Title: Comparing COVID-19 vaccines for their characteristics, efficacy and effectiveness against SARS-CoV-2 and variants of concern

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Abstract

Vaccines are critical cost-effective tools to control the COVID-19 pandemic. However, the emergence of more transmissible SARS-CoV-2 variants may threaten the potential herd immunity sought from mass vaccination campaigns.

The objective of this study was to provide an up-to-date comparative analysis of the characteristics, adverse events, efficacy, effectiveness and impact of the variants of concern (Alpha, Beta, Gamma and Delta) for fourteen currently authorized COVID-19 vaccines (BNT16b2, mRNA-1273, AZD1222, Ad26.COV2.S, Sputnik V, NVX-CoV2373, Ad5-nCoV, CoronaVac, BBIBP-CorV, COVAXIN, Wuhan Sinopharm vaccine, QazCovid-In, Abdala and ZF200) and two vaccines (CVnCoV and NVX-CoV2373) currently in rolling review in several national drug agencies.

Overall, all COVID-19 vaccines had a high efficacy against the traditional strain and the variants of SARS-CoV-2, and were well tolerated. BNT16b2, mRNA-1273 and Sputnik V had the highest efficacy (>90%) after two doses at preventing symptomatic cases in phase III trials. Efficacy was ranging from 10.4% for AZD1222 in South Africa to 50% for NVX-CoV2373 in South Africa and 50 % for CoronaVac in Brazil, where the 501YV.2 and P1 variants were dominant. Seroneutralization studies showed a negligible reduction in neutralization activity against Alpha for most of vaccines, whereas the impact was modest for Delta. Beta and Gamma exhibited a greater reduction in neutralizing activity for mRNA vaccines, Sputnik V and CoronaVac.

Regarding observational real-life data, most studies concerned the Pfizer and Moderna vaccines. Full immunization with mRNA vaccines effectively prevents SARS-CoV-2 infection against Alpha and Beta. All vaccines appeared to be safe and effective tools to prevent symptomatic and severe COVID-19, hospitalization and death against all variants of concern, but the quality of evidence greatly varied depending on the vaccines considered. There are remaining questions regarding specific populations excluded from trials, the duration of immunity and heterologous vaccination. Serious adverse event and particularly anaphylaxis (2.5-4.7 cases per million doses among adults) and myocarditis (3.5 cases per million) for mRNA vaccines ; thrombosis with thrombocytopenia syndrome for Janssen vaccine (3 cases per million) and AstraZeneca vaccine (2 cases per million) and Guillain-Barre syndrome (7.8 cases per million) for Janssen vaccine are very rare. COVID-19 vaccine benefits outweigh risks, despite rare serious adverse effect.

Background

The implementation of SARS-CoV-2 vaccines is a major asset to slow down the COVID-19 pandemic. At the time of writing, more than 100 vaccines have been developed, and 23 vaccines have been evaluated in phase III clinical trials according to the World Health Organization (WHO) (1).

The most common endpoint in phase III clinical trials was the prevention of symptomatic SARS-CoV-2 infection. Observational studies are necessary to assess the real-world impact of vaccination on the transmission of SARS-CoV-2, the prevention of asymptomatic or symptomatic infection, severe COVID-19 and mortality.

Recently, several variants of concern (VOC) have emerged such as Alpha (known as 501Y.V1 with GISAID nomenclature or B.1.1.7 variant with PANGO nomenclature), Beta (501Y.V2 or B.1.351), Gamma (501Y.V3 or P1) and Delta (G/478K.V1 or B.1.617.2). These variants have been associated with an increase in the transmission or the mortality of COVID-19 (2–7) or may escape immunity when compared to the wild type or D614G variant (8–12).

Phase IV studies evaluate the real world effectiveness of the vaccines in an observational design, among a larger general population, unlike phase III trials which assess the efficacy in controlled conditions. Real-world studies bring crucial information about rare or long-term effects, the prevention of asymptomatic infection, the severity of COVID-19, hospitalization and death related to the disease. Moreover, these studies assessed vaccine effectiveness in a real-world setting and have shown encouraging results in several countries(13,14,14–16), suggesting a significant effect on the transmission of SARS-CoV-2 and the control of the pandemic.

The administration of COVID-19 vaccines is a major priority for many countries and many healthcare professionals around the world have been mobilized to accelerate their roll-out. Due to the speed of production of scientific data in this pandemic context, it can be difficult for professionals to update themselves on the latest data concerning COVID-19 vaccines.

The objective of this review is to provide an up-to-date comparative analysis of the characteristics, adverse events, efficacy, effectiveness and impact of the variants of concern on the following fourteen COVID-19 vaccines: BNT16b2, mRNA-1273, AZD1222, Ad26.COV2.S, Sputnik V (Gam-COVID-Vax), NVX-CoV2373, Ad5-nCoV (Convidecia), CoronaVac, BBIBP-CorV, COVAXIN, EpiVacCorona, ZF2001, CVnCoV, Abdala and QazCovid-In and Wuhan Sinopharm inactivated vaccine.

Methods

Electronic searches for studies were conducted on Pubmed until July 29th, 2021 using the search terms “SARS-CoV-2”, “COVID-19”, “efficacy”, “effectiveness”, “neutralization assays”, “neutralization antibodies” in addition to the scientific or commercial name of the vaccines reported by WHO in phase III/IV. The ClinicalTrials.gov database was consulted using the terms “COVID-19” and “vaccine”. BioRxiv and MedRxiv, regulatory drug agencies and pharmaceutical companies’ websites were also consulted for unpublished results and additional information. Vaccines included in this review were approved in at least one country. CVnCoV and NVX-CoV2373 were in rolling review by the European Medicine Agency (EMA) and were included in this review. For each vaccine, we extracted: type of vaccine, dose, injection, condition of use and storage, composition, cost for one dose, efficacy data for symptomatic and severe COVID-19, hospitalization, the rate of serious adverse

events, effectiveness against infection, COVID-19, hospitalization and death and the corresponding study population and time frame.

Efficacy refers to the degree to which a vaccine prevents symptomatic or asymptomatic infection under controlled circumstances such as clinical trials. Effectiveness refers to how well the vaccine performs in the real world. In trials, the main endpoint was the prevention of COVID-19 (symptomatic cases) whereas in observational studies, endpoints were various: SARS-CoV-2 infection (asymptomatic and symptomatic cases), COVID-19, hospitalization or mortality.

Regarding seroneutralization essays, we extracted the age of the study population, dosage, and fold decrease in geometric mean titer for 50% neutralization compared to the SARS-CoV-2 reference strain for each vaccine and each SARS-CoV-2 variant when it was available.

Evidence on vaccine efficacy and effectiveness

Fourteen vaccines have been authorized in at least one country: BNT16b2, mRNA-1273, AZD1222, Ad26.COV2.S, Sputnik V (Gam-COVID-Vax), Ad5-nCoV (Convidecia), CoronaVac, BBIBP-CorV, COVAXIN, EpiVacCorona, ZF2001, QazCovid-In, Abdala and Wuhan Sinopharm inactivated vaccine, and two vaccines (CVnCoV and NVX-CoV2373) are under evaluation.

We briefly compared the COVID-19 vaccines schedule, type of vaccine, manufacturer, dosage, conditions of use/storage/transport, composition and price (**Table 1**). The main results of clinical trials for each vaccine are described in **Table 2 and in Figure 1**). Characteristics of SARS-CoV-2 variants (Alpha, Beta, Gamma, Epsilon, Eta, Zeta, Iota, Kappa and Delta) are described in **Table 3**. The results of observational real-world studies are specified in **Table 4**. A **S1 Table** describes 46 seroneutralization assays of vaccinated participants against SARS-CoV-2 variants. Assays results are summarized in **Figure 2** using boxplots per vaccine and per variant.

