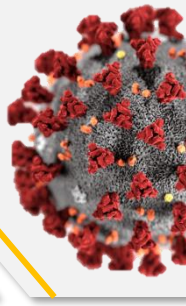
COVID-19 CANDIDATE VACCINES (UPDATE)

Based on available evidence up to 15 February 2021



INTRODUCTION

COVID-19 is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) which responsible for the outbreak began in Wuhan, China, in December 2019 and progressively became pandemic affecting more than 120 countries globally.[1] As of 15 February 2020, confirmed cases of COVID-19 accumulated to 108 million people worldwide, with confirmed death cases of 2,381,295 people.[2]

SARS-CoV-2 is highly transmissible and pathogenic virus and bats are considered as the natural hosts.[3] The virus mainly infect lower respiratory tract and can cause severe pneumonia, which leads to fatal acute lung injury and acute respiratory distress syndrome, resulting in high morbidity and mortality. Currently, the efforts to prevent the spread of COVID-19 is by primary intervention which include physical distancing, practicing proper hand hygiene and routine cleaning of high-touched surfaces with disinfectants.

The sudden emergence and rapid spread of SARS-CoV-2 virus does not only endanger life but has disrupted the social and economic equilibrium, therefore the development of vaccine is urgently needed as an effort to fight against COVID-19. On 22 October 2020, the U.S. Food and Drug Administration approved the antiviral drug Veklury (remdesivir) for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms (about 88 pounds) for the treatment of COVID-19 requiring hospitalization.[4] The aim of vaccines is to induce neutralising antibodies and there could be an advantage of inducing cytotoxic T-lymphocytes.[5] These neutralising antibodies will be targeting S1 receptor-binding-domain (RBD), S1 N-terminal domain, or the S2 region; these antibodies block binding of the RBD to the ACE2 receptor and prevent S2-mediated membrane fusion or entry into the host cell, thus inhibiting viral infection.[6]

Structurally, there are several targets for vaccination on the surface of SARS-CoV-2 which includes the envelope spike protein S, the small envelope protein E, the matrix protein M and the unexposed nucleocapsid protein N.[7] However, the spike protein is the antigen of choice for the vaccine due to its association with strong (neutralizing) antibody response proven pre-clinically against Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV).[5, 7] Since the SARS-CoV-2 virus shares striking structural similarity and sequence conservation with these two lethal coronaviruses, the immunisation strategies exploited against SARS and MERS viruses have been adopted in guiding the design of new SARS-CoV-2 vaccines.[7]

Researchers are currently testing 69 vaccines in clinical trials on humans, and 20 have reached the

final stages of testing. At least 89 preclinical vaccines are under active investigation in animals.[8] The candidate vaccines were developed based on one of the following technology platform:[5, 9]

- Virus: live-attenuated or inactivated viral vaccine
- Viral vector: replicating or non-replicating viral vector vaccine
- Nucleic acid: DNA or RNA vaccine
- Protein-based: protein subunit or virus-like particles vaccine

Live attenuated vaccines (LAV) or weakened vaccine employ viruses that are conventionally weakened or rendered replication-incompetent through different passages in culture that make it mutated and less able to cause diseases. Whereas, inactivated vaccines employ pathogens which have been killed throughout exposure to chemicals and heat to make it non-infectious. Many existing vaccines are made in this way, such as those against measles and polio, but they require extensive safety testing.

Viral vector protein vaccine uses other virus such as measles or adenovirus which is genetically engineered[10] so that it can produces coronavirus proteins in the body. There are two types of viral-vector vaccines; those that can still replicate within cells and those that cannot because key genes have been disabled. The replicating viral vector vaccine replicates within cells and provokes a strong immune response. However, existing immunity to the vector could blunt the vaccine's effectiveness. The non-replicating viral vector vaccines might need booster shots to induce long-lasting immunity.[9] There was concern that the use of an Ad5 vector for immunisation against SARS-CoV-2 infection could increase the risk of HIV-1 acquisition among men based on a few studies on Ad5 vector-based vaccines developed against HIV-infection.[11]

Nucleic-acid vaccines use genetic instructions in the form of deoxyribonucleic acid (DNA) or ribonucleic acid (RNA). The nucleic acid which encodes the virus spike protein is inserted into human cells, which then churn out copies of the virus protein to induce immune responses. Nucleic-acid vaccines are theoretically safe and easy to develop which involves making genetic materials only, not the virus. However, there are no licensed vaccines using this technology.[9]

Protein subunit vaccines are produced in vitro by employing antigenic proteins (virus' spike protein or a key part of it called the receptor binding domain) that induce a protective immune response.[9, 10] These vaccines might require multiple doses to make it work and might require adjuvants which is immune-stimulating molecules delivered with the vaccine.

