

COVID-19 vaccination effectiveness: a review in early vaccine adopters in Asian Countries

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Abstract. – COVID-19 vaccines were designed to stimulate an immunological response, producing neutralizing antibodies against the SARS-CoV-2 spike protein. Vaccine variants such as mRNA, viral vector, whole-cell inactivated virus, and protein subunit vaccines, have been reported to be efficacious in phase III trials and have gained emergency use approval in many countries. However, several adverse effects are reported in certain types of vaccines. All vaccines are being expedited by some Asian countries as part of their national immunization programs. This review primarily discussed the selected manufacturers of the COVID-19 vaccines used and their effectiveness in early-adopting Asian countries. The effectiveness in reducing the infection rate and safety of COVID-19 vaccines in Japan, Thailand, Singapore and Malaysia was also analyzed based on the available data. Strategies that can be used to speed up the vaccination rate in reducing the number of COVID-19 cases were also evaluated.

Key Words:

COVID-19, Vaccine, Effectiveness, Asia, Malaysia.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), known as the coronavirus disease 2019 (COVID-19), was first discovered on December 12, 2019, in Wuhan, China, emerging from the Hunan South China Seafood Market¹. It was presented with pneumonia-like symptoms and is highly transmissible. COVID-19 has spread swiftly to other countries and was classified as a pandemic by the

World Health Organization (WHO) on March 12, 2020. As of November 11, 2021, a total of 249,743,428 confirmed cases of COVID-19 and 5,047,652 deaths due to COVID-19 are reported worldwide. The United States (US) had the highest number of cases (46,146,676) and deaths (747,957). Simultaneously, the number of COVID-19 cases and deaths in Malaysia also increased over time, with 2,506,309 cases and 29,291 deaths by November 11, 2021².

After the announcement of the SARS-CoV-2 genetic sequences on January 11, 2021, collaborations among scientists and biopharmaceutical manufacturers commenced immediately to discover and manufacture vaccines³. At the moment, only one vaccine has received full approval by the US Food and Drug Administration (FDA), i.e., the BNT162b2 (Pfizer). Other vaccines, such as mRNA-1273 (Moderna), ChAdOx1 nCoV-19 (University of Oxford/AstraZeneca), and CoronaVac (Sinovac Biotech), were granted Emergency Use Authorization (EUA) by the FDA from December 2020. Some vaccine manufacturers are still under review by the European Medicines Agency (EMA) and the WHO to be distributed for emergency use. However, these vaccines, namely Gam-COVID-Vax (Sputnik), Ad5-nCoV (CanSino Biologics), and NVX-CoV2373 (Novavax), have been authorized to be used in some countries. For example, CanSino has been administered to the people in Sabah, Malaysia, since August 27, 2021. Therefore, this review aims to explore the efficiency and efficacy of COVID-19 vaccines that have been used, specifically in some Asian countries, namely Thailand, India, Japan, In-

donesia, Singapore and Malaysia. The safety of the vaccines used in Japan, Thailand, Singapore and Malaysia was also discussed according to the available reports from the respective countries. This review also includes suggestions on future actions in tackling COVID-19, especially in Malaysia.

Types of Vaccine

Three main approaches are considered in the design of vaccines to trigger immunological responses against the virus or foreign substances. They are 1) utilization of the whole virus or bacterium, 2) utilization of certain parts of the virus or bacterium, and 3) utilization of the viral or bacterial genetic material^{4,5}. These approaches have been applied in COVID-19 vaccines, and some of these vaccines have been approved by the WHO and FDA for global emergency use.

Table I shows a brief overview of the human study for COVID-19 vaccines, with their reported efficacy. To date, eight of these vaccines have entered phase III clinical trials, and six of them have been reported for their effectiveness (post-implementation)⁶. The already approved vaccines are the mRNA vaccines (BNT162b2 [Pfizer/BioNTech] and mRNA-1273 [Moderna]), adenovirus-based vaccines (ChAdOx1 nCoV-19 [Oxford-AstraZeneca], Ad26.COV2.S [Johnson & Johnson/Janssen], and Gam-COVID-Vac [Sputnik V]), and a whole-cell inactivated virus vaccine (CoronaVac [Sinovac Biotech]). On a similar note, two vaccines, i.e., the protein subunit vaccine NVX-CoV2373 (Novavax) and adenovirus-based vaccine Ad5-nCoV (CanSino Biologics), have shown promising efficacy via official company press releases and media reports, although the effectiveness of these vaccines has not been reported yet (Table I)⁶.

mRNA-Based (Genetic Material) – Pfizer, Moderna

The use of mRNA is a novel approach in vaccine development, utilized for the first time against COVID-19 infection³. mRNA vaccines represent an excellent option to the usual vaccine approaches due to their high potency, rapid development, low-cost manufacture, and safe administration⁷. mRNA vaccines are programmed to “teach” and instruct our cells to make harmless pieces of “spike proteins”^{3,7}. Spike proteins are found on the surface of the COVID-19 virus. After the production of spike protein, the cell breaks down the mRNA and gets rid of them. The cells will display the spike protein on their surface and be recognized by the immune system as foreign. Antibodies will then be generated against the proteins.

According to the Centers for Disease Control and Prevention (CDC), the mRNA approach in vaccine development is still new but in COVID-19, the efficacy is high based on phase III clinical trials. The speed of development of the mRNA vaccine is faster than conventional vaccine production methods but requires specialized storage because lipid nanoparticles must be kept in ultra-cold conditions^{3,5}. The studies of mRNA vaccines have been previously used for Zika, flu, rabies, and cytomegalovirus (CMV)⁴. Future vaccine technology may allow for mRNA vaccines to protect against multiple diseases.

Viral Vector (Adenovirus-Based)

The viral vector vaccine uses a modified version of a different virus (vector) that is safe as a vehicle to deliver specific instructions to patient muscle cells. The vector will use the cell’s machinery to synthesize a harmless piece spike protein or corona spike protein, made up of the S1 subunit consisting of the receptor-binding domain and the S2 subunit consisting of a transmembrane anchor⁸. Similar to the mRNA vaccine, cells will display the spike proteins on their surface, allowing recognition by the immune system to trigger immunological responses to generate specific antibodies against the infection.