173 **Table 1: Characteristics of COVID-19 vaccines**

Vaccine	Manufacturer	Type of vaccine	Dose	Injection	Condition of use/Storage	Composition	Cost for one dose
BNT16b2	Pfizer/BioNtech	RNA-based	30 µg 5-dose vial 0.3mL per dose	Intramuscularly 2 doses 21 days apart	Supplied as a frozen 6 dose-vial. The vaccine must be diluted. Can be stored before dilution: -80°C to -60°C up to the end of its expiry date or at -25°C to -150°C for up to two weeks After dilution: 2°C-25°C Have to be used within 6 hours from the time of dilution	A synthetic messenger ribonucleic acid (mRNA) encoding the Spike protein of SARS-CoV-2, lipids ((4-hydroxybutyl)azanediyl)bis(hexan-6,1-diyl)bis(2-hexyldecanoate), 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-distearoyl-sn-glycero-3-phosphocholine, and cholesterol), potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose	\$14.7-19.5
mRNA-1273	Moderna	RNA-based	100 µg 11 or 15-dose vial 0.5mL per dose	Intramuscularly 2 doses 28 days apart	Supplied as a frozen suspension stored between -50°C to -15°C Unopened vial: 2°C to 8°C for up to 30 days 8°C to 25°C for up to 24 hours After opening: 2°C to 25°C and discarded after 12 hours	A synthetic messenger ribonucleic acid (mRNA) encoding the Spike protein of SARS-CoV-2. The vaccine also contains the following ingredients: lipids (SM-102, 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 [PEG2000-DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), tromethamine, tromethamine hydrochloride, acetic acid, sodium acetate, and sucrose	\$15-18

CVnCoV	CureVac	RNA-based	12 µg xx-dose vial xx mL per dose	Intramuscularly 2 doses 28 days apart	Concentrated CVnCoV will be shipped to the site frozen at below -60° then stored frozen at -60°C (in clinical trial) CVnCoV must be diluted Unopened vial: 3 months at 2°C to 8°C Room temperature for 24 hours	-	-
AZD1222 ChAdOx1 nCoV-19 vaccine	AstraZeneca/ University of Oxford	Non- replicating viral vector	5x10 ¹⁰ viral particles (standard dose) 8 doses or 10 doses of 0.5 ml per vial	Intramuscularly 2 doses 4-12 weeks apart	Do not freeze Unopened vial: 6 months (2°C- 8°C) After opening: no more than 48 hours in a refrigerator (2°C- 8°C) Used at temperature up to 30°C for a single period of up to 6 hours	Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein (ChAdOx1-S)*, not less than 2.5 × 10 ⁸ infectious units (Inf.U)*Produced in genetically modified human embryonic kidney (HEK) 293 cells and by recombinant DNA technology L-Histidine L-Histidine hydrochloride monohydrate Magnesium chloride hexahydrate Polysorbate 80 (E 433) Ethanol Sucrose Sodium chloride Disodium edetate (dihydrate) Water for injection	\$2.15- 5.25

Ad26.COV2 .S	Johnson & Johnson	Non- replicating viral vector	5x10 ¹⁰ viral particles 10 dose of 0.5mL per vial	Intramuscularly A single dose	Should be protected from light Supplied as a liquid suspension Unopened vial Can base stored at 2°C to 8°C until the expiration date or at 9°C to 25°C for up to 12 hours After the first dose has been withdraw: the vial is held between 2°C and 8°C for up to 6 hours or at room temperature for up to 2 hours	replication-incompetent recombinant adenovirus type 26 (Ad26) vector expressing the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike (S) protein in a stabilized conformation. (5×10 ¹⁰ vp) citric acid monohydrate, trisodium citrate dihydrate, ethanol, 2-hydroxypropyl-β- cyclodextrin (HBCD), polysorbate 80, sodium chloride, sodium hydroxide, and hydrochloric acid	\$10
Gam- COVID- Vax Sputnik V	Gamaleya Research Institute	Non- replicating viral vector	10 ¹¹ viral particles per dose for each recombinant adenovirus 0.5 mL/dose	Intramuscularly 2 doses 21 days apart	Transport: two forms: lyophilized or frozen Storage: 2°C to 8°C	Two vector components, rAd26-S and rAd5-S Tris (hydroxymethyl) aminomethane, sodium chloride, sucrose, magnesium chloride hexahydrate, ethylenediaminetetraacetic acid (EDTA) disodium salt dihydrate, polysorbate-80, ethanol 95%, and water for injection	<\$10
NVX- CoV2373	Novavax	Protein- based	5 µg protein and 50 µg Matrix-M adjuvant	Intramuscularly 2 doses 21 days apart	Shipped in a ready-to-use liquid formulation Storage: 2°C to 8°C	SARS-CoV-2 rS with Matrix-M1 adjuvant (5 µg antigen and 50 µg adjuvant)	\$16
EpiVacCoro na	VECTOR	Protein- based	225 µg protein 0.5mL/dose	Intramuscularly 2 doses 21 days apart	Storage between 2°C and 8°C	-	-

ZF2001	Institute of Microbiology, Chinese Academy of Sciences, and Anhui Zhifei Longcom Biopharmaceutical.	Protein-based	25 µg protein 0.5mL/dose	Intramuscular	Storage between 2°C and 8°C	-	-
Convidecia TM Ad5-nCoV	CanSino	Non-replicating viral vector	10 ¹⁰ viral particles per 0.5 mL in a vial.	Intramuscularly Single dose	Not specified	the Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) No details on excipients	-
CoronaVac	Sinovac Biotech	Inactivated virus	3 µg 0.5mL per dose	Intramuscularly 2 doses 28 days apart	Supplied as a vial or syringe of 0.5mL Do not freeze Protected from light Storage and transport between 2°C and 8°C Shake well before use Shelf-life: 12 months	Inactivated CN02 strain of SARS-CoV-2 created with Vero cells Aluminum hydroxide, disodium hydrogen phosphate dodecahydrate, sodium dihydrogen phosphate monohydrate, sodium chloride	\$29.75
BBIBP-COV	Sinopharm/Beijing Institute of Biological Products	Inactivated virus	4 µg 0.5mL per dose	Intramuscularly 2 doses 21 to 28 days apart	Supplied as Pre-filled syringe or vial Cannot be frozen Protected from light Store and transport refrigerated (2°C to 8°C)	Inactivated virus 19nCoV-CDC-Tan-HB02 Excipients: disodium hydrogen phosphate, sodium chloride, sodium dihydrogen phosphate, aluminum hydroxide adjuvant	-
Wuhan	Sinopharm/Chinese Academy of Science	Inactivated virus	-	-	-	-	-