Sixty-nine candidate vaccines are being evaluated clinically with 20 of the products have passed to phase III clinical trials.[12] As to date, only four vaccines have received emergency approval for usage.[8]

Table 1: WHO List of candidate vaccines with its on-going clinical trials.[12]

No	Name	Developer	Vaccine Platform	Clinical Stage
1.	ChAdOx1-S	University of Oxford/AstraZeneca	Non-Replicating Viral Vector	Phase 3 ISRCTN89951424
2.	Coronavac	Sinovac	Inactivated	Phase 3 NCT04456595
3.	Inactivated vaccine	Sinopharm/Wuhan	Inactivated	Phase 3 ChiCTR2000034780
4.	Inactivated vaccine	Sinopharm/Beijing	Inactivated	Phase 3 ChiCTR2000034780

5.	mRNA-1273	Moderna	mRNA	Phase 3 NCT04470427
6.	BNT162 (BNT162b1 & BNT162b2)	BioNTech/Pfizer/Fosun Pharma	mRNA	Phase 3 NCT04368728
7.	Ad5-nCOV	CanSino Biologic	Non-Replicating Viral Vector	Phase 3 NCT04540419
8.	Sputnik V	Gamaleya Research Institute	Non-Replicating Viral Vector	Phase 3 NCT04564716
9.	NVX-CoV2373	Novavax	Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M	Phase 3 2020-004123-16
10.	Ad26COVS1	Janssen Pharmaceutical Companies	Non-Replicating Viral Vector	Phase 3 NCT04505722
11.	Adjuvanted recombinant protein	Anhui Zhifei Longcom Biopharmaceutical/Institute of Microbiology, Chinese Academy of Sciences	Adjuvanted recombinant protein (RBD-Dimer)	Phase 2 NCT04466085
12.	mRNA	Curevac	mRNA	Phase 2 NCT04515147
13.	DNA plasmid vaccine + Adjuvant	Osaka University/ AnGes/ Takara Bio	DNA plasmid vaccine + Adjuvant	Phase 1 / 2 NCT04463472
14.	DNA plasmid vaccine	Cadila Healthcare Limited	DNA plasmid vaccine	Phase 1 / 2 CTRI/2020/07/026352
15.	DNA Vaccine (GX-19)	Genexine Consortium	DNA Vaccine (GX-19)	Phase 1 / 2 NCT04445389
16.	Whole-Virion Inactivated	Bharat Biotech	Whole-Virion Inactivated	Phase 1 / 2 NCT04471519
17.	INO-4700	Inovio Pharmaceuticals/ International Vaccine Institute	DNA plasmid vaccine with electroporation	Phase 1 / 2 NCT04447781
18.	RBD-based	Kentucky Bioprocessing, Inc	RBD-based	Phase 1 / 2 NCT04473690
19.	mRNA	Arcturus/Duke-NUS	mRNA	Phase 1 / 2 NCT04480957
20.	Inactivated	Research Institute for Biological Safety Problems, Rep of Kazakhstan	Inactivated	Phase 1 / 2 NCT04530357
21.	CovidVax	Institute of Medical Biology, Chinese Academy of Medical Sciences	Inactivated	Phase 1 / 2 NCT04470609
22.	S protein (baculovirus	Sanofi Pasteur/GSK	Protein Subunit	Phase 1 / 2 NCT04537208

	production)			
23.	RBD-HBsAg VLPs	SpyBiotech/Serum Institute of India	VLP	Phase 1 / 2 ACTRN12620000817943
24.	Protein Subunit	Clover Biopharmaceuticals Inc./GSK/Dynavax	Native like Trimeric subunit Spike Protein vaccine	Phase 1 NCT04405908
25.	Protein Subunit	Vaxine Pty Ltd/Medytox	Recombinant spike protein with Advax™ adjuvant	Phase 1 NCT04453852
26.	Protein Subunit	University of Queensland/CSL/Seqirus	Molecular clamp stabilized Spike protein with MF59 adjuvant	Phase 1 ACTRN12620000674932p ISRCTN51232965
27.	Measles-vector based	Institute Pasteur/Themis/Univ. of Pittsburg CVR/Merck Sharp & Dohme	Replicating Viral Vector	Phase 1 NCT04497298
28.	LNP-nCoVsaRNA	Imperial College London	mRNA	Phase 1 ISRCTN17072692
29.	mRNA	People's Liberation Army (PLA) Academy of Military Sciences/Walvax Biotech.	mRNA	Phase 1 ChiCTR2000034112
30.	VLP	Medicago Inc.	Plant-derived VLP adjuvanted with GSK or Dynavax adjs.	Phase 1 NCT04450004
31.	S-2P protein + CpG 1018	Medigen Vaccine Biologics Corporation/NIAID/Dynavax	Protein subunit	Phase 1 NCT04487210
32.	Replication defective Simian Adenovirus (GRAd) encoding S	ReiThera/LEUKOCARE/Univercells	Non-Replicating Viral Vector	Phase 1 NCT04528641
33.	Ad5-nCoV	Institute of Biotechnology, Academy of Military Medical Sciences, PLA of China	Non-Replicating Viral Vector	Phase 1 NCT04552366
34.	Ad5 adjuvanted Oral Vaccine platform	Vaxart	Non-Replicating Viral Vector	Phase 1 NCT04563702
35.	MVA-SARS-2-S	Ludwig-Maximilians - University of Munich	Non-Replicating Viral Vector	Phase 1 NCT04569383
36.	RBD + Adjuvant	Instituto Finlay de Vacunas, Cuba	Protein Subunit	Phase 1 IFV/COR/04
37.	Peptide	FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo	Protein Subunit	Phase 1 NCT04527575

38.	RBD (baculovirus production expressed in Sf9 cells)	West China Hospital, Sichuan University	Protein Subunit	Phase 1 ChiCTR2000037518
39.	SARS-CoV-2 HLA-DR peptides	University Hospital Tuebingen	Protein Subunit	Phase 1 NCT04546841
40.	S1-RBD-protein	COVAXX	Protein Subunit	Phase 1 NCT04545749
41.	Intranasal flu-based-RBD	Beijing Wantai Biological Pharmacy/ Xiamen University	Replicating Viral Vector	Phase 1 ChiCTR2000037782

EVIDENCE ON EFFECTIVENESS AND SAFETY

There were 16 articles retrieved from the scientific databases such as Medline, EBM Reviews, EMBASE via OVID, PubMed and from the general search engines [Google Scholar and US Food and Drug Administration (USFDA)] on the effectiveness and safety of COVID-19 vaccines.