According to the WHO, Sputnik V, Johnson & Johnson/Janssen, Oxford-AstraZeneca, and CanSino vaccines use adenovirus as the vector to package genetic materials of SARS-CoV-2. The Oxford-AstraZeneca used a replicant-deficient chimpanzee adenoviral vector, ChAdOx1, containing the spike protein gene. Meanwhile, Johnson & Johnson/Janssen used a recombinant adenovirus serotype 26 (Ad26) vector requiring only a single dose. In contrast, Sputnik V used two adenovirus serotypes, i.e., serotype 26 in the first dose and serotype 5 in the second dose^{3,9,10}. Similar to Johnson & Johnson/Janssen, the CanSino vaccine also requires a single dose, developed using a recombinant adenovirus serotype 5 (Ad5) vector¹¹.

The use of two different adenovirus serotypes in Sputnik V is to overcome the drawback of build-up resistance to the viral vector. Resistance occurs causing the vector to become less effective in future doses. Hence, the use of two different vectors (Ad26 in the first dose and Ad5 in the second dose) enables effective protection against the disease.

Whole-Cell Inactivated Virus

The whole-cell inactivated virus vaccine used killed or modified virus that could no longer replicate in order to trigger the immune system. It

could not cause disease; thus, it is suitable for those with compromised immune systems. The inactivation process usually involves heat, radiation, or chemicals to destroy the genetic material of SARS-CoV-2, stopping it from replicating^{4,12}.

For Sinovac, the virus was propagated in cells and inactivated with beta-propiolactone. Beta-propiolactone modifies the virus's genetic material, causing the virus to be unable to replicate. This vaccine also contains aluminum hydroxide, an adjuvant that boosts the vaccine's effectiveness and helps increase the immunological response¹³.

Protein Subunit

The Novavax COVID-19 vaccine is a protein subunit vaccine that contains protein (from moth

cells) and an adjuvant (made from tree bark). The adjuvant functions to boost a person's immune response and help produce higher antibody levels¹⁴. Novavax uses a piece of the spike protein from SARS-CoV-2 that is harmless to the vaccine recipient. Antibodies will be produced when the immune system encounters the pieces of spike protein in addition to the adjuvant creating a pro-inflammatory environment¹⁴. Unlike other types of vaccines, the spike protein is produced *in-vitro*, and the body will receive the end product, i.e., the spike proteins. It is also noted that the Novavax vaccine technology is more traditional than others as it only contains the protein and not the genetic material similar to a protein-based influenza vaccine. The adjuvant in use here is

Table I. Human Studies of COVID-19 vaccines with reported efficacy.

Vaccine (Developer)	Country of Origin	Type of vaccine	Efficacy against symptomatic infection	Effectiveness (post implementation)
BNT162b2 mRNA (Pfizer-BioNTech)	United States	mRNA (genetic material)	95% after 2 doses; 52% after 1 dose.	Symptomatic infection: <ul style="list-style-type: none"> • 94-96% (2 doses) • 46-80% (1 dose) Hospitalization: <ul style="list-style-type: none"> • 87% (2 doses) • 71-85% (1 dose) Asymptomatic infection: <ul style="list-style-type: none"> • 90% (2 dose) • 79% (1 dose)
mRNA - 1273 (Moderna)	United States	mRNA (genetic material)	95% after 2 doses; 92% after 1 dose.	Symptomatic infection: <ul style="list-style-type: none"> • 90% (2 dose) • 80% (1 dose)
ChAdOx1 nCoV-19 (University of Oxford/AstraZeneca)	Britain	Adenovirus-based (viral vector)	70.4% after 2 doses, 64.1% after 1 dose.	Hospitalization: <ul style="list-style-type: none"> • 80-94% after 1 dose
Gam-COVID-Vac (Gamaleya Research Institute/Sputnik V)	Russia	Adenovirus-based (viral vector)	91% after 2 doses; 74% after 1 dose (moderate to severe infection)	Symptomatic infection: <ul style="list-style-type: none"> • 97.6% after 2 doses
Ad26.COV2.S (Johnson & Johnson/Janssen)	United States	Adenovirus-based (viral vector)	67% after 1 dose	Symptomatic infection: <ul style="list-style-type: none"> • 76.7% after 1 dose
CoronaVac (Sinovac Biotech)	China	Whole-cell inactivated virus	50-84% after 2 doses	Symptomatic infection: <ul style="list-style-type: none"> • 94% after 2 doses Hospitalization: <ul style="list-style-type: none"> • 96% after 2 doses Death: <ul style="list-style-type: none"> • 98% after 2 doses
Ad5-nCoV (CanSino Biologics)	China	Adenovirus-based (viral vector)	66% after 1 dose	No data
NVX-CoV2373 (Novavax)	United States	Protein subunit	90% by 7 days after second dose	No data

Matrix-M which is based on saponin extracted from the soapbark tree. The extract triggers the activation of immune cells via the generation of a pro-inflammatory environment allowing for a more potent immunological response.

The Novavax vaccine is more receptive to those who might not accept mRNA vaccines due to allergies and other concerns. To date, protein subunit vaccines have not been reported to cause allergic reactions compared to the mRNA vaccines. One possible allergen in the mRNA vaccines is polyethylene glycol (PEG) which is not contained in Novavax.

Side Effects of the Vaccine

COVID-19 vaccination reduces the spread and infection of the virus. Studies by the CDC have shown that the COVID-19 vaccine can also provide a boost in protection among those that have recovered from COVID-19. However, a person may experience some common side effects associated with the body building immunity by activating T and B lymphocytes.

According to the WHO and CDC, all COVID-19 vaccines have common side effects, which are¹⁵:

- Fever
- Fatigue
- Headaches
- Body aches
- Chills
- Nausea

A person might also experience pain, redness, and swelling at the injection site, usually at the upper arm. Although the common side effects are expected after vaccination, there have also been reported cases of rare side effects for each vaccine. As for now, Gam-COVID-Vac (Sputnik V), CoronaVac (Sinovac), Ad5-nCoV (CanSino Biologics), and NVX-CoV2372 (Novavax) only cause common side effects with no serious or rare side effects reported. The severe or specific side effects reported for each vaccine are further discussed.

mRNA Vaccine - Pfizer, Moderna

Myocarditis and Pericarditis

As of September 8, 2021, the Vaccine Adverse Event Reporting System (VAERS) has received 1,413 reports of myocarditis or pericarditis among people (30 years old and younger) receiving mRNA COVID-19 vaccines. The CDC and FDA have confirmed 854 reported cases of myocarditis and pericarditis through medical record reviews, particularly in adolescents and young adults aged 16

years or older. This rare report happened after the mRNA COVID-19 vaccination (Pfizer-BioNTech and Moderna) in the US¹⁵⁻¹⁸.

