

Review of COVID-19 vaccine subtypes, efficacy and geographical distributions

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ABSTRACT

As of 1 May 2021, there have been 152 661 445 Covid-19 cases with 3 202 256 deaths globally. This pandemic led to the race to discover a vaccine to achieve herd immunity and curtail the damaging effects of Covid-19. This study aims to discuss the most recent WHO-approved Covid-19 vaccine subtypes, their status and geographical scheduled updates as of 4 May 2021. The keywords "Covid-19, Vaccines, Pfizer, BNT162b2, AstraZeneca, AZD1222, Moderna, mRNA-1273, Janssen, Ad26.COVS.2" were typed into PubMed. Thirty Two relevant PubMed articles were included in the study. The vaccines discussed are Pfizer/BNT162b2, Moderna Vaccine/mRNA1273, AstraZeneca/AZD122/ChAdOx1 n-CoV-19 and the Janssen vaccines/Ad26.COVS.2, as well as their platforms, trials, limitations and geographical distributions. As of 16 May 2021, the number of countries that have approved the use of the following vaccines is Pfizer in 85, Moderna in 46, Oxford/AstraZeneca in 101, and Janssen in 41.

INTRODUCTION

As of 1 May 2021, there have been 152 661 445 confirmed cases of COVID-19 and 3 202 256 deaths globally.¹ As we continue to learn more about this novel virus, it continues to be an unprecedented event in global history. At this point, very few countries in the world have been left unaffected. The USA, India and Brazil have seen the highest number of confirmed cases thus far.

Even though it may seem life as we know it has changed drastically, pandemics are not a stranger to the world. A century ago, the 1918 Spanish influenza pandemic, known as one of the deadliest events in human history, took the lives of 50 million persons or more. Other pandemics in history include the HIV/AIDS pandemic (1981), H1N1 'swine' influenza (2009), Chikungunya (2014) and Zika (2015), as well as pandemic-like emergences of Ebola fever over large parts of Africa (2014 to the present).²

The emergence of the pandemic led to the race to discover a vaccine to achieve herd immunity and curtail the damaging effects of COVID-19. Currently, the efforts to develop a vaccine are paying off. Some vaccine candidates have shown worthy results and roll-outs have begun across nations.³

On 31 December 2020, the Pfizer COVID-19 vaccine (BNT162b2) was issued for emergency use listing by WHO. This was followed by the AstraZeneca/Oxford COVID-19 vaccine, manufactured by the Serum Institute of India and SKBio on 15 February 2021, and most recently, on 12 March

2021, the Ad26.COVS.2, developed by Janssen (Johnson & Johnson) and Moderna on 30 April.⁴

COVAX, coordinated by WHO, Gavi: The Vaccine Alliance, the Coalition for Epidemic Preparedness Innovations (CEPI), acts as a programme that supports the development of COVID-19 vaccine candidates and negotiates their pricing to ensure low-and-middle-income countries have a fair shot at receiving vaccines.⁵

This article aims at discussing the most recent WHO-approved COVID-19 vaccine subtypes, their status and geographical scheduled updates as of 4 May 2021.

COVID-19 EMERGENCE

With the epidemic of pneumonia cases appearing in Wuhan City on 31 December 2020, scientists were able to isolate and identify the virus responsible on 7 January 2020; it was found to be 96% genetically similar to the RaTG13 strain suggesting the disease originated from bats. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) comes from the beta subtype of the Coronaviridae family and is transmitted via droplet transmission greater than 5 µm up to greater than 1 m away.⁶ As the upper and lower respiratory tract are mainly infected, influenza-like symptoms tend to be predominant; however, sites where the ACE2 receptor can also be found such as colons, heart and kidneys can be affected as well. Carriers of the SARS-CoV-2 can present as either symptomatic or asymptomatic.^{7,8}

