time of 2 months after the second dose, the study has more than 83% probability of detecting at least one adverse event, if the true incidence is 0.01%, but it is not large enough to detect less common adverse events reliably. This report includes 2 months of follow-up after the second dose of vaccine for half the trial participants and up to 14 weeks' maximum follow-up for a smaller subset. Therefore, both the occurrence of adverse events more than 2 to 3.5 months after the second dose and more comprehensive information on the duration of protection remain to be determined. Although the study was designed to follow participants for safety and efficacy for 2 years after the second dose, given the high vaccine efficacy, ethical and practical barriers prevent following placebo recipients for 2 years without offering active immunization, once the vaccine is approved by regulators and recommended by public health authorities. Assessment of long-term safety and efficacy for this vaccine will occur, but it cannot be in the context of maintaining a placebo group for the planned follow-up period of 2 years after the second dose. These data do not address whether vaccination prevents asymptomatic infection; a serologic end point that can detect a history of infection regardless of whether symptoms were present (SARS-CoV-2 N-binding antibody) will be reported later.[20] Furthermore, given the high vaccine efficacy and the low number of vaccine breakthrough cases, potential establishment of a correlate of protection has not been feasible at the time of this report.

In another ongoing, placebo-controlled, observer-blinded,

dose-escalation, phase 1 trial conducted in the United States, the investigators randomly assigned healthy adults 18 to 55 years of age and those 65 to 85 years of age to receive either placebo or one of two lipid nanoparticle–formulated, nucleoside-modified RNA vaccine candidates: BNT162b1, which encodes a secreted trimerized SARS-CoV-2 receptor–binding domain; or BNT162b2, which encodes a membrane-anchored SARS-CoV-2 full-length spike, stabilized in the prefusion conformation. 21,22 The primary outcome was safety (e.g., local and systemic reactions and adverse events); immunogenicity was a secondary outcome. Trial groups were defined according to vaccine candidate, age of the participants, and vaccine dose level (10 μg, 20 μg, 30 μg, and 100 μg). In all groups but one, participants received two doses, with a 21-day interval between doses; in one group (100 μg of BNT162b1), participants received one dose.

A total of 195 participants underwent randomization. In each of 13 groups of 15 participants, 12 participants received vaccine and 3 received placebo. BNT162b2 was associated with a lower incidence and severity of systemic reactions than BNT162b1, particularly in older adults. In both younger and older adults, the two vaccine candidates elicited similar dose-dependent SARS-CoV-2–neutralizing geometric mean titers, which were similar to or higher than the geometric mean titer of a panel of SARS-CoV-2 convalescent serum samples. The immune responses elicited by BNT162b1 and BNT162b2 were similar. As has been observed with other vaccines and as is probably associated with immunosenescence,[21,22] the immunogenicity of the two vaccine candidates decreased with age, eliciting lower overall humoral responses in adults 65 to 85 years of age than in those 18 to 55 years of age. Nevertheless, at 7 days and 14 days after the second dose, the 50% and 90% neutralizing GMTs that were elicited by 30 μg of BNT162b2 in older adults exceeded those of the convalescent serum panel. Antibody responses in both younger and older adults showed a clear benefit of a second dose.

The limitations include lack of full characterization of the relative importance of humoral and cellular immunity with regard to protection from Covid-19. Although strong cell-mediated immune responses (Th1-biased CD4+ and CD8+) elicited by BNT162b1 have been observed and reported in the German trial 2 the cellular immune responses elicited by BNT162b2 are still being studied. Second, although the serum neutralizing responses that were elicited by the vaccine candidates relative to those elicited by natural infection are highly encouraging, the degree of protection against Covid-19 provided by this or any other benchmark is unknown. Third, the phase 1 portion of this trial tested many hypotheses and was not powered to make formal statistical comparisons. Fourth, the human convalescent serum panels that have been used by different vaccine developers are not standardized among laboratories, and each represents a unique distribution of donor characteristics and times of collection. Therefore, the serum panel that we used does not provide a well-controlled benchmark for comparisons of the serologic responses elicited by these two BNT162 vaccine candidates with those elicited by other Covid-19 vaccine candidates. Finally, the participants in this early-stage clinical trial were healthy and had limited racial and ethnic diversity as compared with the general population.20-22 Many of the limitations cited above are being addressed in the international, phase 2–3 portion of this trial as summarized in the following study.