Viral Vector Vaccine - AstraZeneca, Johnson and Johnson

Thrombosis with Thrombocytopenia

As of July 26, 2021, more than 13 million doses of the Johnson & Johnson/Janssen COVID-19 vaccine have been distributed in the US. The FDA and CDC confirmed 39 reported cases of people who developed thrombosis with thrombocytopenia after receiving the Johnson & Johnson/Janssen COVID-19 vaccine. These were reported in adult women below 50 years of age¹⁵.

Thrombosis with thrombocytopenia has also been listed as a rare side effect of AstraZeneca. At present, the reported cases occurred within 2 weeks of vaccination and involved women under 60 years old. The EMA'S Pharmacovigilance Risk Assessment Committee (PRAC) stated that blood clots occurred in veins in the brain (cerebral venous sinus thrombosis, CVST) and the abdomen (splanchnic vein thrombosis) together with thrombocytopenia¹⁹. As of March 22, 2021, a total of 62 cases of CVST and 24 cases of splanchnic vein thrombosis were reported to the EU drug safety database^{19,20}.

Guillain-Barré Syndrome

The Guillain-Barre syndrome (GBS) is a rare disorder where the nerve cells are damaged by the body's immune system, resulting in muscle weakness and sometimes paralysis. Although most people fully recover from GBS, some may have permanent nerve damage. As of July 30, 2021, a total of 143 preliminary reports of GBS were identified by VAERS after the administration of more than 13 million doses of the Johnson & Johnson/Janssen COVID-19 vaccine. These cases were reported among men above 50 years of age^{15, 21}.

There were also four reported cases of bifacial weakness in men with paresthesia variant of GBS that happened within three weeks of receiving the Oxford-AstraZeneca COVID-19 vaccination²².

Efficacy in Population Data

BNT162b2 mRNA (BioNTech/Pfizer)

In New York, the phase III clinical trial of BNT162b2 (Pfizer) began on July 27, 2021, involving 43,661 participants (42% of global participants and 30% of the U.S. participants of diverse

ethnicity). Approximately 170 confirmed cases of COVID-19 were evaluated as a primary efficacy analysis against COVID-19 starting 28 days after the first dose. From the 170 cases, 162 cases were found in the placebo group and 8 cases in the vaccinated BNT162b2 Pfizer group. The data analysis by Pfizer Inc. indicates the efficacy rate for the Pfizer vaccine at 95%²³. The efficacy of the vaccine was consistent across gender, age, race, and ethnicity demographics. The efficacy in adults over 65 was observed at 94%. A total of 10 severe COVID-19 cases were observed in the trial, which showed 9 cases occurring in the placebo group and 1 in the BNT162b2 Pfizer vaccinated group. The effectiveness of two Pfizer doses was 93.7% among the populations against the Alpha variant and 88.0% against the Delta variant²⁴. The company announced that the safety milestone required by the US FDA had been achieved for EUA.

mRNA-1273 (Moderna)

The primary efficacy analysis of phase III clinical trial for the mRNA-1273 vaccine involving 30,000 participants showed 196 positive cases of COVID-19. 186 cases of COVID-19 were observed in the placebo group while 10 cases of COVID-19 were observed in the mRNA-1273 vaccinated groups, showing 94.1% vaccine efficacy. A secondary endpoint analysis showed 30 severe cases of COVID-19 occurring in the placebo group and none in the mRNA-1273 vaccinated group. It showed 100% efficacy against severe cases of COVID-19²⁵. The effectiveness of two jabs of Moderna COVID-19 vaccine amongst the populations studied was 100% against the Alpha variant, 96.4% against the Beta variant, and between 66% to 95% against the Delta variant^{26,27}.

ChAdOx1 nCoV-19 (Astrazeneca/Vaxzevria)

The Vaxzevria phase III clinical trial demonstrated statistically significant vaccine efficacy of 79% in preventing symptomatic COVID-19 and 100% efficacy in preventing severe COVID-19 and hospitalization. The clinical trial by Vaxzevria in 2021 involved 32,449 participants, which showed 141 confirmed cases of COVID-19. The vaccine efficacy was also consistent across ethnicity and age²⁸. Meanwhile, the efficacy of the vaccine was 80% for participants aged 65 years and over. The effectiveness of two doses of Vaxzevria was 74.5% against the Alpha variant and 67.0% against the Delta variant²⁴ in the population. The brand name Vaxzevria has been registered and approved by EMA and the Medi-

cines and Healthcare products Regulatory Agency (MHRA) to ease international travel for people vaccinated with AstraZeneca's vaccine²⁹. The name of the vaccine was changed from AstraZeneca to Vaxzevria on 25 March 2021³⁰.

Corona Vac (Sinovac)

The phase III clinical trial of CoronaVac (Sinovac) involved 10,214 participants, which showed 41 confirmed cases of symptomatic COVID-19 happening at least 14 days after the second dose. 32 of the COVID-19 cases were observed in the placebo group and 9 cases were reported in the CoronaVac vaccinated group, resulting in a vaccine efficacy of 83.5% for symptomatic COVID-19³¹. The vaccine also showed a 100% efficacy rate in preventing COVID-19-related hospitalization, as none of the participants in the CoronaVac vaccinated group was hospitalized. In contrast, six participants in the placebo group were hospitalized. However, more studies need to be conducted to gain enough data about the effectiveness against COVID-19 Variants of Concern (VOC).

Gam-COVID-Vac (Sputnik V)

The phase III clinical trial of Gam-COVID-Vac (Sputnik V) was held at 25 hospitals and polyclinics, involving 19,866 participants. All participants received two doses of the vaccine or placebo and were included in the primary outcome analysis. The participants were at least 18 years old, with negative SARS-CoV-2 PCR, no history of infectious disease within 14 days before participation, and no other vaccination 30 days before the enrolment. The vaccines were administered in a 21-day interval between the first (rAd26) and the second (rAd5) dose. Out of 78 confirmed COVID-19 cases, 62 were observed in the placebo group, and 16 in the Gam-COVID-Vac vaccinated group. Furthermore, 20 severe cases of COVID-19 were recorded, none involving the vaccinated group, resulting in a 100% efficacy rate against severe COVID-19. The efficacy rate against symptomatic COVID-19 was 91.6%³². However, the effectiveness of Sputnik V against the VOC requires more data and studies.

Ad26.COV2.S (Johnson and Johnson/Janssen)

The phase III clinical trial of Ad26.COV2.S (Johnson & Johnson/Janssen) involved 40,000 participants, with 464 confirmed cases of COVID-19. From the 464 cases, 348 cases were observed in the placebo group and 116 in the Ad26.COV2.S

vaccinated group. According to Janssen Biotech Inc., the efficacy rate of the Johnson & Johnson/Janssen COVID-19 vaccine is 66.9%, with 31 hospitalized cases³³. 29 of the total cases were observed in the placebo group, while 2 were from the Ad26.COVS vaccinated group, indicating the efficacy rate against severe COVID-19 at 76.7%. More comprehensive studies and data are needed to prove the effectiveness of Johnson & Johnson/Janssen against the VOC²⁷.