Covaxin	Bharat Biotech	Inactivated virus	6µg Single dose: 0.5mL 10-dose or 20-dose vial	Intramuscularly 2 doses 28 days apart	Supplied as a single dose or multidose vial Do not freeze Stored at 2°C to 8°C	6µg of whole-virion inactivated SARS-CoV-2 antigen (Strain: NIV-2020-770), and the other inactive ingredients such as aluminum hydroxide gel (250 µg), TLR 7/8 agonist (imidazoquinolinone) 15 µg, 2-phenoxyethanol 2.5 mg, and phosphate @buffer saline up to 0.5 m	\$2.7-7
CIGB-66 Abdala	Center for Genetic Engineering and Biotechnology (CIGB)	Protein-based	0.05mg recombinant protein 0.5mL per dose	Intramuscularly 3 doses at 0, 14, 28 days	Supplied as a multidose vial Do not freeze Stored at 2°C to 8°C	Recombinant protein of the SARS-CoV-2 virus receptor-binding domain (RBD) 0.05 mg Thiomersal 0.025 mg Aluminum hydroxide gel (Al ³⁺ +) Disodium hydrogen phosphate Sodium dihydrogen phosphate dihydrate Sodium chloride	
QazVac QazCovid-In	Kazakh Research Institute for Biological Safety Problems	Inactivated virus	-	Intramuscularly 2 doses 21 days apart	Stored at 2°C to 8°C	-	-

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*Prices were retrieved from <https://www.bmj.com/content/372/bmj.n281>

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Fig 1: Vaccine efficacy against SARS-CoV-2 infection from clinical trials (in % and 95%CI) according to the number of doses.
Confidence intervals are delimited by the grey rectangular area

Clinical trials

Messenger RNA (mRNA) Vaccines

mRNA-based drugs are new but not unknown. In 1990, the direct injection of mRNA in mouse muscle cells proved the feasibility of mRNA vaccines(17). mRNA instability, high innate immunogenicity and delivery issues were the main obstacles. After overcoming these issues, several vaccines were under assessment against influenza, rabies or Zika (18). BNT162b2 and mRNA-1273 vaccines against SARS-CoV-2 were the first authorized mRNA-based vaccines. These vaccines encode the antigen of interest in mRNA which is injected into cells. Then mRNA is translated into the spike protein to trigger the immune response.

BNT162b2 is an mRNA-based vaccine, developed by Pfizer/BioNtech which codes for the spike protein of SARS-Cov-2 and is encapsulated in lipid nanoparticles. It is administrated in two doses 21 days apart. According to two phase I and I/II trials, this vaccine is well tolerated and induced a humoral response (19,20). A multinational, observer-blinded RCT including 21,720 participants with BNT162b2 and 21,728 with placebo, identified an efficacy of 95.0% (95%CI: 90.3-97.6) in preventing symptomatic COVID-19 at least 7 days after the second dose. Efficacy against severe COVID-19 was 88.9% (95%CI: 20.1 to 99.7) after dose 1 and 75.0% (95%CI: -152.6 to 99.5) after dose 2. The incidence of serious adverse events was low and was similar in the vaccine and placebo groups (21). In the vaccinated group, 0.3% of participants had a lymphadenopathy compared to <0.1% in the placebo group. Four serious adverse events were associated with BNT162b2: shoulder injury related to vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and right leg paresthesia. An update with up to 6 months of follow-up found an efficacy of 91% (95%CI: 89 to 93.2) against COVID-19 at least 7 days after the second dose and efficacy against severe COVID-19 was 97%(22). In South Africa, efficacy against symptomatic infection by Beta was 100%. Decreased appetite, lethargy, asthenia, malaise, night sweats, and hyperhidrosis were new adverse events related to BNT162b2.

A phase II/III trial with 2,200 teenagers followed for 2 months showed an efficacy against COVID-19 of 100% (95%CI: 75.3-100)(23). Following these results, in the USA, BNT162b2 has been approved for 12-15 year-old patients.

mRNA-1273, developed by Moderna/US National Institute of Health is a lipid nanoparticle-encapsulated mRNA-based vaccine coding for the spike protein of SARS-Cov-2. It is administrated in two doses 28 days apart. According to two phase I and I/II trials, this vaccine was well tolerated, and induced humoral and Th1 responses (24,25). Binding and neutralizing antibodies were detected up to 180 days after the second dose of mRNA-1273 in a phase I trial (26).

In a phase III trial with a median follow-up of 2 months post second dose, there were 11 cases in the vaccine group and 185 cases in the placebo group 14 days after the second dose, giving an efficacy at preventing symptomatic COVID-19 of 94.1% (95%CI: 89.3 to 96.8). Efficacy at preventing severe COVID-19 was 100% (95%CI not estimated) (27). In the overall population, the incidence of severe adverse events related to the intervention was higher in the vaccine group (0.5%) than in the placebo group (0.2%). There were 3 cases of Bell's palsy and 74 events of hypersensitivity in the vaccine group and 1 facial paralysis and 45 events of hypersensitivity in the placebo group. There was no imbalance for neurological and thrombotic events. Six deaths occurred in the vaccine group and seven in the placebo group, none of which were associated with intervention. A press communication update including data six months after the second dose was published on April 13 2021, indicating an efficacy of 90% against all COVID-19 and more than 95% against severe cases (28). Preliminary data from a phase II trial showed a booster dose of mRNA-1273.351, based on the Beta variant induced a higher neutralization titers against beta when compared to the mRNA-1273 booster(29).

CVnCoV, developed by CureVac, is an mRNA-based vaccine encapsulated in lipid nanoparticles, encoding for the spike protein. It is administered in two doses 28 days apart. In a phase I interim analysis, this vaccine was well tolerated and induced a humoral response (30). Preliminary results of a phase IIb/III study in ten countries identified an efficacy of 48% against COVID-19 and 100% against hospitalization(31). GlaxoSmithKline has already initiated rolling submission with the EMA for CVnCoV.

Viral vector vaccines

The viral vector is a delivery system containing an antigen encoded onto DNA, based on the ability of viruses to infect cells. For example, the rVSV-ZEBOV vaccine is a replication-competent viral vector vaccine which was previously authorized for use against the vesicular stomatitis virus, expressing the main glycoprotein from the Zaire ebolavirus.

AZD1222, also named ChAdOx1-S (called Covishield in India) and developed by AstraZeneca and Oxford University, is a recombinant replication-deficient chimpanzee adenovirus coding for the spike protein. It was initially administered in two doses 28 days apart. However, the UK vaccination committee recommended extending the interval to 12 weeks since the vaccine demonstrated a higher efficacy with a longer interval (32). According to a phase II/III trial, this vaccine was well tolerated and induced humoral and T-cell responses (33). The first double-blinded RCT in Brazil and the UK provided interim data for 11,636 participants recruited between April 23 and November 4, 2020 (34). Vaccine efficacy in preventing symptomatic COVID-19 was 62.1% (95%CI: 41.0 to 75.7) after two doses. Among participants from UK, vaccine efficacy was 73.5% (95%CI: 55.5 to 84.2) whereas among Brazilian participants efficacy was 64.2% (95%CI: 30.7 to 81.5).

An update was published analyzing 17,178 participants from Brazil, South Africa and the UK from April 23 to December 6, 2020. Overall vaccine efficacy more than 14 days after the second dose was 66.7% (95%CI: 57.4 to 74.0), with 84 (1.0%) COVID-19 cases among 8597 participants in the AZD1222 group and 248 (2.9%) COVID-19 cases among 8581 participants in the control group. There were seven deaths, all considered unrelated to vaccination. A longer prime-boost interval, i.e. ≥ 12 weeks, showed a higher efficacy (81.3%) rather than a shorter period (55.1% of efficacy at < 6 weeks) (32).

An update among 8,534 participants aged 18-55 years in the UK, monitored between October 1, 2020 and January 14, 2021, reported 520 infections (35). Of these, 311 were sequenced, and efficacy at preventing symptomatic COVID-19 was 70.4% (95%CI: 43.6 to 84.5) against the B.1.1.7 variant and 81.5% (95%CI: 67.9 to 89.4) against other variants. Efficacy of ChAdOx1-S at preventing asymptomatic or unknown status for infection was 28.9% (95%CI: -77.1 to 71.4) against B.1.1.7 and 69.7% (95%CI: 33.0 to 86.3) against other variants. Vaccination also induced a reduction in the duration of shedding and viral load which may subsequently reduce transmission of SARS-CoV-2.