Ad26.COV2.S

In this multicenter, placebo-controlled, phase 1–2a trial, studying the vaccine candidate Ad26.COV2.S, a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector encoding a full-length and stabilized SARS-CoV-2 spike protein, healthy adults between the ages of 18 and 55 years (cohort 1) and those 65 years of age or older (cohort 3) were randomly assigned to receive the Ad26.COV2.S vaccine at a dose of 5×1010 viral particles (low dose) or 1×1011 viral particles (high dose) per milliliter or placebo in a single-dose or two-dose schedule. Longer-term data comparing a single-dose regimen with a two-dose regimen are being collected in cohort [2]; those results are not reported here. The primary end points were the safety and reactogenicity of each dose schedule. We randomly assigned healthy adults between the ages of 18 and 55 years (cohort 1) and those 65 years of age or older (cohort 3) to receive the Ad26.COV2.S vaccine at a dose of 5×1010 viral particles (low dose) or 1×1011 viral particles (high dose) per milliliter or placebo in a single-dose or two-dose schedule.[27] Longer-term data comparing a single-dose regimen with a two-dose regimen are being collected in cohort.[2] The primary end points were the safety and reactogenicity of each dose schedule.

After the administration of the first vaccine dose in 805 participants in cohorts 1 and 3 and after the second dose in cohort [1], the most frequent solicited adverse events were fatigue, headache, myalgia, and injection-site pain. The most frequent systemic adverse event was fever. Systemic adverse events were less common in cohort 3 than in cohort 1 and in those who received the low vaccine dose than in those who received the high dose. Reactogenicity was lower after the second dose. Neutralizing-antibody titers against wild-type virus were detected in 90% or more of all participants on day 29 after the first vaccine dose (Geometric Mean Titer [GMT], 224 to 354), regardless of vaccine dose or age group, and reached 100% by day 57 with a further increase in titers (GMT, 288 to 488) in cohort 1a. Titers remained stable until at least day 71. A second dose provided an increase in the titer by a factor of 2.6 to 2.9 (GMT, 827 to 1266). Spike-binding antibody responses were similar to neutralizing-antibody responses. On day 15, CD4+ T-cell responses were detected in 76 to 83% of the participants in cohort 1 and in 60 to 67% of those in cohort 3, with a clear skewing toward type 1 helper T cells. CD8+ T-cell responses were robust overall but lower in cohort 3. Although all ongoing phase 3 studies of other Covid-19 vaccines have assessed two-dose schedules, a single dose of Ad26.COV2.S elicited a strong humoral response in a majority of vaccine recipients, with the presence of S-binding and neutralizing antibodies in more than 90% of the participants, regardless of either age group or vaccine dose. In addition, during 71 days of follow-up after the first dose, antibody titers further increased and stabilized, which suggests durability of the Ad26.COV2.S-elicited immune response.[27] In this regard, it is important to note that an efficacious single-dose Covid-19 vaccine has obvious logistic advantages over a two-

dose vaccine, especially during a pandemic.

(Ad5-nCoV)

Initially, a Phase I, dose-escalating, single center, non-randomized trial was conducted between March 16 and March 27,2020 to assess the safety and immunogenicity profile of a non-replicating Ad5 vectored COVID-19 vaccine, that encodes for the spike protein expressed on SARS-CoV-2 surface.108 participants were allocated to three groups; low dose (5x1010), medium dose (1x1010) and high dose (1.5x1011) group in a dose escalating manner. There was no dose limiting safety concern observed, and the dose escalation intervention was not halted according to prespecified criteria.[15] Baseline characteristics were similar across the groups including pre-existing Ad5 neutralizing antibody titers.