Ad5-nCoV (Cansino Biologics)

CanSino's experimental coronavirus vaccine has shown an efficacy rate of 65.7% at preventing symptomatic cases, according to the analysis from late-stage trials. The administration of the vaccine, which was co-developed by the Chinese military and a Tianjin-based biotech company, is effective against symptomatic COVID-19 infection. A late-stage trial involving 30,000 participants in Pakistan showed a 90.98% effectiveness in preventing severe disease³⁴. However, there is insufficient evidence and data to prove the efficacy in population data for the CanSino COVID-19 vaccine and its efficacy against the VOC.

NVX-CoV2373 (Novavax)

The phase III clinical trial of NVX-CoV2373 (Novavax) involved 14,089 participants in the per-protocol efficacy population. The phase III clinical trial was conducted at 33 locations in the US, involving randomized, observer-blinded, and placebo-controlled participants. Adults between 18 and 84 of age were injected with two doses of NVX-CoV2373 or placebo 21 days apart³⁵. The results showed that 106 cases of infection were reported, of which 10 participants from the vaccinated group and 96 participants in the placebo group, with symptoms starting at least 7 days after the second injection. The data indicate the efficacy rate of the vaccine at 89.7%. No hospitalization or deaths were reported, and only five severe infection cases were reported, all from the placebo group. It indicates the efficacy rate against severe COVID-19 to be 100%. Moreover, a post-hoc data analysis showed an efficacy rate of 86.3% against B.1.1.7 (Alpha) variants and 96.4% against non-B.1.1.7 variants.

The use of these vaccines has been shown to significantly reduce the severity and mortality of COVID-19 infections³⁶. A summary of the efficacy of the vaccine in the population against the variants of concern (VOC) is shown in Table II.

Effectiveness and Safety of COVID-19 Vaccine in Asian Countries

Japan

On January 16, 2020, Japan reported the first confirmed case of COVID-19 in Kanagawa Prefecture residents who returned from Wuhan, China. The first confirmed death case from COVID-19 was recorded on February 14, 2020. From the beginning of the outbreak, the number of cases in Japan has risen in four main periods, i.e., around April 2020, August 2020, November 2020 to January 2021, and April 2021 to May 2021³⁷. The COVID-19 vaccination distribution in Japan started on February 17, 2021, mainly to health professionals³⁸. The Japanese government-initiated vaccine administration for the public, starting with the elders aged 65 and older, on April 12, 2021. By the middle of June 2021, 3% of the population had their second dose of the vaccine. The only authorized vaccine used in Japan is the Pfizer-BioNTech mRNA type vaccine.

The study by a research team at the Yokohama City University showed that almost 90% of people who received a full dose of the Pfizer-BioNTech vaccine were found to develop protection and antibodies against COVID-19 variants detected in Japan³⁹. The study involved 105 people who had been fully vaccinated without contracting COVID-19 and checked for immunity against all the variants in Japan. Of the 105 people, 90% to 94% of those receiving the Pfizer vaccine developed antibodies against variants originally found in the United Kingdom (UK, Alpha), South Africa (Beta), and Brazil (Gamma). The study also showed 97% effectiveness in developing antibodies against variants detected in India (Delta)³⁹. It was also effective against the original coronavirus present in Japan from the start of the outbreak at a rate of 99%.

On May 22, 2021, the Japanese government granted a fast-track approval to COVID-19 vaccines developed by Moderna Inc. from the US and AstraZeneca Plc from Britain³⁷. The Health Ministry of Japan stated that both vaccines are safe and effective as a major step towards hastening its slow inoculation drive to achieve herd immunity. The Moderna vaccine was scheduled to be administered at mass vaccination centers handled by the Self-Defense Forces in Osaka and Tokyo, with similar facilities set up by some cities, towns, and districts.

However, the AstraZeneca shot was not administered immediately like the Moderna vaccine

Table II. Efficacy in population data and its effectiveness against VOC based on vaccine brand.

Vaccine	Efficacy in population data	Effectiveness against VOC
BNT162b2 mRNA (BioNTech/Pfizer)	Efficacy: 95% 43,661 participants: 170 confirmed cases - 162 placebo, 8 vaccinated 10 severe cases: 9 placebo 1 vaccinated 94% Efficacy in adult over 65 years	93.7% against Alpha variant 88.0% against Delta variant
mRNA - 1273 (Moderna)	Efficacy: 94.1% 30,000 participants: 196 confirmed cases - 185 placebo, 11 vaccinated 30 severe cases: 30 placebo 100% efficacy against severe COVID-19	100% against Alpha variant 96.4% against Beta variant 66% - 95% against Delta variant
ChAdOx1 nCoV-19 (University of Oxford/AstraZeneca)	Efficacy: 79% 32,449 participants: 141 confirmed cases 100% efficacy against severe COVID-19	74.5% against Alpha variant 67.0% against Delta variant
Gam-COVID-Vac (Gamaleya Research Institute/Sputnik V)	Efficacy: 91.6% 19866 participants: 78 confirmed cases - 62 placebo, 16 vaccinated 20 severe cases: 20 placebo 100% efficacy against severe COVID-19	No data
Ad26.COVS.2.S (Johnson & Johnson/Janssen)	Efficacy: 66.9% 40,000 participants: 464 confirmed cases - 348 placebo, 116 vaccinated 31 hospitalized: 29 placebo, 2 vaccinated - 76.7% efficacy against severe COVID-19	No data
CoronaVac (Sinovac Biotech)	Efficacy: 83.5% 10,124 participants: 41 confirmed cases - 32 placebo, 9 vaccinated	No data
Ad5-nCoV (CanSino Biologics)	No data	No data
NVX-CoV2373 (Novavax)	Efficacy: 89.7% 14,039 participants: 106 confirmed cases - 96 placebo, 10 vaccinated 5 severe cases: 5 placebo 100% efficacy against severe COVID-19	86.3% against the Alpha variant 96.4% against non Alpha variant

because there are still concerns about the former vaccine that causes rare and unusual blood clots (thrombosis with thrombocytopenia) being reported overseas. The AstraZeneca vaccine has a lower efficacy rate compared to the other two, at 70% compared to Moderna (94%) and Pfizer (95%). However, the efficacy rate is still considered high for an influenza vaccine.