VACCINE SUBTYPES

mRNA

BNT162b2/ Pfizer

This is a lipid nanoparticle-formulated, nucleoside-modified RNA vaccine that works against the S protein of the SARS-CoV-2 virus.⁹ This vaccine allows for the body to create an antibodies response to neutralise the virus which is dependent on the S protein for entry via the ACE2 receptor on type 2 alveolar cells.

mRNA-1273/Moderna

This is a lipid nanoparticle-encapsulated nucleoside-modified messenger RNA (mRNA)-based vaccine. It encodes the prefusion stabilised full-length spike protein of SARS-CoV-2. This spike glycoprotein moderates host cell attachments. Hence, it is essential for viral entry and thus the primary vaccine target. The vaccine gives rise to a vigorous binding and neutralising



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antibody response.¹⁰ This also includes CD4⁺ T-cell and CD8⁺ cytotoxic T-cell response to eliminate the virus.¹¹

Adenoviruses

Viral vectors provide an avenue for vaccines. The vectors may generally be classified as replicating or non-replicating vectors. Adenoviruses (Ads) are an example of vectors with both traits.¹² This platform was explored by the Oxford/AstraZeneca vaccine and the Janssen Pharmaceuticals vaccine by Johnson & Johnson. Both these vaccines encode the S protein of the SARS-CoV-2 virus.¹³ After vaccination, it is expected that the surface spike protein is produced, encouraging the immune system to attack when it encounters the SARS-CoV-2 virus. ChAdOx1-S- (AZD1222) uses a chimpanzee adenovirus vector while Ad26.COV2.S relies on a recombinant human-based adenovirus vector. However, the Janssen vaccine is advantageous over the other candidate, as it is administered in only one dose, which reduces manufacturing costs.¹³

Oxford/AstraZeneca/AZD1222

The University of Oxford and the British-Swedish pharmaceutical company AstraZeneca partnered to develop a non-replicating chimpanzee viral vector vaccine, formerly known as ChAdOx1nCoV-19 and now called AZD1222.¹⁴ It is branded and popularly known as the 'AstraZeneca Vaccine' or 'Covishield Vaccine' if manufactured by the Serum Institute of India. 'Covishield' is produced based on the same technology by the Serum Institute of India to supply low-to-middle-income countries through COVAX.

Janssen vaccine/Ad26.COV2.S

This is a non-replicating, recombinant human adenovirus type 26 which contains a full-length SARS-CoV-2 S protein that induces an antibody response against the SARS-CoV-2 infection. Antibody directed against the S protein prevents invasion of the SARS-CoV-2 virus in type 2 alveolar cells of the lungs, thus reducing the severity and morbidity of the infection.¹⁵

Advantages of adenoviral vectors are adjuvant qualities, scalability and their broad tissue tropism.¹¹ On the downside, there is likely to be a slower pace of vaccine manufacturing in an outbreak setting, such as the current pandemic, as these laboratories need to have biosafety level 2. In addition, there is the possibility of pre-existing immunity to viral vectors, decreasing the effectiveness of the vaccine. The Oxford/AstraZeneca was able to overcome this disadvantage by using the Chimpanzee adenovirus (ChAdOx1) which represents an alternative to the human Ad vector and lacks preexisting immunity in humans.^{16 17}

TRIALS AND LIMITATIONS

Pfizer vaccine/BNT162b2

Trial

A randomised controlled trial was designed to evaluate the efficacy of the Pfizer vaccine which consisted of a group of

participants aged 16 and over. In total, 43 548 participants were randomised in a 1:1 ratio with one group receiving the vaccine and the other a placebo.