Primary outcome of adverse events within the first 7 days after vaccination was not significant across the low, medium, and high dose groups.[16] The most commonly reported systemic adverse event was fever and muscle pain. 42%,42% and 56% of participants reported fever in the low, medium, and high dose group, respectively. 14% of the participants in the high dose group presented with grade 3 fever compared to 6% and 6% in the low and medium dose group, respectively. Secondary outcomes of adverse reactions with 28 days were not reported. T-cell responses peaked at day 14 after vaccination and statistically insignificant (p value 0.77) four-fold increase in neutralizing antibodies at day 28 in the low (97%), medium (94%) and high dose (100%) group.[15,19]

Limitations of study include a non-randomized design, small sample size and short duration of trial.[15] Six months follow up of the participants is planned to be evaluated and a larger trial of older patients is ongoing to assess candidate vaccine immunogenicity and efficacy.

A later randomized, double-blind, placebo-controlled, phase 2 trial of the Ad5-vectored COVID-19 vaccine was done in a single center in Wuhan, China, aiming to determine an appropriate dose of the candidate vaccine for an efficacy study. [19] Healthy adults aged 18 years or older, who were HIV-negative and previous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection-free, were eligible to participate and were randomly assigned to receive the vaccine at a dose of 1 × 1011 viral particles per mL or 5 × 1010 viral particles per mL, or placebo. Investigators allocated participants at a ratio of 2:1:1 to receive a single injection intramuscularly in the arm. The primary endpoints for immunogenicity were the Geometric Mean Titers (GMTs) of specific ELISA antibody responses to the Receptor Binding Domain (RBD) and neutralizing antibody responses at day 28.

Both doses of the vaccine induced significant neutralizing antibody responses to live SARS-CoV-2, with GMTs of 19·5 (95% CI 16·8–22·7) and 18·3 (14·4–23·3) in participants receiving 1 × 1011 and 5 × 1010 viral particles, respectively. Specific interferon γ enzyme-linked immunospot assay responses post vaccination were observed in 227 (90%, 95% CI 85–93) of 253 and 113 (88%, 81–92) of 129 participants in the 1 × 1011 and 5 × 1010 viral particles dose groups, respectively. Solicited adverse reactions were reported by 183 (72%) of 253 and 96 (74%) of 129 participants in the 1 × 1011 and 5 × 1010 viral particles dose groups, respectively. Severe adverse reactions were reported by 24 (9%) participants in the 1 × 1011 viral particles dose group and one (1%) participant in the 5 × 1010 viral particles dose group.[19]

Overall, both studies showed that the Ad5-vectored COVID-19 vaccine at 5 × 1010 viral particles is safe and induced significant immune responses in the majority of recipients after a single immunization.[15,19]

The results of these COVID-19 vaccine candidates in phase I/II trials have been shown to elicit levels of NAbs being equal to or higher than those observed in convalescent patients, and cellular immune responses.[7,9,13,15,19-31] However, the results are difficult to compare due to different assays and readouts were used.[23] Excitingly, the preliminary analysis demonstrated the efficacy of COVID-19 vaccine candidates, ranging from 70% to 95%.[21,24,25,27,32] The promising results will contribute to identify COVID-19 correlates of protection on the basis of data collected from phase III efficacy trials.

New Variants

In recent months, a number of notable SARS-CoV-2 variants have been identified. In the United Kingdom (UK), SARS-CoV-2 (known as 20I/501Y.V1, VOC 202012/01, or B.1.1.7) was first isolated and has now been detected in numerous countries globally.[28,29] This N501Y variant possesses a mutation in the Receptor Binding Domain (RBD) of the spike protein at position 501, where the amino acid asparagine (N) has been replaced with tyrosine (Y) and is associated with increased transmissibility.[33-36] This variant has several other mutations, including a 69/70 deletion and the P681H near the S1/S2 furin cleavage site.[34-36] Early reports found no evidence to suggest that the variant has any impact on the severity of disease or vaccine efficacy.[33-36] However, in early 2021, UK scientists reported evidence suggesting the B.1.1.7 variant may be associated with an increased risk of death.[33]

In South Africa, another variant of SARS-CoV-2 (known as 20H/501Y.V2 or B.1.351) emerged independently of B.1.1.7 but shares similar mutations. Like N501Y, this variant has been detected in multiple countries. The variant has various mutations in the spike protein, including K417N, E484K, N501Y. Yet, unlike the B.1.1.7 lineage, this variant does not contain the deletion at 69/70.[33-36] Currently there is no evidence to suggest that this variant has any impact on disease severity. Nevertheless, there is some evidence to indicate that one of the spike protein mutations, E484K, may affect neutralization by some polyclonal and monoclonal antibodies. [36-37]