Table 2 Summary Of Evidence Retrieved On Candidate Vaccines.

Name of technology & Developer	Summary of Technology	Clinical trials	Remarks
mRNA-1273 by: Moderna	Using mRNA technology It is a lipid nanoparticle (LNP)-encapsulated mRNA based vaccine that encodes full-length, perfusion stabilized spike protein of SARS-COV-2. IM 0.5ml Day 1 & Day 29 (on Deltoid)	**Phase 1 study (NCT04283461)**[13] -open-label trial -Days 1 and days-29 vaccination schedule across 3 dose levels (25, 100, 250 µg) n= 45 healthy adults (18 to 55 years old) with n=15 participant for each dosage group. *Participants were not screened for SARS-CoV-2 infection by serology or polymerase chain reaction before enrollment. <u>Safety</u> -Adverse Events (AEs) were generally transient and mild to moderate in severity. No serious AEs. -One participant in the 25-µg group developed transient urticaria at day 5 post-vaccination. -The most commonly reported AE : pain at the injection site (100%), fatigue (80%), chills (80%), headache (60%) &myalgia (53%). <u>Efficacy</u> -neutralizing antibody titers were detected at Day 43 in all participants in all dose cohorts after second vaccinations. -after 1st vaccination, seroconversion in all participants by day 15	Initially received Fast Track Designation by US FDA.[16] On December 18, 2020, the U.S. FDA issued an **emergency use authorization (EUA)** for the prevention of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2(SARS-CoV-2).[17] **APPROVED FOR USE IN:** Switzerland.

		-geometric mean titers of antibody titers were 2.1-fold higher than those seen in convalescent sera (n=38) among 25-µg group and the titer is higher among higher dosage group. **Phase 1 trial among healthy participants who were 56 years of age or older. (NCT04283461)[14]** N=40 older adult (56 to 70 years or ≥71 years) given 2 doses of either 25 µg or 100 µg of vaccine administered 28 days apart. -The study did not screen for evidence of past or current SARS-CoV-2 infection by testing blood or nasal specimens before enrollment. <u>Safety</u> -No serious AEs were reported. -The most common solicited AEs were headache, fatigue, myalgia, chills, and injection-site pain. -These symptoms typically occurred on the day of vaccination or 1 day afterward and resolved quickly. -3 participants had erythema that lasted for 5 - 7 days. <u>Efficacy</u> -The 100-µg dose induced higher binding- and neutralising-antibody titers than the 25-µg dose in older group. -The vaccine elicited a strong CD4 cytokine response involving type 1 helper T cells. **Phase 3 COVE Study (NCT04470427)[15]** -randomised, stratified, observer-blinded, placebo-controlled trial. -N=30,420 18 years and older with healthy adults & medically stable condition participants in 99 sites in USA. <u>Efficacy</u> -primary endpoint: • the efficacy of the mRNA-1273 vaccine in preventing a first occurrence of SYMPTOMATIC COVID-19 by calculating vaccine efficacy which was defined as the precentage reduction in the hazard ratio for the primary end point (MRNA-1273 vs placebo) • Findings: 196 cases of COVID-19 were diagnosed: • 11 cases in the vaccine group (3.3 per 1000 person-years; 95% CI: 1.7, 6.0) • 185 cases in the placebo group (56.5 per 1000 person-years; 95% CI: 48.7, 65.3) **indicating 94.1% efficacy** of the mRNA-1273 vaccine (95% CI: 89.3, 96.8%; P<0.001) for the prevention of	**EMERGENCY USE IN**: Canada, European Union, Iceland, Israel, Mongolia, Norway, Qatar NEW, Singapore, United Kingdom, United States.