Efficacy

Results showed 180 cases of SARS-CoV-2, 8 coming from the vaccinated group and 172 coming from the placebo group.⁹ This indicates a 95% effectiveness at preventing COVID-19 infections.¹⁸

Adverse effects

For the safety of this trial, local and systemic symptoms were solicited and unsolicited (using an electronic diary) adverse effects following 28 days after the first dose of Pfizer, and unsolicited adverse effects 6 months after the second dose. It was seen that more of the vaccinated group reported adverse side effects versus the placebo group. Reports of adverse events were 27% for vaccinated and 12% for placebo patients. Among the vaccinated group, shoulder injury related to vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and right leg paresthesia were reported.⁹

Moderna/mRNA-1273

Trial

According to the dose-escalation, open-label clinical study, done in March 2020, the two-dose vaccine series was determined necessary and had no serious toxicity. Reactogenicity was greater following the second dose of Moderna, and immunogenicity was determined as it induced a robust binding antibody response in all participants.¹⁰

Efficacy

Under another randomised, stratified, observer-blinded, placebo-controlled study, Moderna has an efficacy of 94.1%. This study consisted of 30 420 medically stable adults with no known history of COVID-19 or high risk of severe COVID-19 infection. Participants were randomly allocated to receive either two doses of the Moderna vaccine or saline placebo in a 1:1 ratio. This was done 28 days apart in the same arm.

At least 14 days after the second injection, Moderna efficacy was 94.1% for the prevention of symptomatic SARS-CoV-2 in comparison with the saline placebo. This included 196 seropositive COVID-19 cases, of which 185 were in the saline placebo group and 11 in the Moderna group.

Moderna efficacy 14 days after the first dose was 95.2% at preventing severe COVID-19. Another analysis incorporated participants who were SARS-CoV-2 seropositive before the administration of Moderna or saline placebo. This also indicated a vaccine efficacy of 93.6%. Lastly, 30 participants had severe COVID-19, which came exclusively from the saline placebo group, thus indicating vaccine efficacy of 100% for severe COVID-19. However, this 95% CI could not be estimated to 1.0. A single death among these participants was associated with COVID-19.

This Corona Virus Efficacy (COVE) phase III trial also stated that the vaccine efficacy to prevent COVID-19 was harmonious across subgroups. These included stratification by demographic and baseline characteristics such as age and health risk which incorporated comorbidities like chronic lung, cardiac and liver disease. It also included severe obesity and diabetes.¹⁸

Table 1 Upcoming vaccines in phase III trials as of 4 May 2021³⁶, table 1

Name	Platform	Countries that are producing it	WHO status	Anticipated release date
Sinovac	Inactivated, produced in Vero cells	China	In progress	Early May
Sinopharm	Inactivated, produced in Vero cells	Beijing	In progress	Early May