In Brazil, a variant of SARS-CoV-2 (known as P.1) emerged with 17 unique mutations, including three in the receptor binding domain of the spike protein K417T, E484K, and N501Y. There is evidence to suggest that some of the mutations in the P.1 variant may affect its transmissibility and antigenic profile, which may affect the ability of antibodies generated through a previous natural infection or through vaccination to recognize and neutralize the virus.[33-38]

Both vaccination and natural infection with SARS-CoV-2

produce a polyclonal response that targets several components of the spike protein.[37] Most experts believe the virus will likely need to accumulate multiple mutations in the spike protein to evade immunity induced by vaccines or by natural infection and accelerate emergence of such variants.[36-37] South Africa, nonetheless, ceased using Astra Zeneca's vaccine against the B.1.351 variant on February 7, 2021.

Since November 2020, the Centers of Disease Control (CDC) has been contracting with large national reference labs to provide sequence data from across the United States. In addition, public health agencies have been regularly sending SARS-CoV-2 samples to the CDC for sequencing and further characterization. [36-37]

SARS-Cov 2 Variants and Vaccine Effectiveness

The recent emergence of the new and highly transmissible SARS-CoV-2 variants with mutations in the S gene, found in the United Kingdom (the B.1.1.7 lineage) and in South Africa (the B.1.351 lineage) and are spreading globally, has led to concerns about increased transmission and the potential of these variants to circumvent immunity elicited by natural infection or vaccination.

Moderna mRNA-1273

Wu et al[34] used an recombinant vesicular stomatitis virus (rVSV)–based SARS-CoV-2 (a pseudovirus-based model) neutralization assay to assess the neutralizing activity of serum obtained from participants who had received the mRNA-1273 vaccine in the phase 1 trial against the full-length spike protein of the original Wuhan-Hu-1 isolate, the dominant strain in 2020 (D614G variant), the B.1.1.7 and B.1.351 variants, and other variants (20E [EU1], 20A.EU2, N439K D614G, and the mink cluster [5] variant that was first identified in Denmark). They observed levels of neutralization against these variants that were similar to those against the Wuhan-Hu-1 (D614) isolate, but the protection against the B.1.351 variant conferred by the mRNA-1273 vaccine remains to be determined. Their findings underscore the importance of continued viral surveillance and evaluation of vaccine efficacy against new viral variants.[39]

Moderna mRNA-1273.214

Chalkias et al.[40,41] have studied the immunogenicity and safety of the bivalent vaccine mRNA-1273.214 against the omicron variant compared to the initial mRNA-1273 vamRNA-1273, both administered as a second booster regimen. To study the efficacy of the mRNA-1273.214 booster, 377 individuals received a second booster dose of 50-µg mRNA-1273, while 437 individuals received a second booster dose of 50-µg mRNA-1273.214 consisting of two mRNAs,1:1 ratio, 25 µg each, encoding the prefusion-stabilized spike glycoproteins of ancestral SARS-CoV-2 and the omicron variant (BA.1). Most common local AEs after administration of both boosters was injection-site pain, and the most frequent reactions were fatigue, myalgia, and arthralgia in both groups. The majority of grade and grade 2 AEs were mild to moderate for both doses. Grade 3 events were similar in mRNA-1273.214 and mRNA-1273 groups, and the most common such events were fatigue and myalgia, while no grade 4 events occurred in either group. Overall, incidences of AEs were reported to be 5.7% and 5.8% respectively. No fatal events or AEs leading to study discontinuation were reported. GMTs against ancestral SARS-CoV-2 (D614G) were 5977.3 (95% CI, 5321.9 to 6713.3) and 5649.3 (95% CI, 5056.8 to 6311.2) and against omicron were 2372.4 (95% CI, 2070.6 to 2718.2) and 1473.5 (95% CI, 1270.8 to 1708.4) 28 days after the mRNA-1273.214 and mRNA-1273 boosters, respectively. [40-42]