		symptomatic SARS-CoV-2 infection ascompared with placebo). -Secondary endpoint: • prevention of severe COVID-19. • Findings: 30 participants in the trial had severe COVID-19; all were in the placebo group (indicating vaccine efficacy of 100% [95% CI, could not be estimated to 1.0]), and one death among these participants was attributed to Covid-19. <u>Safety</u> -Injection-site AEs (mainly grade 1 or 2) lasted a mean of 2.6 and 3.2 days after the first and second doses, respectively. -The most common was pain after injection (86.0%). -Solicited systemic AEs lasted a mean of 2.6 days and 3.1 days after the 1st and 2nd doses, respectively. The most common AEs included fatigue (1.5%) and headache (1.4%). -Two death in the vaccine group (one from cardiopulmonary arrest and one by suicide).	
Cominarty **Previously known as BNT162 (BNT162b1&BNT162b2)** by: BioNTech, Pfizer & Fosun Pharma -USA & Germany	Using mRNA technology. It encodes an optimized SARS-CoV-2 full length spike glycoprotein (S).	**Phase 1/2 study** (NCT04368728)[18] **(BNT162b1)** -n= 45 healthy adults age 18 to 55 years old -30 µg dose level in a 2 dose regimen (21 days apart) <u>Safety</u> -No serious adverse events were reported. -severe AE: 1 fever post-vaccine and 1 sleep disturbance <u>Efficacy</u> -RBD-binding IgG concentrations and SARS-CoV-2 neutralizing titers in sera increased with dose level and after a second dose. -Geometric mean neutralizing titers reached 1.8- to 2.8-fold that of a panel of COVID-19 convalescent human sera. **Phase 3 (NCT04368728)[19]** -N=43,538 participants (16 years or older who were healthy or had stable chronic medical condition) -Vaccine candidates versus placebo. -Primary end point: efficacy of vaccine against confirmed COVID-19 (symptoms and positive SARS-COV-2 by nucleic acid amplication-based testing.) -Secondary endpoint: efficacy against Severe COVID-19. <u>Efficacy</u> -Number of COVID-19 cases: Group without prior evidence of COVID-19 infection (n=36523)	Both vaccines initially received Fast-Track Designation from US FDA.[21] On December 11, 2020, the U.S. Food and Drug Administration issued the first **emergency use authorization (EUA)** for a vaccine for the prevention of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older.[22] **APPROVED FOR USE IN:** Bahrain, New Zealand, Saudi Arabia, Switzerland.

		• 8 - vaccine group. • 162 - placebo group. • Corresponds to **95% vaccine efficacy** • (95% CI: 90.3, 97.6) Group with and without evidence of prior infection (n=40137) • 9 cases in vaccine recipients • 169 in placebo recipients • corresponding to **94.6% vaccine efficacy** (95% CI: 89.9, 97.3). -Secondary endpoint: Occurrence of severe COVID-19 after 7 days of 2nd dose • Vaccine group: 1 • Placebo: 4 • corresponding to 75% vaccine efficacy (95% CI: -152.6, 99.5). <u>Safety</u> -Local AE: pain at injection site (most commonly reported) -Systemic AE: fatigue (59%), headache (52%), fever (16%) 4 serious AE in vaccine group: -Shoulder injury related to vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia and right leg paresthesia -2 patient died: one from arteriosclerosis and one from cardiac arrest. **Case report: Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine[20]** -During December 14 to 23, 2020, after administration of a reported 1 893 360 first doses of Pfizer-BioNTech COVID-19 vaccine, CDC identified 21 case reports of anaphylaxis, corresponding to an estimated rate of 11.1 cases per million doses administered. -Four patients (19%) were hospitalized (including 3 in intensive care), and 17 (81%) were treated in an emergency department; 20 (95%) are known to have been discharged home or had recovered at the time of the report. No deaths from anaphylaxis were reported.	**EMERGENCY USE IN:** Argentina, Australia, Canada, Chile, Colombia, Costa Rica, Ecuador, European Union, Iceland, Iraq, Israel, Jordan, Kuwait, Lebanon, Malaysia, Mexico, Mongolia, Norway, Oman, Panama, Peru, Philippines, Qatar, Serbia, Singapore, Tunisia, United Arab Emirates, United Kingdom, United States. Emergency use validation from the World Health Organization.
NVX-CoV2373 by: Novavax -USA	Using recombinant nanoparticle technology to generate antigen derived from the	**Phase 1/2 (NCT04368988)[23]** evaluated two doses (5 and 25 µg) n= 131 healthy adults ages 18-59 years old. (vaccine with adjuvant= 83, without adjuvant= 25, and placebo =23). <u>Safety</u> - No serious adverse events (SAEs) were reported	

	coronavirus spike (S) protein and contains Novavax' patented saponin-based Matrix-M™ adjuvant to enhance the immune response and stimulate high levels of neutralizing antibodies.	<u>Efficacy</u> -The vaccine induced neutralization titers in 100% of participants -Both 5 µg and 25 µg adjuvanted doses generated peak geometric mean titer (GMT) greater than 1:3,300 . -Matrix-M™ adjuvant induced robust polyfunctional CD4+ T cell responses. **Phase 3 (press)[24]** -Preliminary result -N=15,000 volunteers, aged 18-84 -All participants were serologically negative at baseline. <u>Efficacy</u> -Primary endpoint: PCR-confirmed COVID-19 62 cases of COVID-19 (56 in placebo vs 6 in vaccine group). Vaccine efficacy: • 95.6% against original COVID-19 strain • 85.6% effective against B 1.1.7 (UK variant) - One severe case in the placebo group. <u>Safety</u> There were no differences in AEs between vaccine and placebo.	
Coronavac by: Sinovac Biotech Ltd (Sinovac Life Sciences) - China	Inactivated strain of SARS-CoV-2 vaccine created from African green monkey kidney cells (Vero cells) that have been inoculated with SARS-CoV-2 (CN02 strain). -2 doses 14 days apart -0.5 ml injection	**Phase 1/2 in China[25]** **(press)** -n = 743 (143 phase I & 600 phase II healthy volunteers aged 18-59 years old) <u>efficacy</u> -Induces neutralizing antibodies 14 days after vaccination. -Seroconversion rate was 90% <u>Safety</u> -no serious adverse event after vaccination **Phase 1 / 2 (NCT04352608)[26]** -randomised, double-blind, placebo-controlled, phase ½ in Suining County of Jiangsu province, China -n= healthy adults aged 18–59 years • phase 1 (n=144) were randomly assigned (2:1) to either 3µg or 6µg CoronaVac or placebo given either 2 vaccine schedule (14-days interval or 28-days interval) • phase 2 n=600 was initiated after all participants in phase 1 has finished a 7-day safety observation period after the first dose.	-Late August 2020, CoronaVac was **approved** for **emergency use as part of a program in China to** vaccinate high-risk groups such as medical staff.[28] -Phase III trial in Brazil partnering with Butantan Institute, Sao Paolo is on-going **APPROVED FOR USE IN**: China. **EMERGENCY USE IN**: Azerbaijan, Brazil, Chile, Colombia, Indonesia, Laos, Turkey, Uruguay.