In a small double-blinded RCT among HIV-negative adults (n=2021) in South Africa, conducted between June 24 and November 9, 2020, overall efficacy against mild-to-moderate COVID-19 was 21.9% (95%CI: -49.9 to 59.8). Among people infected by the B.1.351 variant, efficacy fell as low as 10.4% (95%CI: -76.8 to 54.8) (36).

A press communication released on March 25th 2021, reported an efficacy at preventing symptomatic cases of 76.0% (95%CI: 68.0 to 82.0), 15 days after the two doses in the USA among 32,449 participants. Efficacy was 85.0% (95%CI: 58.0 to 95.0) among adults of 65 years and older. Efficacy was 100% for preventing hospitalization and preventing severe/critical COVID-19. No safety concerns related to AZD1222 were identified (37).

Ad26.COV2.S, developed by Johnson & Johnson/Beth Israel Deaconess Medical Center, is a replication-incompetent recombinant adenovirus type 26 (Ad26) vector expressing the spike protein. A phase I/IIa trial showed that this vaccine was safe and induced neutralizing-antibody and Th1 responses (38). Interim analyses from a phase III trial including 43,783 adults from the US, Latin America and South Africa, indicated a 66.9% (95%CI: 59.0 to 73.4) efficacy in preventing confirmed moderate to severe/critical COVID-19 after at least 14 days, and 66.1% (95%CI: 55.0 to 74.8) after 28 days, with a single dose (39,40). Beyond 14 days post vaccination, there were 348 cases in the placebo group and 116 cases in the vaccine group. Considering cases 28 days and onwards since vaccination, there were 193 cases in the placebo group and 66 cases in the vaccine group. In stratified analyses per region, efficacy 28 days after vaccination was 72%, 64% and 61% in the US, in South Africa and in Latin America, respectively. Protection against severe and critical COVID-19 28 days after vaccination was 85.4% (95%CI: 54.2 to 96.9). Against hospitalization, efficacy was 100% (95%CI: 15.7 to 100) at 28 days. Variant 501Y.V2 was present in 94.5% of sequenced cases in South Africa.

Sputnik V, also called Gam-COVID-Vac, is a combined vector vaccine composed of rAd type 26 (rAd26) and rAd type 5 (rAd5)—both of which carry the gene for the SARS-CoV-2 Spike protein. It is administered in two doses 21 days apart. An open non-randomized phase I/II trial showed Sputnik V was safe and induced humoral and T-cell responses (41). Interim analyses from a phase III trial in Russia among 19,886 adults receiving two doses indicated a 91.6% (95%CI: 85.6 to 95.2) efficacy in preventing symptomatic COVID-19 (42). Sputnik V is authorized in more than 30 countries.

CanSino's vaccine (Convidecia) is a non-replicating adenovirus type 5 vector, developed by the Beijing Institute of Biotechnology and CanSino Biologics, expressing the full-length spike gene based on the Wuhan-Hu-1 strain. Phase I and II trials confirmed the safety of this vaccine, and induction of a significant immune response after a single dose (43,44). A press released from CanSino Biologics Inc. including data from a 40,000 volunteer phase III trial in Pakistan, Mexico, Russia, Chile and Argentina (45) indicated an overall efficacy of 65.28% at preventing symptomatic COVID-19 28 days after single dose and 90.07% at preventing severe COVID-19 28 days after single dose vaccination.

Inactivated and protein subunit vaccines

Inactivated vaccines are whole viruses that cannot infect cells and replicate. The concept of inactivation through heat or chemical treatment was developed at the end of the 19th century (46). Subunit vaccines are made of fragments of proteins or polysaccharides. Both trigger an immune response and are already in widespread use against hepatitis A (inactivated vaccines) or against hepatitis B (subunit vaccines).

NVX-COV2373, developed by Novavax, is a recombinant nanoparticle vaccine with a saponin-based adjuvant and constructed from the full wild type SARS-CoV-2 spike protein optimized in a baculovirus *Spodoptera frugiperda* (Sf9) insect cell-expression system. This vaccine is administered in two injections 21 days apart. Two phase I/II and phase II trials confirmed the safety of NVX-CoV2373 which induced humoral and Th1 responses (47,48). A phase III trial indicated an efficacy of 89.7% (95%CI: 80.2 to 94.6) at preventing COVID-19 at least 7 days after the 2nd dose without prior infection among 15,187 UK participants. Vaccine efficacy was 86.3% against the Alpha variant. Serious adverse events were infrequent and balanced between both groups (49). A phase IIb trial in South Africa indicated a 60.0% efficacy (95%CI: 19.9 to 80.1) at preventing symptomatic COVID-19 ≥ 7 days after the second dose among 2,684 participants who were HIV-negative. In the overall population, efficacy fell to 49.4% (95%CI: 6.1 to 72.8). Only one severe COVID-19 occurred in the

placebo group but no severe case was reported in the vaccine group. Among the 27 sequenced cases, 92.6% were infected by the 501Y.V2 variant (50). No serious adverse events were associated with the intervention.

CoronaVac developed by Sinovac Biotech is a β -propiolactone-inactivated vaccine produced in Vero cells inoculated with the CN02 strain and administrated in two doses 14 days apart. A phase I/II trial was well tolerated and induced neutralizing response against SARS-CoV-2 among n=743 18-59 year-old Chinese participants (51). T-cell responses were not tested. A phase III trial in Turkey showed an efficacy of 83.5% (95%CI: 65.4 to 92.1) against symptomatic COVID-19 at least 14 days after the second dose and 100% against hospitalization(52). Only one grade 3 systemic allergic reaction after the 1st dose was reported and associated with CoronaVac.

BBIBP-CorV developed by Sinopharm and the Beijing Institute of Biological Products, is an β -propiono-lactone-inactivated vaccine based on the 19nCoV-CDC-Tan-HB02 strain delivered in two doses 21-28 days apart (53). Phase I/II trial showed that BBIBP-CorV was safe and induced humoral responses and neutralizing antibody titers. Interim analyses from a phase III study indicated a 78.1% (95%CI: 64.8 to 86.3) efficacy at preventing symptomatic COVID-19 14 days after the second dose(54). There were 21 COVID-19 cases in the vaccine group (n=12,726) and 95 COVID-19 cases in the placebo group (n=12,737). This trial involved participants aged at least 18 years from the United Arab Emirates (Abu Dhabi, Sharjah) and the Kingdom of Bahrain. The proportion of people aged 60 or over was 1.6%.

The Wuhan vaccine, developed by Sinopharm and the Chinese Academy of Science, is a β -propiolactone-inactivated vaccine based on WIV04 strain (isolated from a patient in the Jinyintan Hospital, Wuhan). Two phase I and II trials showed this vaccine induced neutralizing antibodies (55). A phase III trial indicated an efficacy of 72.8% (95%CI: 58.1 to 82.4) against COVID-19 at least 14 days after the second vaccine dose(54).