The Health Ministry also stated that the Japanese government has already secured sufficient Pfizer and Moderna vaccines for people 16 years or older. The decision was taken after a further review because some countries have temporarily banned the use of the AstraZeneca vaccine and put restrictions on its use on younger people due to rare cases of blood clots³⁸. Japan has set a benchmark, i.e., to administer up to 10,000 shots per day, following the supply agreements of Japan to receive 50 million doses of the Moderna vaccine, 120 million doses from AstraZeneca, and 194 million doses from Pfizer by September 2021.

Japan has reported some adverse effects (AEs) due to the COVID-19 vaccines. A total of 733 (85 males [12%], 647 females [88%], 1 unknown [$<1\%$]) AEs have been reported. The most common effects reported were local adverse events (71%). Systemic adverse events occurred in 48% of participants. The most common adverse event was myalgia or muscle pain (34%). Other non-serious effects include headache, fatigue, and nausea. A more serious effect reported was anaphylaxis, involving 181 people. Almost all of them were from receiving the first dose^{39,40}.

India

On January 30, 2020, the first confirmed cases of COVID-19 in India were reported in three towns of Kerala, involving three medical students who had returned from Wuhan⁴¹. The Indian government began the inoculation of COVID-19 vaccines on January 16, 2021. Initially, India approved the Oxford-AstraZeneca vaccine manu-

factured by the Serum Institute of India under the name Covishield and Covaxin, developed locally by Bharat Biotech. The government also added other vaccines to their emergency use list, such as Sputnik V, Moderna, and Johnson & Johnson/Janssen vaccines. The first dose of the vaccine was administered to a healthcare worker at the All-Indian Institute of Medical Sciences in the capital, New Delhi, which was the Covishield vaccine. However, six months after India began the world's largest inoculation drive, the program covered just over 5% of its population. Despite a promising start in January 2021, the program has been delayed due to low supply and delays in approving new vaccines.

In India, both local vaccine candidates, Covishield and Covaxin, got the emergency use approval on January 3, 2021⁴². A study has been conducted involving all healthcare and frontline workers, where its effectiveness among the Indian population was observed from January 16 to May 30, 2021.

The study also aimed to measure the effectiveness of the Covishield vaccine on the occurrence of deaths due to COVID-19. The results showed that the number of daily deaths in the group of unvaccinated, partially vaccinated, and fully vaccinated people were 37, 16, and 7 people, respectively, from February 2021 to May 2021. The effectiveness of the Covidshield vaccine in preventing COVID-19-related deaths was 98.53%. The study also showed that the inoculation of the Covishield vaccine reduced the infections risks by 91% to 94%⁴³. The study also demonstrated that the Covishield vaccine is effective against the Delta and Kappa variants.

On July 3, 2021, a vaccine produced by India's Bharat Biotech, Covaxin, showed an effective rate of 93.4% against severe symptomatic COVID-19. The data also showed that it is effective against the Delta variant at 65.2%. The variant was first identified in India, leading to a large increase in infections and daily death cases from April to May. The Covaxin vaccine also showed 77.8% effectiveness against symptomatic COVID-19⁴⁴.

Thailand

The COVID-19 vaccination rollout in Thailand started on February 28, 2021, with the first administration using the China-made vaccine, Sinovac⁴⁵. The vaccine also helped Thailand start its national vaccination program and become the primary vaccine in the national program. Later, the AstraZeneca COVID-19 vaccine was also approved, with a total of 11.3 million doses to be

delivered by the end of July 2021. However, the AstraZeneca vaccine used in Thailand is manufactured by a local manufacturer, Siam Bioscience⁴⁶. The locally manufactured AstraZeneca vaccine is Thailand's original vaccination plan. The Ministry of Public Health also stated that Thailand also used the Sinopharm vaccine from China, bringing the number of available vaccines in the country to three, i.e., Sinovac and Sinopharm vaccines from China and the AstraZeneca vaccine from Britain¹¹.

In Thailand, a field study was conducted by the Ministry of Public Health among high-risk groups that had completed a full two-dose of Sinovac in three regions with the highest cases of COVID-19. The results showed that two doses of the Sinovac vaccine could develop strong protection and immunity against COVID-19 infection and pneumonia for cases caused by either the Alpha or Delta variant¹¹. The study was conducted from April 2021 to June 2021, when the Alpha variant was dominant. Two doses of Sinovac provided 90% protection against COVID-19 infection and an 85% effectiveness rate against lung infection. However, the Sinovac jabs showed a slight decrease in effectiveness against the Delta variant, at 75%.

Another study¹¹ by the Center of Excellence in Clinical Virology of the Faculty of Medicine at Thailand's Chulalongkorn University showed that the Sinovac vaccine has high efficacy in boosting the immune response against COVID-19. The study found that 99.49% of the individuals that completed the two jabs had developed antibody responses four weeks after the second dose. Meanwhile, the effectiveness of the AstraZeneca vaccine is around 80%–90% against severe disease and hospitalization and is highly effective against all VOC. The overall safety of the AstraZeneca vaccine is still under control due to the rare blood clots events, which can be treated with early diagnosis, and there is no increased risk of rare blood clots events after the second dose.

However, in July 2021, Thailand's health ministry reported that more than 600 fully vaccinated medical workers with the Sinovac vaccine were infected with COVID-19, causing growing questions about the effectiveness of the vaccine. On July 12, 2021, Thailand decided to start heterologous vaccination. The AstraZeneca COVID-19 vaccine as a second dose was provided to those who had received their first Sinovac vaccine⁴⁷. The Public Health Minister also stated that this strategy provides better protection against the Delta variant.

The ministry also announced the booster shot vaccination for the frontline medical workers who had received two shots of the Sinovac COVID-19 vaccine. The booster shot will be either the AstraZeneca or the Pfizer vaccine. As for now, the AstraZeneca vaccine will be used only for the cross-vaccination program and as a booster dose because the Pfizer vaccine is not offered in the national inoculation program at the moment^{41, 45, 47}. As for now, Thailand has so far approved six vaccines on their emergency list, but only three of them are currently used, i.e., the AstraZeneca, Sinovac, and Sinopharm vaccines.

Indonesia

COVID-19 was confirmed to have spread in Indonesia on March 2, 2020. The first shot of the COVID-19 vaccine in Indonesia was the Sinovac vaccine, which was first received by the Indonesian President, Joko Widodo, on January 13, 2021, after it was granted approval for emergency use by the government and started to vaccinate millions of people in one of the world's most populous countries^{48,49}. The mass vaccination program in Indonesia is the first large-scale use of the Sinovac vaccine outside of China. The vaccine has also been given to top military, police and medical officials, healthcare workers, business providers, and social media influencers to encourage others to follow once it is available for them⁵⁰.