Pfizer-BioNTech BNT162b2

Liu et al., analyzed effects on neutralization elicited by BNT162b2, using engineered S mutations from the B.1.351 lineage into USA-WA1/2020, a relatively early isolate of the virus (in January 2020), subsequently producing three recombinant viruses. The first had an N-terminal domain deletion and the globally dominant D614G substitution (Δ242-244+D614G),[2,3] the second had mutations affecting three amino acids at the receptor-binding site (K417N, E484K, and N501Y) and a D614G substitution (B.1.351-RBD+D614G), and the third had all the mutations found in the S gene in the B.1.351 lineage (B.1.351-spike). All the mutant viruses yielded infectious titers exceeding 107 plaque-forming units per milliliter. The B.1.351-spike virus formed plaques that were smaller than those of the other viruses.

To study the ability of BNT162b2 to neutralize these recombinant mutants, they performed 50% Plaque Reduction Neutralization Testing (PRNT50) using 20 serum samples that had been obtained from 15 participants in the pivotal trial, 2 or 4 weeks after the administration of boost immunization with 30 µg of BNT162b2 (which occurred 3 weeks after the first immunization). All the serum samples neutralized USA-WA1/2020 and all mutant viruses at titers of 1:40 or greater. As compared with neutralization of USA-WA1/2020, neutralization of Δ242-244+D614G virus was similar, and neutralization of the B.1.351-spike virus was weaker by approximately two thirds. These results are also consistent with poorer neutralization of the virus with the full set of B.1.351-spike mutations than virus with either subset of mutations and suggested that virus with mutant residues in the receptor-binding site (K417N, E484K, and N501Y) is more poorly neutralized than virus with Δ242-244, which is located in the N-terminal domain of the spike protein. Thus, it is unclear what effect a reduction in neutralization by approximately two thirds would have on BNT162b2-elicited protection from Covid-19 caused by the B.1.351 lineage of SARS-CoV-2.[40-42]

COVID-19 Disease and Transmission in Children and Adolescents

Children and adolescents usually demonstrate fewer and milder symptoms of SARS-CoV-2 infection compared to adults and are less likely than adults to experience severe COVID-19.[43-45] An age-dependent risk of severe disease with those under one year of age experiencing more severe disease has been suggested44,45, although several reviews show that neonates (infants in the first 28 days of life) have mild disease when compared with other pediatric patients.[46,47] It is important to note that children under the age of five years have a higher risk of other diseases with clinical presentations that overlap with

COVID-19, such as pneumonia and other viral upper respiratory tract infections, which may lead to misclassification. Children and adolescents can experience prolonged clinical symptoms (known as "long COVID-19", post COVID-19 condition[48], or post-acute sequelae of SARS-CoV-2 infection), however, the frequency and characteristics of these conditions are still under investigation. Additionally, a hyperinflammatory syndrome, referred to as pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in Europe and multisystem inflammatory syndrome in children (MIS-C) in the United States, although rare, has been reported to occur world-wide and complicate recovery from COVID-19.[49] Several risk factors for severe COVID-19 in children have been reported recently, including older age, obesity, and preexisting conditions. The preexisting conditions associated with higher risk of severe COVID-19 include type 2 diabetes, asthma, heart, and pulmonary diseases, and neurologic, neurodevelopmental (in particular, Down Syndrome) and neuromuscular conditions. [50] The preponderance of evidence on the risk for severe COVID-19 and death in children and adolescents comes from studies in high resource settings, so the applicability of the following observations to lower resource settings remains to be determined.

Multiple population-based SARS-CoV-2 seroprevalence and viral shedding studies have investigated whether children and adolescents are infected at the same rate as adults, but the results have been mixed, possibly because of the studies being conducted at different time points in the pandemic when populations were subjected to different public health and social measures (PHSM).[51] Overall, it appeared that whether schools were open or closed, infection rates in children and adults were similar. Thus, it appears that children of all ages can become infected and can spread the virus to others. Amongst individuals positive for SARS-CoV-2 who were tested at the same time point after symptom onset, levels of SARS-CoV-2 viral RNA shedding in the respiratory tract appeared similar in children, adolescents, and adults.[52] The relationship between age, viral load, and transmission across the full symptom spectrum of SARS-CoV-2 infection has not been comprehensively investigated because people with no, or mild symptoms are seldom tested systematically. The relative transmissibility of SARS-CoV-2 at different ages remains uncertain, largely due to the challenges involved in disentangling the influences of biological, host, virus, variants of concern, and environmental factors.[53]