		<u>Safety</u> -primary endpoint: AEs within 28 days after injection in all participants who were given at least one dose of study drug ➔ The most common symptom was injection-site pain ➔ Most adverse reactions were mild (grade 1) in severity and participants recovered within 48h ➔ one case of acute hypersensitivity (urticaria) 48 h after the first dose reported in the 6 µg group. ➔ No vaccine-related serious adverse events were noted within 28 days of vaccination ➔ incidence of adverse reactions in the 3 µg and 6 µg group were similar, indicating no dose-related safety concerns <u>Efficacy</u> -primary outcome: seroconversion rates of neutralising antibodies to live SARS-CoV-2 at day 14 (14-days interval group), and at day 28 (28 days-s interval group) who completed their allocated two-dose vaccination schedule (per-protocol population). -Seroconversion of neutralising antibodies: 14-days interval: • 3 µg group: 109 (92%) of 118 • 6 µg group: 117 (98%) of 119 • placebo group: 2 (3%) of 60 28-days interval: • 3 µg group: 114 (97%) of 117 • 6 µg group: 118 (100%) of 118 • placebo group: none (0%) of 59 -In post-hoc analyses, the neutralising antibody titres after the second dose of vaccine was lower in all participants who received the vaccine than was detected in 117 convalescent asymptomatic patients who had previously had COVID-19. -no data on T-cell responses. -Immune responses induced 28-days schedule were larger than those induced by 14-days schedule, regardless of the dose. **Phase 3 (press)[27]** **-** Double-Blind, Randomised, Placebo-Controlled -n= 12688 participants (healthcare professionals) -Vaccine efficacy of 78 % -Preventing severe and moderate infections: 100 %	

BBIBP-CorV by: Sinopharm Group (China National Biotec Group – CNBG) – China	Inactivated virus received 3 intramuscular injections at days 0, 28, and 56.	**Phase 1 / 2 Interim Analysis (ChiCTR2000031809)[29]** Phase 1 recruited 96 participants (aged 18-59 years old) - 3 doses group (2.5, 5, and 10 μg/dose) and adjuvant-only group (n=24 each group) Phase 2 recruited 224 adults -were randomised to • 5 μg/dose in 2 schedule groups (injections on days 0 &14 [n = 84] vs alum only [n = 28] • 5 μg/dose in day 0 & 21 [n = 84] vs alum only [n = 28] <u>Efficacy</u> -Induces antibodies in 28 days -100% seroconversion rate <u>Safety</u> -The most common AEs: injection site pain, followed by fever, which were mild and self-limiting -no serious adverse reactions were noted **Phase 1 / 2 (ChiCTR2000032459)[30]** -randomised, double-blind, placebo-controlled, phase 1/2 trial at Shangqiu City Liangyuan District Center for Disease Control and Prevention in Henan Province, China. -recruiting healthy people aged 18–80 years, who were negative for serum-specific IgM/IgG antibodies against SARS-CoV-2 -phase 1 (n= 192) randomized into 2-dose immunisations schedule (on days 0 and 28) at all doses (2 μg, 4 μg, 8 μg or placebo) in two age groups (18–59 years and ≥60 years). -phase 2 (n=448) four immunisation schedules were tested three schedules of two doses of BBIBP-CorV at 4 μg total protein each or placebo, and one schedule of one shot of BBIBP-CorV at 8 μg total protein or placebo. <u>Safety</u> -The most local reaction was pain, which was reported in 34 (24%) of 144. -Most commonly reported systematic AE was fever 5 (4%) of 144 vaccine recipients. Other: fatigue (two [3%]), inappetence (one [1%]), nausea (one [1%]), constipation (one [1%]), mucocutaneous abnormalities (two [3%]), headache (one [1%]), vomiting (one [1%]), and itch (non-injection site; one [1%]. - All AEs were mild or moderate in severity. -No serious AEs was reported within 28 days post vaccination for all cohorts. <u>Efficacy</u> -induced neutralising antibodies in 100% of vaccine recipients in all cohorts.	-United Arab Emirates (UAE) **approved** the vaccine for emergency use, making China's Sinopharm the first vaccine maker to receive approval to deploy a COVID-19 candidate in a foreign country. -Phase III trial is still ongoing in UAE in partnership with Abu Dhabi's G42 Healthcare **APPROVED FOR USE IN**: Bahrain, China, United Arab Emirates. **EMERGENCY USE IN:** Cambodia, Egypt, Hungary, Iraq, Jordan, Pakistan, Peru. **LIMITED USE IN**: Serbia, Seychelles.