Covaxin/BBV152 Bharat Biotech India (BBIL) and the National Institute of Virology developed 3 formulations of Covaxin: BBV152A (3 μ g+alum+imidazoquinoline), BBV152B (6 μ g+alum+imidazoquinoline), and BBV152C (6 μ g+alum). These vaccines are based on a β -propiolactone-inactivated whole virion (strain NIV-2020-770) produced in Vero cells and containing the Asp614Gly mutation isolated from a COVID-19 patient, initially delivered in two doses 28 days apart. However, the Indian Health Ministry increased the interval to 4-8 weeks (56). BBV152 has completed phase I/II trials and is currently under phase III trials. In phase I, the overall incidence of solicited local and systemic adverse events in this study was 14–21% in all vaccine-treated groups and BBV15 induced a neutralizing antibody response (57). A phase II study identified that BBV152 generated neutralizing antibodies, humoral, and cell-mediated responses. No serious adverse events were reported (58). In a press communication, Bharat Biotech reported that BBV152 had an efficacy of 78% (95%CI: 61 to 88) in preventing symptomatic COVID-19 (mild, moderate, severe) at least 14 days after the second dose in a phase III study including 25,800 participants negative to SARS-CoV-2 at baseline and aged 18-98 years. 127 symptomatic cases occurred. The frequency of adverse events was low and balanced between groups (59).

EpiVacCorona, developed by Siberia's Vector Institute is a protein subunit vaccine, composed of three synthetic fragments bound to a carrier protein MBP-6xHis-N_nCoV-2019 (made of SARS-CoV-2 N protein). A phase II trial of 86 participants reported that this vaccine induced neutralizing activity (60). No proof of efficacy against COVID-19 was reported.

RBD-Dimer, also named ZF2001 was developed by the Institute of Microbiology, Chinese Academy of Sciences and Anhui Zhifei Longcom Biopharmaceutical. RBD-Dimer is composed of a SARS-CoV-2 Receptor Binding Domain (RBD) antigen expressed in recombinant CHO cells. Two phase I/II trials showed ZF2001 was well tolerated, induced neutralizing antibodies (61) and TH1 and Th2 responses were elicited after vaccination. No on-going phase III results were communicated.

QazVac is an inactivated vaccine. Abdala (called CIGB-66) is a Cuban vaccine formulated from the protein's RBD with an aluminum-based adjuvant(62). El Centro de Ingeniería Genética y Biotecnología communicated an efficacy of 92.3% at preventing COVID-19 in a press release(63). However, at the time of our review, no further information was provided for these two authorized vaccines.

396 **Table 2: Phase III Trials for COVID-19 vaccines**

Vaccine	Author	Study population	Cut-off date	Main endpoint	Symptomatic COVID			Severe COVID-19	Hospitalization	Any unsolicited Serious adverse event	
					Vaccine	Placebo	Efficacy (% 95%CI)	Efficacy (% 95%CI)		Vaccine	Placebo
BNT162b2	Polack et al.	USA, Argentina, Brazil, Germany, S. Africa, Turkey	November 14, 2020	After dose 1	50/21,314	275/21,258	82% (75.6 to 86.9)	88.9% (20.1 to 99.7)			
				After dose 2 Covid-19 with onset at least 7 days after the second dose without prior infection	8/18,198	162/18,325	95% (90.3 to 97.6)	75% (-152.6%-99.5%)	In placebo group, 1 subject was hospitalized and 1 was in ICU for heart block	0.6%	0.5%
	Thomas et al. (Preprint)	≥16 years	March 13, 2021	After dose 2 Covid-19 with onset at least 7 days after the second dose without prior infection	77/20,998	850/20,713	91.3% (89.0 to 93.2)	97% (80 to 99.9)	-	1.2%	0.7%
	Frenck et al.	USA 12-15 years	January 12, 2021	After dose 2 Covid-19 with onset at least 7 days after the second dose without prior infection	0/1,005	16/978	100% (75.3 to 100)	No cases of severe Covid-19 were observed	-	0.4%	0.1%
mRNA-1273	Baden et al.	USA ≥ 18 years	November 21, 2020	After dose 1	7/996	39/1079	80.2% (55.2 to 92.5)	42.6% (-300.8 to 94.8)			
				After dose 2 Covid-19 with onset at least 14 days after the second dose without prior infection	11/14,134	185/14,075	94.1% (89.3 to 96.8)	100% (no CI estimated)	3 severe COVID-19 resulted in hospitalization in the placebo group and one participant was hospitalized in the vaccine group	0.6%	0.6%

	Modern a press commu nicatio n		April 9 th , 2021	14 days after the second dose			90%	95%			
CVnCoV	Clinical trials.g ov	Argentina, Belgium, Colombia, Dominican Republic, Germany, Mexico, Netherlands , Panama, Peru, Spain	Estimated completion date: May 15, 2022	On going	More than 35,000 adults		On going	On going	On going	On going	On going
AZD1222 ChAdOx1 nCoV-19 vaccine	Emary et al.	UK	January 14, 2021	Symptomatic Covid- 19 with onset at least 14 days after the second dose without prior infection	59/4,244	210/4,290	Alpha: 70.4% (43.6 to 84.5) Non-VOC lineages: 81.5% (67.9 to 89.4)	-	There were no cases of hospitalization or death	-	-
	Voysey et al.	UK/Brazil/S outh Africa ≥ 18 years	December 7, 2020	Symptomatic Covid- 19 with onset at least 14 days after the second dose without prior infection	84/8,597	248/8,581	66,7% (57,4% to 74%)	Efficacy against hospitalization from 22 days after vaccination: 100%	In the vaccine group, two participants were admitted to hospital and 22 participants were hospitalized in the control group	0.7%	0.8%
	Madhi et al.	South Africa ≥ 18 years	November 9, 2020	Mild-to-moderate Covid-19 with onset at least 14 days after the second dose without prior infection	19/750	23/717	21.9 (-49.9 to 59.8)	No participant had severe COVID-19	There were no cases of hospitalization for severe Covid-19 observed in this study	14 events	13 events
				Against B.1.351 variant at least 14 days after the second	19/750	20/714	10.4% (-76.4 to 54.8)				

				dose without prior infection							
	Press communication	USA ≥ 18 years	March 25, 2021	Preventing symptomatic COVID-19	190 cases among 32,449 participants		76% (68 to 82)	100%	Efficacy against hospitalization: 100%	-	-
Ad26.COV2.S	US FDA and EMA	Brazil, Chile, Argentina, Colombia, Peru, Mexico, US, South Africa ≥ 18 years Variant D614G 96.4% in the US Beta (94.5% in South Africa) Variant P2 (69.4% in Brazil)	January 22, 2021	Prevent confirmed, moderate to severe/critical COVID-19 at least 14 days after vaccination without prior infection	116/19,514	348/19,544	All: 66.9% (59.1 to 73.4) USA: 74.4% (65 to 81.6) South Africa: 52% (30.3 to 67.4) Latin America: 64.7% (54.1 to 73)	All: 76.7% (54.6 to 89.1)	93.1% (72.7 to 99.2) *any positive PCR	0.4%	0.4%
				Prevent confirmed, moderate to severe/critical COVID-19 at least 28 days after vaccination without prior infection	66/19,306	193/19,178	All: 66.1% (55.0 to 74.8) USA: 72% (58.2 to 81.7) South Africa: 64% (41.2 to 78.7) Latin America: 61% (46.9 to 71.8)	All: 85.4% (54.2 to 96.9)	100% (74.3 to 100) *any positive PCR		
Gam-COVID-Vax Sputnik V	Logunov et al.	Russia ≥ 18 years	November 24, 2020	First confirmed COVID-19 after the first dose	79/16,427	96/5,435	73.1% (63.7 to 80.1)	-	-	0.3%	0.4%
				First confirmed COVID-19 after the second dose	16/14,964	62/4,902	91.6% (85.6 to 95.2)	100% (94.4 to 100) **Moderate or	-		