A study conducted by the Indonesian government found that the effectiveness of the Sinovac vaccine is 85% against symptomatic infection and reduced to 35% if only the first shot is administered⁵⁰. The Sinovac vaccine also showed high effectiveness in preventing deaths at 95% and 92% against hospitalization among the older people in Jakarta. The study enrolled 89,936 Jakarta residents aged 60 and older between March and April 2021. The effectiveness of the Sinovac vaccine in Indonesia was also higher than those reported by Chile, and the Indonesian government aims to inoculate 214 million people by the end of 2021⁵¹.

On February 16, 2021, the Indonesian government decided that the COVID-19 vaccination was compulsory for citizens and allowed private health providers to help administer the vaccine to the population to increase the vaccination rate. The private sector will open the self-funded vaccine, but they must use different brands than the free rollout used in the government vaccination program. Indonesia has so far only used China's Sinovac vaccines and will start receiving other brands of COVID-19 vaccines, i.e., AstraZeneca

from Britain, Pfizer from the US, and Novavax from the US and Canada⁴⁹. The private sector's brand could include other than these vaccines, which are Sinopharm and Anhui from China, Moderna from the US, Sputnik V from Russia, and Johnson & Johnson/Janssen from the US. As for now, Indonesia is conducting three approaches to combating COVID-19 waves, which are boosting immunity through the vaccination program, especially in regions and districts with high economic activities, imposing strict health protocols, and ramping up testing and tracing.

Indonesia received the first batch of AstraZeneca COVID-19 vaccines from the COVAX facility on March 9, 2021. However, the batch that consists of 448,480 doses had been temporarily suspended, pending an investigation after a young man died after being administered the AstraZeneca vaccine on May 17, 2021⁵². Fortunately, Indonesia has continued using the AstraZeneca vaccine after a test showed no relationship between the quality of the COVID-19 vaccine with the post-immunization event reported on May 27, 2021. The distribution of the doses is continued in Jakarta and the province of North Sulawesi.

Singapore

Singapore confirmed its first case of COVID-19 on January 23, 2020, a few weeks after the first case in Wuhan, China, was detected. The Singapore government began a COVID-19 vaccination program on December 30, 2020, with a nurse receiving the first dose, making it among the first Asian countries to rollout vaccination campaigns. The city-state became the first country in Asia to approve the Pfizer-BioNTech vaccine use as a primary vaccine, and its campaign started among healthcare workers⁵³. After the healthcare workers, the COVID-19 vaccination will roll out among the elderly and the rest of the population in Singapore.

However, on July 23, 2021, despite data showing the efficacy of the vaccines in preventing death, the new case continued to rise even with 75% of its population receiving the vaccine⁵⁴. Singapore focused on reducing the number of deaths and serious diseases caused by COVID-19 through vaccination campaigns in order to reopen its economic sector. Singapore primarily uses the Pfizer and Moderna vaccines in its national vaccination program.

A study was conducted by the National Center for Infectious Disease and Ministry of Health, involving 1,000 household contacts of COVID-19

cases between September 2020 and the end of May 2021⁵⁵. The results showed that the mRNA vaccines used in the inoculation drive in Singapore have an effectiveness rate of 69% against the Delta variant of COVID-19. Recently, the effectiveness of both mRNA vaccines, Pfizer and Moderna vaccines, had registered 69% effectiveness. The data also reported that the mRNA vaccines showed 80% to 90% protection against symptomatic COVID-19, and 93% of vaccine receivers developed protection against severe symptoms, such as requiring oxygen supplementation or intensive care and death⁵⁵.

Singapore has also reported some adverse effects from the COVID-19 vaccines that they receive. Of the total number of vaccines administered (including Pfizer, Moderna and Sinovac), 0.13% were reported to experience side effects, and from this, a total of 0.006% were serious⁵⁶. The most common side effects reported were allergic reactions (such as rash, itch, hives and swelling of eyelids, face and lips), dizziness, shortness of breath, chest tightness/discomfort, palpitations, injection site reactions, such as pain and swelling and fever. All of these effects resolved after a few days.

More serious effects, such as myocarditis and pericarditis were also reported with an incidence rate of 0.63 per 100,000 doses. The risk of these effects is shown higher in dose 2, which is 64% of the reported cases. A higher incidence of myocarditis has been reported with Moderna/Spikevax COVID-19 vaccine (1.29 per 100,000 doses administered) compared to PfizerBioNTech/Comirnaty COVID-19 vaccine (0.62 per 100,000 doses administered) in individuals aged 18 years and above who have taken Dose 1 or Dose 2 of the vaccines⁵⁶.

Singapore has also reported cerebral venous thrombosis (CVT) and Bell's Palsy as side effects from COVID-19 vaccines (13 and 109 reports, respectively)⁵⁶. All of these effects were resolved within days to weeks.

Malaysia

COVID-19 in Malaysia began with the first confirmed cases of COVID-19 reported among travelers from China in Johor via Singapore on January 25, 2020. Even though the outbreak was originally limited to a few imported cases, several local clusters started to emerge in March 2020. The most unforgettable cluster was a Tabligh religious gathering in Kuala Lumpur that caused a massive spike in local cases and imported cases to neighboring countries, such as Indonesia and

Thailand^{57,58}. The first wave of COVID-19 was from January 25 to February 16, 2020, with the second wave occurring between February 27 to June 30, 2020. The third wave of infection that hit Malaysia led to a sudden surge of cases caused by the Sabah state election in September 2020 and several cases at the industrial facilities in late 2020.

As of February 24, 2021, Malaysia started its COVID-19 inoculation program called the National COVID-19 Immunization Program, with the first person to receive the jab being the Prime Minister at that time, Muhyiddin Yassin. The Prime Minister and the nation's Health Director-General, as well as healthcare workers, were among the first group that received the first Pfizer-BioNTech jab in Putrajaya⁵⁹. The first batch of Pfizer-BioNTech COVID-19 vaccine in Malaysia landed with 312,390 doses, and the first phase of the vaccine rollout in April 2021 involved about 500,000 healthcare workers, frontliners, defense and security personnel, and teachers with co-morbidities⁵⁹. Other than the Pfizer-BioNTech vaccine from the US, the inoculation program also includes other vaccines, such as the AstraZeneca vaccine from Britain and the Sinovac vaccine from China.