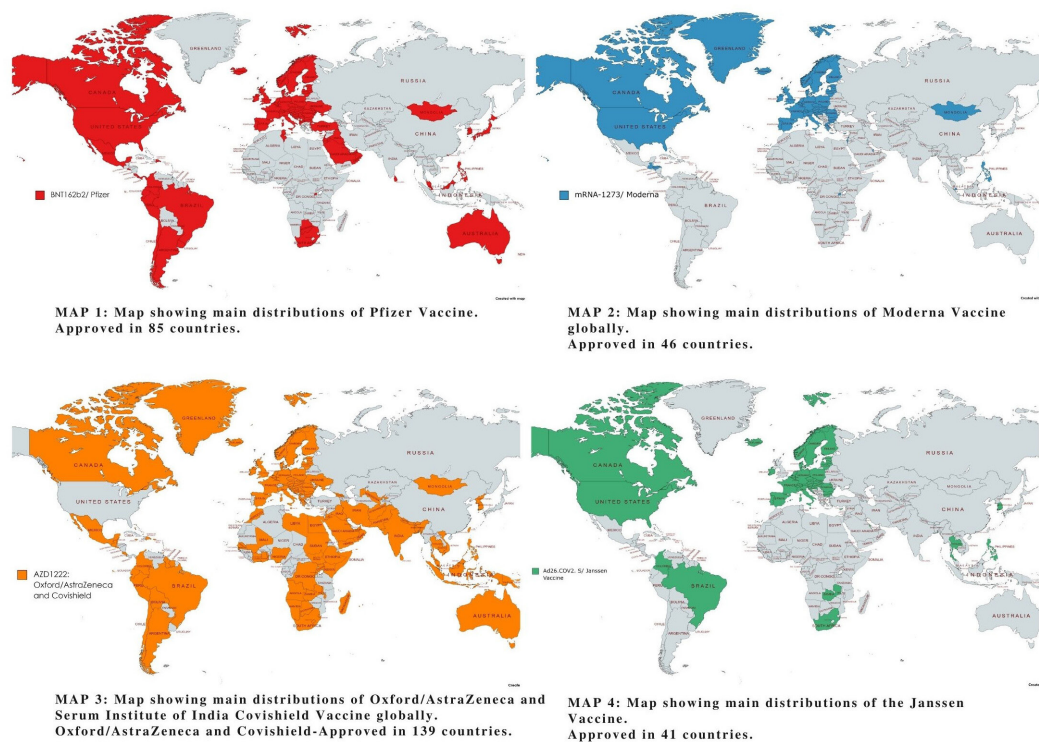


Figure 1 Image showing main distribution of vaccines as of 16 May 2021.^{34 35}

Adverse events

Under the same study, adverse events developed more frequently in the Moderna group following the first and second doses. Mild injection site pain was common and lasted approximately 3 days. However, the delayed injection-site reactions which included erythema, tenderness and induration were uncommon and generally resolved within 4 to 5 days. Fatigue, myalgia, arthralgia and headaches increased after the second dose of the Moderna vaccine and lasted approximately 3 days. The incidence of adverse events in the Moderna group was not affected by age and had no sequelae.¹⁸ Another study included localised axillary swelling or tenderness ipsilateral to the injection site and systemic rash as adverse events.¹⁹ In another trial extension of 40 participants, half were between the ages of 56 and 70 years. The other half was more than 71 years of age. In both age groups, the adverse events were mainly mild or moderate.²⁰

Hypersensitivity reactions were reported in both groups but were slightly higher in the Moderna vaccine (1.5%) compared with the placebo (1.1%).¹⁸ A questionnaire and an allergology study (skin prick testing with the vaccine) can be used in the selection of patients with severe allergic reactions to determine who could safely receive the Moderna or Pfizer vaccines. In 129 administered vaccines, 128 had no reaction resulting in 99.22% of patients with previous severe allergic diseases tolerating the mRNA vaccination.²¹

AstraZeneca/ChAdOx1 nCoV-19/AZD1222

Trials

Four ongoing randomised, controlled trials were done across three countries: (1) COV001-phase I/II in the UK; (2) COV002-phase II/III in the UK; (3) COV003-phase III in Brazil; (4) COV005-phase 1/2 in South Africa. All are single-blinded except COV005 which is a double-blind study.²² Social distancing was successful in reducing transmission in the UK; hence, countries such as Brazil and South Africa were recruited for vaccine trials

due to their large number of active COVID-19 cases.²³ Participants randomly received either the ChAdOx1 nCoV-19 vaccine or control. The control was either meningococcal conjugate vaccine (MenACWY) or saline depending on the trial. Three of the trials also did not restrict enrolment based on age or the presence of comorbidities.²⁴ The trials also differed in some ways.

In COV002, there were two dosage groups: low dose/standard dose (LD/SD) or two standard doses (SD/SD). The LD/SD group received 2.2×10^{10} viral particles as their first dose and then boosted with the standard dose. In COV003, those at high risk of exposure to the virus such as healthcare workers were mainly targeted. All participants were offered two doses of the vaccine at a dose of $3.5\text{--}6.5 \times 10^{10}$ viral particles, up to 12 weeks apart.^{22 24} In COV005, healthy adults aged 18–65 years living without HIV were targeted. Those living with HIV were also enrolled. Eleven participants were offered two doses of the vaccine, $3.5\text{--}6.5 \times 10^{10}$ viral particles, administered 4 weeks apart. A small subgroup of 44 participants received a half-dose vaccine (21 as their first dose and 23 as their second dose).^{22 24}