		-100% seroconversion rate was reached earlier for group aged 18–59 years after the first vaccine dose (day 14). -For the group aged 60 years and older, the seroconversion rate of the 4 μg and 8 μg dose recipients reached 100% on day 28, and the 2 μg group was 100% seroconverted by day 42. **Phase 3 trial (press)[31]** -vaccine efficacy: 79%	
Ad5-nCOV By: CanSino Biologics - China	Using Adenovirus-based viral vector vaccine technology -cloned optimised full-length spike gene based on Wuhan-Hu-1 with tissue plasminogen activator signal peptide gene into E1 and E3 deleted ad5 vector	**Phase 1** n=108, (healthy, age 18-60 years old) <u>Safety:</u> No severe AEs reported <u>Efficacy:</u> -ELISA antibodies and neutralising antibodies increased significantly at day 14 and peaked at day 28 post-vaccine. -Specific T-cell response peaked at Day 14. **Phase 2 (NCT04341389)[32]** -randomised, double-blind, placebo-controlled -Total of 508 participants receive the vaccine at a dose of • 1×10^{11} viral particles per mL (n=253) • 5×10^{10} viral particles per mL (n=129) • Placebo (n=126) <u>Efficacy</u> Both doses of the vaccine induced significant neutralising 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 1×10^{11} and 5×10^{10} viral particles, respectively. **Seroconversion at D28** • The vaccine induced seroconversion of the neutralising antibodies in 59% and 47% of participants,and seroconversion of binding antibody in 96% and 97% of participants, in the 1×10^{11} and 5×10^{10} viral particles dose groups, respectively. **Tcell responses** -At Day 28, vaccine induced significant SARS-CoV-2 spike glycoprotein-specific IFNγ-ELISpot responses in 90% patients (95% CI 85–93) receiving the 1×10^{11} viral particles dose, and 88% (95% CI 81–92) receiving the 5×10^{10} viral particles dose. <u>Safety</u> -Most common systematic AEs reported: fatigue, fever, headache, injection site pain. -No serious AEs reported. No retrievable data on Phase 3.	China **approved** limited use of CanSino's vaccine for its military in June 2020. Starting September 2020, phase 3 trial of Ad5-nCoV vaccine candidate is being tested on 40,000 participants in Russia, Saudi Arabia, Pakistan and Mexico. **EMERGENCY USE IN**: Mexico. **LIMITED USE IN**: China.

ChAdOx1 nCoV-19 By: AstraZeneca - UK	Using chimpanzee adenovirus-vectored vaccine expressing the SARS-CoV-2 spike protein (ChAdOx1)	**Phase 1/2 (NCT04324606)[33]** Single-blind, RCT, multicenter n= 1077 participants (aged 18–55 years old) were enrolled and assigned to receive either ChAdOx1 nCoV-19 (n=543) or meningococcal conjugate vaccine MenACWY (n=534) 10 participants assigned to a non-randomised, unblinded ChAdOx1 nCoV-19 prime-boost group received a two-dose schedule, with the booster vaccine administered 28 days after the first dose. <u>Safety (at day 28)</u> -most reported AE: pain, feeling feverish, chills, muscle ache, headache and malaise -no serious AEs reported <u>Efficacy</u> - Neutralising antibody responses detected 91% after a single dose when measured in microneutralisation assay (MNA_{80}) and in 100% participants when measured in 50% plaque reduction neutralisation assay ($PRNT_{50}$). -After a booster dose, all participants had neutralising activity -T-cell response that peaked by day 14 and maintained two months after injection was observed in all subjects **<u>Pooled interim analysis of 4 RCTs[34] (NCT04324606, NCT04400838, and NCT04444674)</u>** Data cutoff on Nov 4, 2020. -ongoing blinded, randomised, controlled trials done across the UK, Brazil, and South Africa. -(n=11636) aged 18 years and older -randomly assigned (1:1) to ChAdOx1 nCoV-19 vaccine or control (meningococcal group A, C, W, and Y conjugate vaccine or saline). <u>Efficacy</u> -Based on COV002 (phase 2/3; UK) and COV003 (phase 3; Brazil) -Timing of priming and booster vaccine administration varied between studies -Primary efficacy analysis: symptomatic COVID-19 in seronegative participants with a nucleic acid amplification test-positive swab more than 14 days after a second dose of vaccine. -**symptomatic COVID cases**: • Vaccine group: 30 (0.5%) out of 5807 participant • Control group: 101 (1.7%) out of 5829 participant • **Vaccine efficacy: 70.4% (54.8 to 80.6)** in all participants who received either	-The United Kingdom and Argentina were the first countries to give the vaccine **emergency authorization**, on Dec. 30, and since then a number of other countries have also done the same. On Jan. 3, India, approved a version called Covishield, made by the Serum Institute of India. Covishield will make up a large fraction of the vaccines distributed by Covax to middle- and low-income countries. On Feb. 10 a World Health Organization expert committee recommended the vaccine in adults 18 or older.[8] **EMERGENCY USE IN:** Algeria, Argentina, Bangladesh, Bhutan, Brazil, Chile, Dominican Republic, Egypt, El Salvador, European Union, Iceland, India, Iraq, Kuwait, Maldives, Mexico, Mongolia, Morocco, Nepal, Norway, Pakistan, Philippines, Seychelles, Sri Lanka, South Africa, South Korea, Thailand, United Kingdom.