								severe			
NVX-CoV2373	Shinde et al.	South Africa ≥ 18 years Beta: 90% of cases in South Africa	November 25, 2020	Preventing symptomatic COVID-19 at least 7 days after the 2 nd dose without prior infection	44/1,357	29/1,327	All: 49.4% (6.1 to 72.8%) HIV-negative participants: 60% (19.9 to 80.1)	56% **Moderate or severe	-	0.4%	0.2%
	Heath et al.	UK ≥ 18 years	-	Symptomatic COVID-19 at least 7 days after the 2 nd dose without prior infection	10 cases	96 cases	89.7% (80.2 to 94.6) 86.3% (95%CI: 71.3 to 93.5) against Alpha	1 severe COVID-19 in placebo group	-	0.5%	0.5%
	Novavax press release	USA and Mexico	April 30, 2021 (Alpha predominant)	Symptomatic COVID-19 with onset at least 7 days after the second dose without prior infection	14	63	90.4% (82.9 to 94.6) 93.2% (83.9 to 97.1) against variants (mainly Alpha)				
Convidecia™ Ad5-nCoV	CanSino Biologicals Inc document	Pakistan, Mexico, Russia, Chile and Argentina ≥ 18 years	8 February, 2021	Symptomatic COVID-19 disease 14 days after single dose	-	-	68.83%	95.47%	-	-	-
				Symptomatic COVID-19 disease 28 days after single dose	-	-	65.28%	90.07%	-	-	-
CoronaVac	Sinovac document	Brazil, Turkey, Indonesia ≥ 18 years	December 16, 2020	Symptomatic COVID-19 at least 14 days after two doses	Brazil: 253 cases/12,396 health workers Turkey: 29 cases/1,322		Brazil all: 50.65% Turkey: 83.5% Indonesia: 65%	Brazil: 100%	-	-	-

	Tanriover et al.	Turkey ≥ 18 years	January 6, 2021	Symptomatic COVID-19 at least 14 days after two doses	9/6,559	32/3,470	83.5% (65.4 to 92.1)	-	100% (20.4 to 100)	0.1%	0.1%
BBIBP-CorV	Al Kaabi et al.	Bahrain, China, Pakistan, and the UAE ≥ 18 years	December 20, 2020	Symptomatic COVID-19, 14 days after the second dose without prior infection at baseline	21/12,726	95/12,737	78.1 (64.8 to 86.3)	100% (NA)	-	0.4%	0.6%
Wuhan inactivated vaccine	Al Kaabi et al.	Bahrain, China, Pakistan, and the UAE ≥ 18 years	December 20, 2020	Symptomatic COVID-19, 14 days after the second dose without prior infection at baseline	26/12,743	95/12,737	72.8% (58.1 to 82.4)	100% (NA)	-	0.5%	0.6%
COVAXIN	Bharat Biotech	India ≥ 18 years	-	Symptomatic COVID-19, 14 days after the second dose without prior infection at baseline	127 symptomatic cases among 25,800 participants		78% (61 to 88)	100% (60 to 100)	-	-	-
Curevac	Curevac Press release	Ten countries in Latin America and Europe. ≥ 18 years	Not specified	COVID-19 disease of any severity, including single non- respiratory mild symptoms, 14 days after the second dose	83	145	All population: 48% (42% to 67%) 18-60 years old: 53%	77% (moderate COVID-19)	100% (hospitalization or death)	-	-
Abdala	Press release			COVID-19 (not specified)	-	-	92.3%	100%	-	-	-

- means missing or not reported data

Challenges with variants of concern and neutralization assays

Mutations and variations occur in the SARS-CoV-2 virus due to evolution and adaptation processes(64). Some SARS-CoV-2 variants of concern with mutations in the spike protein were identified with an increased transmissibility(3,65–69), which may be explained by an enhanced spike protein binding affinity for the ACE2 receptor. For example, Alpha and Beta have been shown to have a 1.98-times and 4.62-times greater binding affinity than ancestral strain(70). Delta was also associated with lower Ct values and a longer viral shedding compared to wild-type SARS-CoV-2 and Alpha. These variants may cause more severe disease(5) and/or have a potential ability to escape the host or vaccine-induced immune response (8,11) (**Table 3**). Results from several seroneutralization assays to assess the neutralizing response of vaccine-induced antibodies are described in **S1 Table** and in **Figure 2**. In general, B.1.1.7 had a minimal impact on neutralization activity of antibodies by post-vaccination sera. Neutralization was further reduced for variants with mutation E484K, and P1. Beta had the highest reduction in neutralizing titers.

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Fig 2: Average fold reduction in neutralizing response against SARS-CoV-2 variant versus wild type/D614G SARS-CoV-2 for each COVID-19 vaccine in 36 seroneutralization assays. The line in the middle of the box is the median. The box edges are the 25th and 75th percentiles

424 **Table 3: COVID-19 vaccines and variants**

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SARS-CoV-2 variants	B.1.1.7 501Y.V1	B.1.351 501Y.V2	B.1.1.28.1 .P1 501Y.V3	B.1.617.2	B.1.617.1
WHO nomenclature	Alpha	Beta	Gamma	Delta	Kappa
Key spike mutations	69/70del, 144del, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H	D80A, D215G, 241/243del, K417N, E484K, N501Y, D614G, A701V	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G H655Y, T1027I, V1176F	T19R, T95I, G142D, E156-, F157-, R158G, , L452R, T478K, D614G, P681R, D950N ± (V70F, A222V, W258L, K417N)	G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H ± (T95I)
First detection	UK	South Africa	Brazil and Japan	India	India
Transmission compared to non-VOC/VOI	+56% in the UK +56-74% in Denmark, Switzerland, US 43-100% higher reproductive number	+50% in South Africa	+160% in Brazil	+40 to 60% in the UK (compared to Alpha) +97% higher reproductive number	Under investigation
Risk of mortality	Increased 61-64% mortality in the UK	Under investigation	Under investigation	Under investigation	Under investigation
Impact on post-vaccination sera (reduction in neutralization activity)	No/Minimal: BNT162b2, mRNA-1273, Sputnik V, Covaxin, NVX-CoV2373, BBIBP-CorV, CoronaVac Minimal/Moderate: AZD1222	Minimal/Modest: BBIBP-CorV, CoronaVac Minimal to substantial : BNT162b2, mRNA-162b2, AZD1222, Sputnik V, NVX-CoV2373, CoronaVac	Minimal to moderate: BNT162b2 and mRNA-1273, AZD1222 Modest: CoronaVac	Minimal/Modest: Covaxin, mRNA-1273, BN162b2 (sublineage unspecified)	Likely
Efficacy/effectiveness against disease or infection	Protection retained for infection, COVID-19 and severe COVID-19	Protection retained for severe COVID-19 Possible reduced protection for infection and COVID-19	Limited evidence	Protection retained for severe COVID-19 Possible reduced protection for infection and COVID-19	Limited evidence

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SARS-CoV-2 variants	B.1.525	P2	P3	B.1.526	B.1.427	B.1.429
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						CAL.20C
	Eta	Former Zeta	Former Theta	Iota	Former Epsilon	Former Epsilon
Key mutations	Q52R, A67V, 69/70del , 144del, E484K, D614G, Q677H, F888L	E484K, D614G, V1176F	141/143del, E484K, N501Y, D614G, P681H, E1092K, H1101Y, V1176F	L5F, T95I, D253G, D614G, A701V+(E484K or S477N)	S13I, W152C, L452R, D614G	S13I, W152C, L452R, D614G
First detection	Multiple countries	Brazil	Philippines	USA	USA	USA
Transmission	Under investigation	Under investigation	Under investigation	Under investigation	+18.6 to 24% in California	+18.6 to 24% in California
Risk of mortality	Under investigation	Under investigation	Under investigation	Under investigation	Under investigation	Under investigation
Efficacy/effectiveness against disease or infection	Limited evidence	Limited evidence	Limited evidence	Limited evidence	Limited evidence	Limited evidence