Efficacy

Overall, the vaccine's efficacy varies by the dosing interval. Interestingly, the studies were initially planned as single-dose studies. However, after a review of phase I data showed a significant increase in neutralising antibodies with a second dose of the vaccine, the study was amended to explore this finding more. This is an advantage as a 3-month dose interval can protect a large percentage of the population when vaccine supplies are low, while simultaneously improving protection after the second dose. In an interim study, the efficacy of two doses of the vaccine was 70.4% and protection of 64.1% after at least one standard dose, against symptomatic disease. Based on this study, the vaccine was authorised for emergency use in the UK on a regimen of two standard doses administered 4–12 weeks apart for adults aged 18 years and older. Many other countries also use

this plan. It was also advised that when vaccine supply is scarce, countries should vaccinate with a single dose. This may provide better overall protection in the population than vaccinating half the number of individuals with both doses.²⁵ Another study reports that vaccine efficacy is generally reported as a relative risk reduction (RRR). For the AstraZeneca–Oxford vaccine, the RRR is 67%.²⁶

Adverse effects

The occurrence of any serious adverse events (SAE) was evaluated in 12 174 ChAdOx1 nCoV-19 recipients and 11 879 control recipients.²⁴

The vaccine group had 0.7% SAEs compared with 0.8% in the placebo group. There were three cases of transverse myelitis (two cases with the vaccine; one case with placebo), but these were deemed unrelated to the vaccine. Overall mortality is similar between groups.²⁷

Janssen vaccine/Ad26.COV2.S

Trial

One study conducted for the single-shot Janssen vaccine showed that this vaccine is effective at preventing severe SARS-CoV-2 infections. This study consisted of a total of 43 783 seronegative participants who were further subdivided into two age groups: 18–59 years; 60 and over. These participants were randomised into two similar groups into a 1:1 ratio with one receiving the placebo and the other receiving the vaccine.¹⁵

Efficacy

After 14 days of vaccine administration, a total of 468 confirmed cases were obtained from the trial group. In total, 464 were of mild to moderate severity with 116 cases from the vaccinated group versus 348 in the placebo group; this indicated efficacy of 66.9%. After 28 days of follow-up, 66 more cases of moderate to severe-critical cases were confirmed belonging to the vaccinated group and 193 belonging to the placebo; there were also fewer severe-critical cases among older patients than younger patients, which indicates possible early protection from the vaccine, especially in the elderly. After 28 days, the efficacy of the vaccine equalised across all age groups.¹⁵

Adverse effects

For safety, a subset of 3356 vaccinated participants and 3380 of the placebo group were monitored for 7 days after receiving either the placebo or vaccine. It was noted that more adverse effects were seen in the vaccinated group versus the placebo group for ages 18–59. However, for ages 60 and over, there were fewer adverse effects compared with ages 18–59.

Adverse effects are reported mostly but not limited to local signs such as pain at the inoculation site and systemic signs such as fever, headache, myalgia, or nausea.¹⁵

Limitations

Long-term outcome

Efficacy was based on short-term data and waning of efficacy over time has been demonstrated with other vaccines. Moderna's antibody activity remained high in all age groups and persisted throughout the 6 months following the second dose. There is no information thus far after the 6 months.²⁸ In addition, no long-term complications can be determined from current trials.

Pregnancy

COVID-19 infection in pregnancy is associated with an increased risk of morbidity and mortality.²⁹ Pregnancy safety and efficacy were not evaluated for the vaccines in the aforementioned trials. In another study investigating the safety of Moderna in pregnancy, the proportion of adverse pregnancy and neonatal outcomes in persons vaccinated against COVID-19 were similar to those who were not vaccinated.³⁰ However, pregnant women should consult with their health-care provider to make an individual and autonomous decision after weighing the benefits and risks of vaccination.