		low-dose (LD)/standard dose(SD) and SD/SD. • received SD/SD: vaccine efficacy was 62.1% (95% CI: 41.0, 75.7) • received LD/SD: efficacy was higher at 90.0% (95% CI: 67.4, 97.0), p=0.010. -**Severity of COVID cases**: **All cases were in the control group.** 10 participants were hospitalised due to COVID-19 (defined as WHO clinical progression score ≥4), 2 of whom were having severe COVID-19 (WHO score ≥6), including one fatal case. <u>Safety</u> -The safety of the vaccine is being assessed using data from all 4 studies who received at least one dose of any vaccine in any study. **-Serious AEs and AEs of special interest balanced across the study arms.** -Serious AEs occurred in 168 participants, 79 from vaccine group and 89 of control group. -A case of transverse myelitis was reported 14 days after ChAdOx1 nCoV-19 booster vaccination as being possibly related to vaccination. However, the independent neurological committee considered the most likely diagnosis to be of an idiopathic, short segment, spinal cord demyelination. -One death in vaccine group (not related to vaccine)	
Gam-COVID-Vac (Sputnik V) **By: Gamaleya Research Institute, Russia**	recombinant adenovirus type 26 (rAd26) vector and a recombinant adenovirus type 5 (rAd5) vector, both carrying the gene for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike glycoprotein (rAd26-S and rAd5-S)	**<u>Phase 1/2 studies</u>** (NCT04436471 and NCT04437875)[6] **-non-randomised, multi-center, testing on vaccine with two formulations (frozen [Gam-COVID-Vac] and lyo-philised [Gam-COVID-Vac-Lyo]).** -n= 76 , healthy adult age: 18–60 y.o -Phase 1 (n=38) IM on day 0 either rAd26 or rAd5, safety assessed at day 28. -Phase 2 (n=38) IM rAd26-S given on day 0 and rAd5-S on day 21. <u>Safety</u> Most common AE: • pain at injection site (44 [58%] • hyperthermia (38 [50%]) • headache (32 [42%]), • asthenia (21 [28%]) • muscle & joint pain (18 [24%]) There was no serious AE detected. <u>Efficacy</u> -Antigen-specific IgGs: Seroconversion rate of 100% on day 28 and day 42. -Cellular immune responses showed formation of antigen-specific cells of both T-helper ($CD4^+$)	- On 11th August 2020, Sputnik V was **approved** for usage in Russia **EARLY USE IN**: Russia. **EMERGENCY USE IN**: Algeria, Argentina, Armenia, Bahrain NEW, Belarus, Bolivia, Bosnian Serb Republic, Guinea, Hungary, Iran, Kazakhstan, Lebanon, Mexico, Mongolia NEW, Myanmar, Nicaragua, Pakistan, Palestinian Authority, Paraguay, Serbia,

		and T-killer ($CD8^+$) and an increase in the concentration of interferon-γ secretion in peripheral blood mononuclear cells, in 100% of volunteers at day 28 post-vaccination. **<u>Phase 3 (NCT04530396)[35] interim Analysis</u>** -Database lock till 24.11.2020 -Randomised 3:1, double-blind, placebo-controlled, multi-center (25 hospitals and polyclinics) in Moscow, Russia. -N= 21 977 (18 years and older) with negative HIV, hepatitis B and C, and syphilis test results; negative anti-SARS-CoV-2 IgM and IgG antibody and SARS-CoV-2 PCR tests. Vaccine Group (n=14964) Placebo Group (n=4902) <u>Efficacy:</u> Primary outcome: the proportion of participants with COVID-19 confirmed by PCR from day 21 after receiving the first dose. • Vaccine Group: 16 (0.1%) of 14 964 • Placebo Group: 62 (1.3%) of 4902 • **vaccine efficacy was 91.6%** (95% CI: 85.6, 95.2) Secondary outcome: severity of COVID-19. • vaccine group: no cases • placebo group: 20 cases • **vaccine efficacy against moderate or severe COVID-19 was 100%** (94.4–100.0). <u>Safety:</u> -The most common adverse events were flu-like illness in 156 (15·2%) and local reaction in 56 (5·4%) of 1029 participants in the vaccine group. -70 serious AEs considered not related to COVID-19 were recorded in 68 participants. • vaccine group: 45 (0·3%) of 16427 • placebo group: 23 (0·4%) of 5435 -None were considered associated with vaccination. -Full adverse events data has not yet been processed. -**four deaths** were recorded: Vaccine group: 3 (<0·1%) of 16 427 • 1 fracture ofthe thoracic vertebra • 2 were associated with COVID-19 Placebo group: 1 (<0·1%) of 5435 • Haemorrhagic stroke. -**No vaccine-related deaths were reported.**	Tunisia, Turkmenistan, United Arab Emirates, Venezuela.