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Alpha

Alpha was identified in the south of the UK in December 2020. Several published and unpublished neutralization assays tested vaccinated serum against Alpha (compared to wild-type strain). They indicated a reduction in neutralizing antibody activity ranging from no reduction to 3.3-fold for BNT162b(10,71–82) ; from no reduction to 2.3-fold reduction for mRNA-1273(9,10,76,83) ; 2.1-fold reduction for AZD1220(78) and NVX-CoV2373(84); from 1.5 to 2.5-fold reduction for CoronaVac(85,86). No reduction was observed for Covaxin, Sputnik V and BBIBP-CorV(79,85,87) with the wild type SARS-CoV-2 or D614G as reference strains. Overall, experimental studies with Alpha suggested no/minimal impact on post-vaccination sera.

Beta

Beta was identified in South Africa and harbors 3 mutations in the receptor-binding domain (RBD) that SARS-CoV-2 uses to bind to the human ACE2 receptor: amino acid changes K417N, E484K and N501Y (88). Reduction in neutralizing response was more important against 501Y.V2 with a reduction from 1.3 to 38.45 for BNT162b(8,10,71–74,76,77,80,81,89) ; from 3.3 to 23.45 for mRNA-1273(10,76,83,90,91) ; 6.1-fold reduction for Sputnik V(79) ; from 3.3 to 5.3 reduction for CoronaVac(85,86) and no reduction for BBIBP-CorV(85,92) with the wild type SARS-CoV-2 or D614G, as reference strains.

Gamma, Zeta, Eta, Iota and Epsilon

Gamma variant was first identified in Brazil, and in travelers from Brazil in Japan and South Korea. Gamma, Zeta, Eta and Epsilon variants contain the E484K mutation which is associated with partial or complete escape from neutralizing antibodies (12,93). According to two preprints, Gamma could be 1.4 to 2.6 times more transmissible than previous variants in Brazil (4,7). In the USA, Epsilon showed an 18.6-24.0% increase in transmission relative to wild type circulating strains in California (94). These Californian variants were associated with a 2-fold increased viral shedding in vivo. A preprint reported an emerging variant Iota first identified in New York City, with a detection rate in sequenced genomes increasing from 1.3% in early November to 12.3% in February 2021, with three main mutations (E848K and N501Y, D253G)(95). Several other variants such as Zeta in Brazil and Delta in India are under investigation. Four assays testing serum for mRNA vaccines found a reduction in neutralizing response from 1.2 to 6.7-fold against the Gamma variant(71,73,76) ; a 2-fold reduction against Epsilon (CAL.20C) variant and a 3.3-3.6-fold reduction against the B.1.526 variant. For CoronaVac, fold decrease in pseudovirus neutralization was 1.25; 3.92 and 4.03 for Epsilon; Gamma and Iota respectively(86).

Delta

By the end of March 2021, the B.1.617 variant was present in 15-20% of Indian samples. At the time of this review, Delta is becoming worldwide dominant. Delta is 40-60% more transmissible than Alpha with a higher secondary attack rate(68,69). Neutralization essays reported a reduction in neutralizing response from 1.4 to 11.14-fold (median: 2.7) for BNT162b2(96–101) ; from 2.1 to 3.3-fold for mRNA-1273(96,101,102) ; from 3.1 to 4.3-fold for AZD1222(97,99) ; from 1.6 to 5.4-fold for Ad26.COV2.S(101,103) ; 2.5-fold for CoronaVac(104) ; 3-fold for ZF2001(104) ; 2.5-fold for Sputnik V(105) and 4.6-fold for Covaxin(106). Overall, vaccine sera exhibit reduced neutralization capacity against Delta when compared to non-VOC, but they effectively neutralize Delta in vitro.

Several neutralization assays have suggested that a single dose of BNT16b or mRNA-1273 among previously infected subjects could boost the cross-neutralization response against emerging variants

such as B.1.1.7, B.1.351 or P1(82,107). These studies have demonstrated the potential benefits of vaccinating both non-infected and previously infected people. Finally, several studies suggested that a single dose of mRNA vaccine may be sufficient to boost the antibody response in previously infected subjects and that the benefit of the second dose may be small (108–112). Limitations concerning neutralizing essays should be underlined 1) most studies are preprints 2) results cannot be directly translated into a clinical setting 3) methods of the studies varied (replicating, non-replicating pseudovirus vs SARS-COV-2) 4) the time post-vaccination and study populations were not always comparable regarding age or COVID-19 history 5) T-cell response was not assessed. A study based on seven vaccines reported a high correlation between neutralization titers and protection estimated in Phase III trials(113). A 50% protection against SARS-CoV-2 infection corresponded to a neutralization level of 20.2% of the mean convalescent level.

REAL WORLD STUDIES

Post-marketing surveillance studies results are presented in **Table S2**.

Effectiveness against SARS-CoV-2 infection

Following a single dose in general population or healthcare workers in Qatar(114,115), the USA(116–121), Israel(122–124), UK(125,126), Italy(127,128) and Denmark(129), effectiveness of mRNA vaccines was 46-78% ; 29.5-81.6% and 16.9-47.9% against unspecified SARS-COV-2 strain, Alpha, and Beta respectively (**Fig 3**). CoronaVac effectiveness against Gamma was 35,1%(130) whereas Ad26.CoV1.S(131) and AZD1222(132,133) had an effectiveness of 55-79.7% against unspecified strain.

After full immunization, effectiveness increased to 90-92% for AZD1222 or BNT162b2, and against unspecified strain. For mRNA vaccines, effectiveness against infection was 89.5-99.2% against Alpha, 75-96.4% against Beta and 80-98.2% against unspecified strain.

Fig 3: Vaccine effectiveness against SARS-CoV-2 infection from real world studies (in % and 95%CI) according to the number of doses.

Confidence intervals are delimited by the grey rectangular area. Blue dots refer to one vaccine dose and orange dots refer to two doses.

Effectiveness against COVID-19 (symptomatic disease)

Following the administration of a single dose in general population or healthcare workers in France(134), Canada(135), Qatar(114,115), Israel(122,123,136), UK(137), Italy(128), effectiveness of mRNA vaccines against COVID-19 was 38.2-88% against Alpha ; 0-83% against Beta/Gamma ; 35.6-72% against Delta and 57-90% when the strain was not sequenced (**Fig 4**). AZD1222 in Canada(135), France(138) and UK(137), had an effectiveness of 48.7-64 against Alpha ; 48% against Beta/gamma and 30-67% against Delta. In Chile(139) and in Brazil(130), CoronaVac had an effectiveness of 15.5 – 49.6% against Alpha/Gamma.

After full immunization, mRNA vaccines effectiveness against disease increased to 88-100% against Alpha, 76-100% against Beta/Gamma, 87-88% against Delta, and to 89-100% when SRAS-CoV-2 strain was not sequenced. AZD1222 effectiveness against disease increased to 74.5% against Alpha and 67% against Delta in the UK. CoronaVac effectiveness was 65.9-73.8% against Alpha/Gamma/D614G strain in Chile and Brazil.