Age groups

Further assessment of the efficacy of all the vaccines is warranted in all age groups and individuals with comorbidities. Pfizer vaccine trials included individuals over the age of 16 years.⁹ However, the Moderna, Oxford/AstraZeneca and Janssen trials included individuals 18 years and older. As of now, Oxford/AstraZeneca appears to be better tolerated in older adults than in younger adults and has similar immunogenicity across all age groups after a booster dose.³¹

External factors

The Moderna vaccine COVE trial included participants from 99 centres across the USA. Thus, efficacy was determined in a setting of US recommendations for masking, consistent hand washing and social distancing. This may have contributed to decreased transmissibility.¹⁸

Ethnic variations

The relatively small number of participants from ethnic or racial minority groups in these studies limited efficacy evaluations in the aforementioned groups. This also occurred in participants who were previously infected by COVID-19.¹⁸

Variant protection

New variants of SARS-CoV-2 have the potential to complicate the effectiveness of current vaccines. In the UK, ChAdOx1 demonstrated 75% protection against B.1.1.7 (including asymptomatic infection). However, the AstraZeneca vaccine showed only 10% protection against the B.1.351 variant in a young population with a median age of 30 in South Africa, hence their AstraZeneca roll-out was ceased.^{32 33}

Main points

- ▶ Pfizer is a lipid nanoparticle–formulated, nucleoside-modified RNA vaccine. It has an efficacy of 95% and was approved in 85 countries as of 16 May 2021.
- ▶ Moderna/mRNA-1273 vaccine is a nanoparticle–encapsulated nucleoside-modified messenger RNA (mRNA)–based vaccine. It has an efficacy of 94.1% and was approved and distributed in 46 countries as of 16 May 2021.
- ▶ The Oxford/AstraZeneca/AZD122/ChAdOx1 n-CoV-19 vaccine is a viral vector vaccine. It has an efficacy of 70.4% and was approved and distributed in 139 countries as of 16 May 2021.
- ▶ Janssen is a non-replicating, recombinant human adenovirus type 26 with an efficacy of 66.9% and was approved in 41 countries as of 16 May 2021.

GEOGRAPHICAL DISTRIBUTION

See figure 1.^{34 35}

CONCLUSION

The vaccines discussed in this study are Pfizer/BNT162b2, Moderna vaccine/mRNA1273, AstraZeneca/AZD122/ChAdOx1 n-CoV-19 and Janssen vaccine/Ad26.COV2.S. In addition, their platforms, trials, limitations and geographical distributions were also reviewed. The platforms used were mRNA and adenoviruses.

It can be seen that the efficacies of the vaccines are Pfizer—95%, Moderna—94.1%, AstraZeneca—70.4% and Janssen—66.9%, proving that these vaccines are effective at reducing the incidence and severity of SARS-CoV-2 infection among the study populations.

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Self-assessment questions

1. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) comes from the delta subtype of the Coronaviridae family.
2. The mRNA-1273 vaccine is a lipid nanoparticle-encapsulated, nucleoside-modified RNA vaccine that works against the S protein of the SARS-CoV-2 virus.
3. The Oxford/AstraZeneca is a viral vector that uses a chimpanzee adenovirus (ChAdOx1).
4. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) invades only type 2 alveolar cells via the ACE2 receptor in the human body.
5. When previously infected by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the BNT162b2/Pfizer vaccine shows no immunogenicity because the body is already responding to the previous infection.

As of 16 May 2021, the number of countries that have approved the use of the following vaccines is Pfizer in 85, Moderna in 46, Oxford/AstraZeneca and Covishield in 139 and Janssen in 41.

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Ethics approval Not required

Provenance and peer review Not commissioned; internally peer reviewed.

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Answers to questions

1. False
2. True
3. True
4. False
5. False