Ad26.COV2.S **By:** **Janssen Vaccines & Prevention B.V.**	Non-replicating adenovirus 26 vector expressing the stabilized pre-fusion spike (S) protein of SARS-CoV-2.	**Phase 1/2a (NCT04436276)[36]** **randomised, double-blinded, placebo-controlled** cohort 1a & cohort 1b (aged 18-55 years old, n= 402) cohort 3 (aged 65–75years old, n=394). Ad26.COV2.S were given $5x10^{10}$ or $1x10^{11}$ vp or placebo (0.9% saline) administered intramuscularly (IM) as single-dose or two-dose schedules, 8 weeks apart. Safety -most frequent local AE : injection site pain -most frequent systematic -AE: fatigue, headache and myalgia -two serious AEs: • one hypotension judged by the investigator to not be vaccine related because of a past history of recurrent hypotension • one participant with fever : judged by the investigator to be vaccine-related Efficacy **S-binding antibody titers** -By Day 29 after vaccination, GMTs had increased to respectively 528 (95% CI: 442-630) and 695 (95% CI: 596- 810), with 99% seroconversion in each dose group. **Neutralizing antibodies** -Similarly, high response rates were observed in a wild-type virus neutralization assay (wtVNA). 29 days post vaccination, 98% of the participants had detectable neutralizing antibodies. 92% of cohort 1a participants and respectively 6 out of 6, and 5 out of 6 recipients of the $5x10^{10}$ vp and $1x10^{11}$ vp dose level in cohort 3, seroconverted for SARS-CoV-2 neutralizing antibodies. **Interim Analysis of its Phase 3 ENSEMBLE Trial (press)[37]** N=43,783 participants, 18 years and older evaluate the efficacy and safety of the Janssen COVID-19 vaccine candidate in protecting moderate to severe COVID-19, with co-primary endpoints of 14 days and 28 days following vaccination. Efficacy -66% effective overall in preventing moderate to severe COVID-19, 28 days after vaccination -protection against moderate to severe COVID-19 infection (28 days post-vaccination) was • 72% in the United States • 66% in Latin America • 57% in South Africa Safety Overall fever rates were 9% and Grade 3 fever 0.2%. Overall serious AEs reported were higher	

		in participants who received placebo as compared to the active vaccine candidate. No anaphylaxis was observed.	
EpiVacCorona **By:** **Vektor State Research Center of Virology and Biotechnology in Russia**	peptide vaccine	**Phase 1 / 2 (press)**[38] Participants: 57 volunteers, while 43 received a placebo two injections administered 14 to 21 days apart. -No details of the clinical trials mentioned.	EpiVacCorona received **approval** in Russia before a Phase 3 trial to demonstrate that it was safe and effective. **EARLY USE IN**: Russia.

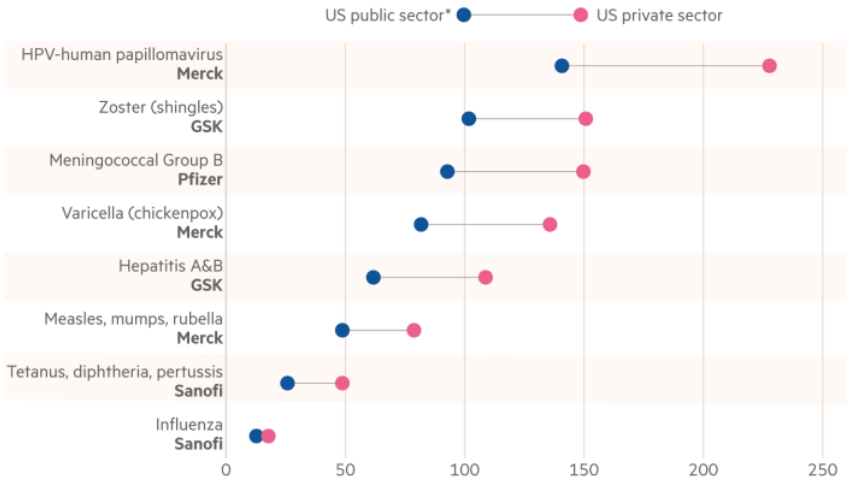
Cost

There were no retrievable evidences on the cost-effectiveness of the above-mentioned candidate vaccines. The price of COVID-19 candidate vaccines ranges from USD 3 to 30 per dose which equivalent to RM 12.30 to RM123.00. [39]

AstraZeneca expected to sell its ChAdOx1-S vaccine at about USD 3 to USD 4 per dose, whereas Moderna's mRNA-1273 was sought to sell at about USD 50 to USD 60 for its course of two injections. Meanwhile Sinovac, has began selling its vaccine in selected cities at USD 60 (~RM 246.15) for two shots as part of an emergency use programme with hundreds of thousands of participants.[39]

The price range of currently available vaccines is shown below. (Figure 1)

Figure 1 Price Range of Existing Vaccines



Source: Financial times

Other issue

The government has to provide effective vaccine cold chain to maintain its potency from the time of manufacture until the point of administration. The key procedures must be observed (as recommended by WHO) include:[40]

- store vaccines and diluents within the required temperature range at all sites
- pack and transport vaccines to and from outreach sites according to recommended procedures
- keep vaccines and diluents within recommended cold chain conditions during immunization sessions.

CONCLUSION

According to interim data of several phase 3 trials listed above, several COVID-19 candidate vaccines has shown potential efficacy in reducing new cases of COVID-19 among the intervention group as compared with the placebo group. Majority of adverse events of the studied vaccines were mild in severity. However, there was growing concerns on several case reports on anaphylaxis incidence among high-risk group in Cominarty study. Though the candicate vaccines have shown potential efficacy and has tolerable adverse events, few other factors need consideration including immunologic correlation of the antibody produced in the study with its protection against the disease and the emerging variants of COVID-19, duration of protection of the vaccine against the disease and the vaccine efficacy for vulnerable group such as immuno-compromised person, children and pregnant women.

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