Fig 4: Vaccine effectiveness against SARS-CoV-2 asymptomatic or symptomatic infection from real world studies (in % and 95%CI) according to the number of doses.

Confidence intervals are delimited by the grey rectangular area. Blue dots refer to one vaccine dose and orange dots refer to two doses.

Overall, mRNA-vaccines seem to offer the strongest protection against COVID-19 for all variants after full immunization. Despite a high level of protection, a small proportion of fully vaccinated individuals will develop asymptomatic or symptomatic SARS-CoV-2 infections. Following the second dose, 1% of 13,048 nursing home residents in the USA who received both doses of vaccine were infected(140). Two studies in Israel and in the USA indicated that among participants vaccinated with mRNA-vaccines, infections were associated with a lower viral load and a reduced duration of illness(141,142). Among 28,342 vaccinated healthcare workers in India, 5,3% and 5% were infected after a single dose and two doses of Covishield respectively. Most infections were mild and did not results in severe COVID-19(143). A study in England reported a reduced transmission associated with BNT162b2 or AZD1222 vaccines among household setting(144) and two other preliminary analyses confirmed these results(145,146).

After a single dose, mRNA vaccines or AZD1222(121,123,135,147–150) had an effectiveness against COVID-19 hospitalization or death of 37.5%-94% when the strain was not sequenced, 80% against Alpha, 77% against Beta/gamma, and 78% against Delta (**Fig 5**). After full immunization, mRNA vaccine or AZD1222 effectiveness against hospitalization or death was over 87-94%(123,151) when the strain was not sequenced, 95% against Alpha, 95% against Beta/Gamma. CoronaVac also had a strong effectiveness against hospitalization (87.5%) or mortality (86.3%) after full immunization(139).

Fig 5: Vaccine effectiveness against SARS-CoV-2 hospitalization or death from real world studies (in % and 95%CI) according to the number of doses.

Confidence intervals are delimited by the grey rectangular area. Blue dots refer to one vaccine dose and orange dots refer to two doses.

Severe side effects

Among adults, the main severe side effect reported were very rare: anaphylaxis (2.5-4.7 cases per million doses among adults) and myocarditis (3.5 cases per million) for mRNA vaccines ; thrombosis with thrombocytopenia syndrome for Janssen vaccine (3 cases per million) and AstraZeneca vaccine (2 cases per million) and Guillain-Barré syndrome (7.8 cases per million) for Janssen vaccine.

A cohort of 627,383 vaccinated individuals who were able to self-report their post-vaccination symptoms through an app, showed systemic and local side-effects were reported at lower frequencies than were declared in phase III trials(152). Anaphylaxis, an acute allergic reactions associated with both mRNA-vaccines, occurred rarely, typically within 15 minutes after vaccine administration. 2.5-4.7 cases were reported per million dose administered in the USA (2.5-4.7 cases/1,000,000 doses) (153).

For AZD1222; concerns have been raised regarding unusual blood clots in the brain with low platelet counts (known as cerebral venous sinus thrombosis (CVST)) by several health authorities. The US Center for Disease Control and prevention (US CDC) reported about 5-6 cases of CVST per million SARS-CoV-2 infections(154). On April 23, the EMA estimated 2 cases of thrombosis with thrombocytopenia (TTS) per 100,000 doses for people aged 20-49 years old, 1 case/100,000 doses for those aged 50-69 years old and even lower case rates (< 1/100,000 doses) for older people. By May 19, 2021, the UK reported an overall incidence of 13 cases of TTS per one-million AstraZeneca doses.

Reported incidence is higher among females. The balance of benefits and risks is very favorable for older people but it is less clear for younger people. For instance, the EMA estimated that the AstraZeneca vaccine could prevent 2-3 COVID-19 ICU admission/100,000 among people aged 20-29 years old, whereas about the case-rate for TTS was around 1.9 cases/100,000 doses in this age group(155).

Similar to AZD1222, as of July 8, 2021, the US CDC reported 38 confirmed cases of TTS among 12.5 million doses administered, although under-reporting is likely due to a passive surveillance system(156). Case-rate among females was the highest (8.8 per million) for those 30-49 years old. Overall TTS case-rate was 3 per million doses among adults. Guillain-Barré syndrome was also reported to have a case-rate of 7.8 cases per million doses among adults.

Heterologous prime-boost vaccination

Changing recommendations for young people regarding use of AZD1222 and the need to accelerate the vaccination campaign has led some countries to advise heterologous prime-boost vaccination with a second dose of mRNA vaccines. An RCT conducted in the UK indicated an increase in systemic reactogenicity in a heterologous vaccination context vs homologous vaccination(157) but efficacy data has not been yet published. A press communication from El Instituto de Salud Carlos III about a phase II trial in Spain showed that the combination of AZD1222 and BNT162b2 induced a strong humoral response when compared to no second dose(158).

Difficulties when comparing COVID-19 vaccines

Our review present several limitations. Several analyses were not peer-reviewed and only press communications or regulatory market authorization files were available for CoronaVac, BBIBP-CorV, Wuhan inactivated vaccine, Covaxin and NVX-CoV2373. Clinical trials used different definitions for COVID-19 and different primary endpoints which make direct comparisons difficult. Janssen's primary endpoint is moderate/severe/critical COVID-19 whereas Pfizer and Moderna included mild COVID-19. The endpoint time was also heterogenous across trials, but most trials used 14 days after the full immunization. Real world studies present large variations in time post-vaccination, exposition to SARS-CoV-2 strain, susceptibility to infection (previously infected or not), study population (healthcare workers, older adults, immunodepressed, chronic medical conditions ...). For example, healthcare workers treating COVID-19 patients may be more frequently exposed to SARS-CoV-2, leading to decreased estimates of effectiveness. Data for specific population such as immune-suppressed patients (typically excluded from trials) is lacking. A few immunogenicity studies patients with transplants, and patients with cancer identified a poor antibody response after a single dose of Pfizer vaccine (159,160) . Most of studies have focus on periods that are 90 days or less from the time of vaccination. The latest durability data also shoe a clear trend of steady waning of neutralizing antibodies over the first 6 months after the second dose of mRNA-1273(161). Ad26.COV2.S vaccine induced a durable humoral and cellular response for at least 8 months after immunization(162).

Conclusion

Only 6 months occurred between the declaration of COVID-19 as a pandemic and the launch of the first phase III vaccine trials.

Overall, COVID-19 vaccines appear to be safe and effective tools to prevent symptomatic and severe disease, hospitalization and death against all variants of concern, confirming the results from phase III clinical trials. However, to date, available data vary greatly depending on the vaccines considered.

mRNA vaccines were shown to reduce the incidence of asymptomatic COVID-19 and viral load and thus, potentially transmission.

According to safety monitoring, reported serious adverse events were very rare and were mostly anaphylaxis and myocarditis for mRNA vaccines, thrombosis with thrombocytopenia syndrome after Ad26.COV2.S or AZD1222 administration and Guillain-Barre Syndrome for Ad26.COV2.S. The benefits of COVID-19 vaccination far outweigh the potential risks.

Vaccinating previously infected people with a single dose provided an equivalent neutralizing response compared to people vaccinated with two doses against the variants. More research is needed for specific population group (immunodepressed, pregnant women...), heterologous vaccination, dosing intervals, vaccine breakthrough and duration of vaccine immunity.

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Authorship statement

TF and NPS designed and conducted the research. TF wrote the first draft of the paper. All authors (TF, YK, CJM, JG, NPS) contributed to the data interpretation, revised each draft for important intellectual content, and read and approved the final manuscript.

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