COVID-19 Vaccination for Children and Adolescents

Although the majority of COVID-19 vaccines are approved for use in adults aged 18 years an older, an increasing number of vaccines are now authorized for use in adolescents and children. Some countries have even expanded emergency use authorization for mRNA vaccines in the pediatric population as well. NT162b2 developed by Pfizer, and mRNA 1273 developed by Moderna. In November 2021, one stringent regulatory authority approved the mRNA vaccine BNT162b2 for the use in children aged 5-11. Both Pfizer –BioNTech and Moderna's immunization schedule includes individuals 6 months and older; Novavax and Johnson & Johnson's Janssen (J&J/Janssen) for persons at least 12 and 18 years respectively.1 Trials in children as young as age 3 years were completed for two inactivated vaccines (Sinovac-CoronaVac and BBIBP-CorV) and these products were approved by Chinese authorities for the age indication of 3-17 years; although these vaccine products have received EUL for adults, they have not yet received WHO EUL for children. Covaxin, an adjuvanted inactivated vaccine developed by Bharat, was approved in India for the age indication of 12-17 years; but not yet received WHO EUL for this age indication. The Indian regulatory authorities have given approval to ZycovD, a novel DNA vaccine, for ages 12-17 years; however, this vaccine has not yet received WHO EUL. Several COVID-19 vaccines are undergoing trials in younger age groups (including as young as 6 months of age), but results have not yet been published. [1-2]

In Phase 2/3 trials for both mRNA vaccines, efficacy and immunogenicity were similar or higher compared to adults; safety and reactogenicity profiles in adolescents were similar to young adults. A very rare signal of myocarditis/pericarditis has been reported with mRNA COVID-19 vaccines as some countries have started to use these vaccines in their COVID-19 programs. These cases occurred more often in younger men (16-24 years of age) and after the second dose of the vaccine, typically within a few days after vaccination. As the mRNA vaccines are just being rolled out in adolescents in some countries, the risk of myocarditis in that age group has not yet been fully determined. Available data suggest that the cases of myocarditis and pericarditis following vaccination are generally mild and respond to conservative treatment and are less severe with better outcomes than classical myocarditis or COVID-19. The risk of myocarditis/pericarditis associated with SARS-CoV-2 infection is higher than the risk after vaccination.[54-56] In October 2021, the Global Advisory Committee on Vaccine Safety (GACVS) concluded that in all age groups the benefits of mRNA COVID-19 vaccines in reducing hospitalizations and deaths due to COVID-19 outweigh the risks. The risk of Thrombosis with Thrombocytopenia Syndrome (TTS) following adenoviral-vector vaccines, although overall low, was higher in younger adults compared to older adults, but no data are available on the risk below the age of 18 years.[32]

Conclusion

Efficacious vaccines are urgently needed to contain the ongoing Coronavirus Disease 2019 (Covid-19) pandemic of infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Candidate vaccines such as mRNA based BNT162b2 vaccine and mRNA-1273 vaccine; Adenovirus-vectored ChAdOx1 nCoV-19 vaccine, (also known as AZD1222), Non-replicating recombinant adenoviral Gamaleya Center/ Sputnik V, Ad5-nCoV and Ad26.COV2.S Covid-1927 as well as inactivated virus based CoronaVac, BBIBP-CorV vaccines in clinical trials with preliminary reports have demonstrated disadvantages and advantages in terms of their reactogenicity and immunogenicity profiles. Out of these the first 3 have also received Emergency use Authorization in the US, UK and other countries in the world based on promising short-term safety and efficacy data. In addition, there are other vaccines that have been developed in China (CoronaVac, BBIBP-CorV) and Russia