On April 19, 2021, a real-world study on the effectiveness of the Pfizer-BioNTech vaccine was conducted among 426 healthcare workers⁶⁰. The result (Table III) shows that the Pfizer vaccine has an effectiveness of 65% after the first dose. Moreover, the vaccine showed 95% effectiveness in preventing COVID-19 21 days after the second dose. It indicates that the Pfizer vaccine is extremely effective in providing protection against COVID-19 to those who received the shots. However, an effectiveness study was not conducted for the AstraZeneca, Sinovac, and CanSino vaccines in Malaysia. Its effectiveness could be inferred from countries that had given Pfizer and AstraZeneca vaccines, such as Saudi Arabia, which showed high effectiveness against various variants found in the country⁶¹. The immunization program was implemented in phases, from February 24, 2021, to February 2022, organized by the Ministry of Health and the Special Committee for Ensuring Access to COVID-19 Vaccine Supply (JKJAV). It is the biggest immunization program in the history of Malaysia, and it aims to achieve herd immunity, with at least 80% of the population in Malaysia being fully vaccinated against COVID-19. Now, the Malaysian government is in the process of bringing other vaccines,

such as Johnson & Johnson/Janssen, Sinopharm, and Moderna⁶². CanSino was the latest vaccine approved by the Malaysian government on June 15, 2021 and was distributed to the citizens in the state of Sabah from August 27, 2021^{63,64}.

Figure 1 illustrates the percentage of individuals who have completed their vaccinations (two weeks after receiving the second dose) per total adult population according to the states in Malaysia until August 2021. Figure 1 indicates five states with more than 90% of their adult population already vaccinated, i.e., Wilayah Persekutuan Labuan, Perlis, Klang Valley (comprises of Kuala Lumpur Putrajaya, and Selangor), Pulau Pinang, and Negeri Sembilan. The coverage of the reduced impact of previously reported infectious diseases is $\geq 90\%$, with the lowest of 61%-74% for hepatitis A, B, and rotavirus vaccines⁶⁵. It was previously reported that an 80% cut-off of total vaccination in the population would be enough to reduce the severity of COVID-19 symptoms and manage its spread in the community⁶⁶. However, since some states showed slower progress in achieving that number compared to others, the Malaysian government raised the bar to 90% to ensure more states will achieve that mark, or at least the minimum 80% of fully vaccinated adults, before re-

lieving the previous restrictions imposed to flatten the curve of COVID-19 infection⁶⁷. Klang Valley exhibits more than 100% vaccination among adults. The percentage discrepancy did not take into account the change in population since the last census, which was performed in 2020⁶⁸. The number of vaccinated adults also includes undocumented immigrants that would not be included in the population data. This is also true for other states that may show more than 100% vaccinated adults in the future.

To date, the vaccinations in Malaysia reduced the number of those infected, where most of the COVID-19 infection cases were among those who were unvaccinated (Figure 2), which illustrates the percentage of cases according to those vaccinated and unvaccinated throughout August 2021. As reported by the Malaysian Ministry of Health, the vaccines have also successfully reduced the number of complications due to COVID-19, where the number of patients admitted to the intensive care units (ICUs) or needed ventilation due to an acute respiratory distress syndrome (ARDS) showed a downward trend from the beginning of the vaccination program that begins in March 2021 until early October 2021⁶⁴. However, it is difficult to determine the statistical significance of the changes

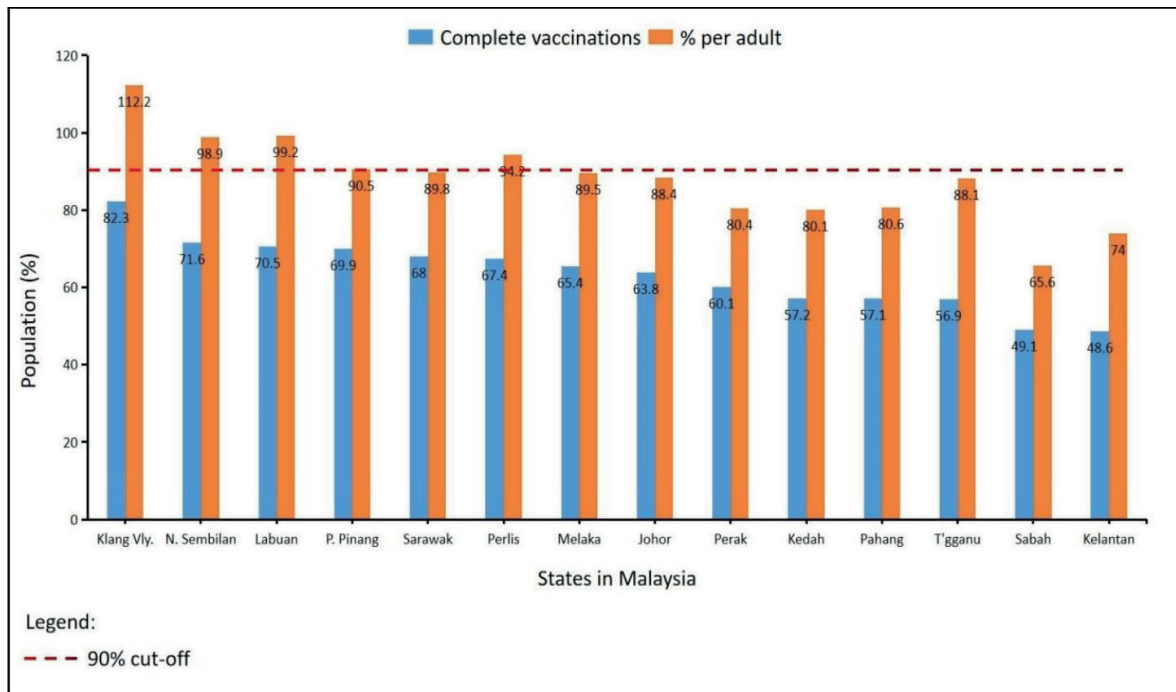


Figure 1. The vaccination rate (%) per population (blue bar) and per adult population (orange bar) according to the states in Malaysia until 11th October 2021. The percentage was calculated based on the number of those who have completed vaccinations (two weeks after receiving the second dose) against the population and adults in each state. The red dotted line indicates the 90% cut-off from the population percentage.

in the infection rate due to the emergence of new variants.

From the data reported by the Ministry of Health, vaccinations, irrespective of the type of vaccines used, can manage the infectivity of COVID-19, especially in terms of reducing the severity and complications. A cohort study needs to be conducted to have more concrete evidence to show the efficacy of vaccines in protecting the Malaysian population from COVID-19.