(Sputnik V), that some internationally accessible published data, but nonetheless approved for emergency use in other countries like China, Russia, UAE, Egypt, Bahrain, India, Argentina, Dominican Republic, El Salvador, Mexico, and Morocco. But the lack of standards and use of different assays complicate the comparison of performance of the various Covid-19 vaccines that are currently in development. The potential of these and other candidate vaccines to protect against SARS-CoV-2 is still yet to be determined and assessed in ongoing clinical trials. Evaluation of the vaccine efficacy based on efficacy trials capturing clinical disease and/or infection as endpoints is the most direct approach to show the protection of vaccine candidate. However, phase 3 efficacy trials are very costly and time-consuming, which involve more than thousands of individuals in risk of SARS-CoV-2 exposure in order to provide enough power to show the protective efficacy of vaccine over the placebo. In addition, in the settings of available Covid-19 vaccines approved for emergency use or licensed, a question of ethics to design a randomized placebo-controlled trials for assessing the efficacy of sequent vaccine candidates is expected to arise.

Because hundreds of millions of people in some priority groups will eventually be vaccinated against Covid-19, the world needs highly reliable evidence of vaccine safety that can be straightforwardly and convincingly explained to the public. Indeed, the ultimate impact of Covid-19 vaccines in a population may depend more on the prevalence of hesitancy or strong disinclination to receive a Covid-19 vaccine than on whether the vaccine has 95%, 80%, or 70% efficacy. Current phase 3 studies typically provide controlled data on about 20,000 vaccine recipients and 20,000 placebo recipients. Although these numbers should suffice for detecting relatively common adverse events, there is a risk of missing or exaggerating less common but clinically important events. Because large numbers of people will rapidly be vaccinated, vaccination will inevitably seem to be temporally associated with some uncommon adverse events. A large, simple trial18 to evaluate serious safety outcomes, in which many participants (even hundreds of thousands) are randomly assigned to vaccine or placebo and those who receive placebo are vaccinated only about 2 months later could identify any rare but serious short-term side effects or show that there were none. Such a trial could be conducted either during a period of emergency use or immediately after licensure and could be viewed as a fair way of allocating initially limited vaccine supplies.

There are now already 8 vaccines that are either approved or authorized for emergency use for protection against Covid-19 that are being administered in various countries as well as other promising vaccines that are candidates for approval in the near future, including live viruses, recombinant protein subunits, and nucleic acids that may ultimately offer promise as preventive vaccines against COVID-19. However, each of these vaccines may require additional manufacturing steps and formal toxicology testing before submitting a regulatory package to national regulatory agencies and be able to commence the clinical development, first with phase 1 clinical trials for safety and immunogenicity, and later, phase 2 and phase 3 trials for both safety and efficacy. Additional vaccines with worthwhile efficacy would still be desirable, especially if they could be readily deployed on a large scale or if safety concerns emerge with the first vaccines. For example, a 70% effective single-dose vaccine may be more valuable than a two-dose regimen with 90% efficacy and greater implementation challenges. Important gaps in our knowledge of the vaccines can be addressed with continued follow-up of placebo recipients in phase 3 trials, use of placebo controls in large, simple safety trials, and clinical data from placebo-controlled, randomized trials evaluating new vaccines. A concerted global effort to collect such data while it's still possible would increase the likelihood of reliably identifying multiple vaccines with favorable benefit–risk profiles. These studies would go far toward earning the broad public confidence required for widespread vaccine acceptance in order to bring this pandemic to an end.

There are benefits of vaccinating children and adolescents that go beyond the direct health benefits. Vaccination that decreases COVID transmission in this age group may reduce transmission from children and adolescents to older adults and may help reduce the need for mitigation measures in schools. Minimizing disruptions to education for children and maintenance of their overall well-being, health and safety are important considerations. Countries' strategies related to COVID-19 control should facilitate children's participation in education and other aspects of social life, and minimize school closures, even without vaccinating children and adolescents. UNICEF and WHO have developed guidance on how to minimize transmission in schools and keep schools open, regardless of vaccination of school-aged children. Given current global inequity in vaccine access, the decision to vaccinate adolescents and children must account for prioritization to fully protect the highest risk subgroups through primary vaccination series, and as vaccine effectiveness declines with time since vaccination, through booster doses. As such, before considering implementing primary vaccination series in adolescents and children, attaining high coverage of primary series - and booster doses as needed based on evidence of waning and optimizing vaccination impact - in highest risk subgroups, such as older adults, must be considered.

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