Vaccine Side Effects and Safety Reported in Malaysia

As the safety data in regard to the adverse effects following immunization (AEFI) of the vaccines used in some Asian countries are not publicly available, we could only discuss in detail the data reported in Malaysia. According to the Ministry of Health in Malaysia, there are a total of 7.5 reported cases of serious adverse effects following immunization (AEFI) per 100,000 peo-

Table III. Effectiveness of vaccine administered in Asian Countries.

Country	Vaccines used	Vaccinated population	Effectiveness
Japan	Pfizer	86.65 Million fully vaccinated	Pfizer 90% to 94% against COVID-19 infection (Alpha, Beta, Gamma variant) 97% against Delta variant 99% against original coronavirus Moderna - No data available
	Moderna	5.69 Million fully vaccinated 46.42% fully vaccinated 11.01% partly vaccinated Total: 57.43% [54]	
India	Moderna AstraZeneca	10.61% fully vaccinated 25.06% partly vaccinated Total: 35.67% [54]	Moderna - No data available Covishield (AstraZeneca) 91-94% against infection 98.53% against death Sputnik V - No data available Covaxin 93.4% against severe symptomatic infection 77.8% against COVID-19 infection 65.2% against Delta variant
	Sputnik V Covaxin		
Thailand	Pfizer AstraZeneca	7,144,092 fully vaccinated 31,812,726 fully vaccinated	Pfizer - No data available Astrazeneca 80%-90% against severe disease and hospitalization Sinovac 90% against covid-19 infection (Alpha variant) 85% against lung infection 75% against Delta variant (two sinovac jabs) Sinopharm - No data available
	Sinovac Sinopharm	27,539,245 fully vaccinated 13,498,338 fully vaccinated 11.12% fully vaccinated 22.33% partly vaccinated Total: 33.45% [54]	
Indonesia	Moderna AstraZeneca Pfizer Sinopharm Sinovac	12.97% fully vaccinated 9.86% partly vaccinated Total: 22.83% [54]	Sinovac 85% against symptomatic infection 92% against hospitalization 94% against infection 95% against death Pfizer, Moderna, AstraZeneca, Sinopharm - No data available
Singapore	Pfizer Moderna	75.15% fully vaccinated 2.82% partly vaccinated Total: 77.97% [54]	Pfizer - 69% against Delta variant Moderna 69% against Delta variant 80-90% against symptomatic disease 93% against severe symptom and death Sinovac - No data available
	Sinovac		
Malaysia	Pfizer AstraZeneca Sinovac CanSino	12,696,878 fully vaccinated (51.8%) 1,979,791 fully vaccinated (8.0%) 9,527,921 fully vaccinated (39.1%) 177,424 fully vaccinated (0.4%)	Pfizer 65% effective after first dose 95% effective after second dose No data available for AstraZeneca, Sinovac and CanSino

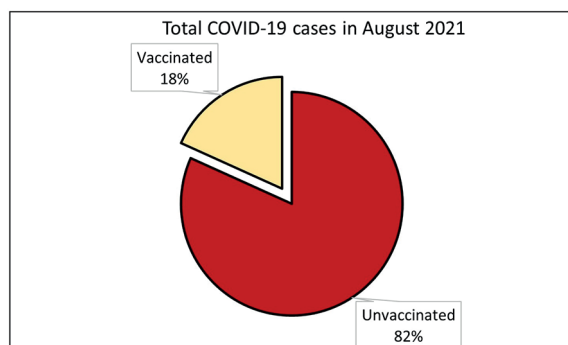


Figure 2. COVID-19 cases in Malaysia based on the number of those who are fully vaccinated and unvaccinated.

ple that received the vaccines⁶⁹. All of the effects reported so far only required brief hospitalization without any serious complications or death. The serious effects reported according to the types of vaccines received are listed in Table IV.

As of Nov 2021, out of the 76.5% of the vaccinated population in Malaysia, almost 100% of the side effects reported were not serious, as shown in Figure 3.

There are a total of 12 side effects listed as common upon receiving the vaccines, either for the first or second dose. From the data presented in Table V, the most common side effect reported was site pain after receiving the first dose, which means soreness or pain at the site of injection (64.8%). This side effect is to be expected in any form of injection. However, this effect is less reported after the second dose (4.1%). The highest reported site pain effect was from the AstraZeneca vaccine (74.6%). The least common side effects reported were rash (0.2%) and site redness upon receiving the second dose. Based on the data, those who received Pfizer mostly reported experiencing site pain (65.4%), followed by tiredness (38.1%) and headache (30.7%). All of these side effects were from receiving the first dose of the Pfizer vaccine. Sinovac and AstraZeneca reported a similar pattern. However, Sinopharm showed tiredness (65.9%) and headache (43.9%) as the highest side effects reported. Weakness (36.6%)

and muscle pain (31.7%) were also reported high among Sinopharm recipients, similar to AstraZeneca (50.4% and 45.4%, respectively).

Based on the overall data reported, the AEs from COVID-19 vaccines have been relatively minor. All of the effects were resolved, either by themselves after a few days or through treatments given. The benefits of the vaccine against COVID-19 and severe complications due to COVID-19 were proven to outweigh the risk. Each country has also taken the necessary measures to evaluate and monitor the effects of the vaccines used.

Suggestions for Future Protection Against Severe Disease

Mobile Vaccination Program

The mobile vaccination program is a good initiative that can be done to bring vaccination services closer to communities or groups in need on a small scale⁷⁰. Although the government in the Asian countries had prepared various strategies to organize a safe and effective inoculation campaign that reaches people in all communities and strategies to increase the vaccination rate among high-risk populations, issues such as traveling distance, limited access to vaccine clinics, mobility issues, lack of public transportation and family care schedules made it difficult for some people to get vaccinated, especially those living in the rural areas.

Mobile vaccination programs are already happening worldwide, and more are planned to reach specific populations with specific criteria like high-risk groups, essential healthcare workers, and rural communities. The public health departments coordinate these vaccination sites in indoor or outdoor settings, with cooperation from local public health clinics, pharmacies, healthcare providers, faith-based organizations, employers, and private sector vaccinators⁷⁰. The Federal Emergency Management Agency (FEMA) and CDC have provided materials to assist authorities in setting up mobile vaccination sites and expanding their use as the supply of vaccines increases.

For instance, the Malaysian government began the mobile vaccination program inoculating

Table IV. Serious adverse effects following immunization (AEFI) reported in Malaysia according to the types of vaccines.

Vaccine types	Suspected anaphylaxis	Acute facial paralysis	Venous thromboembolism	Myopericarditis
Pfizer	96	108	40	7
Sinovac	39	77	28	0
AstraZeneca	5	12	12	1

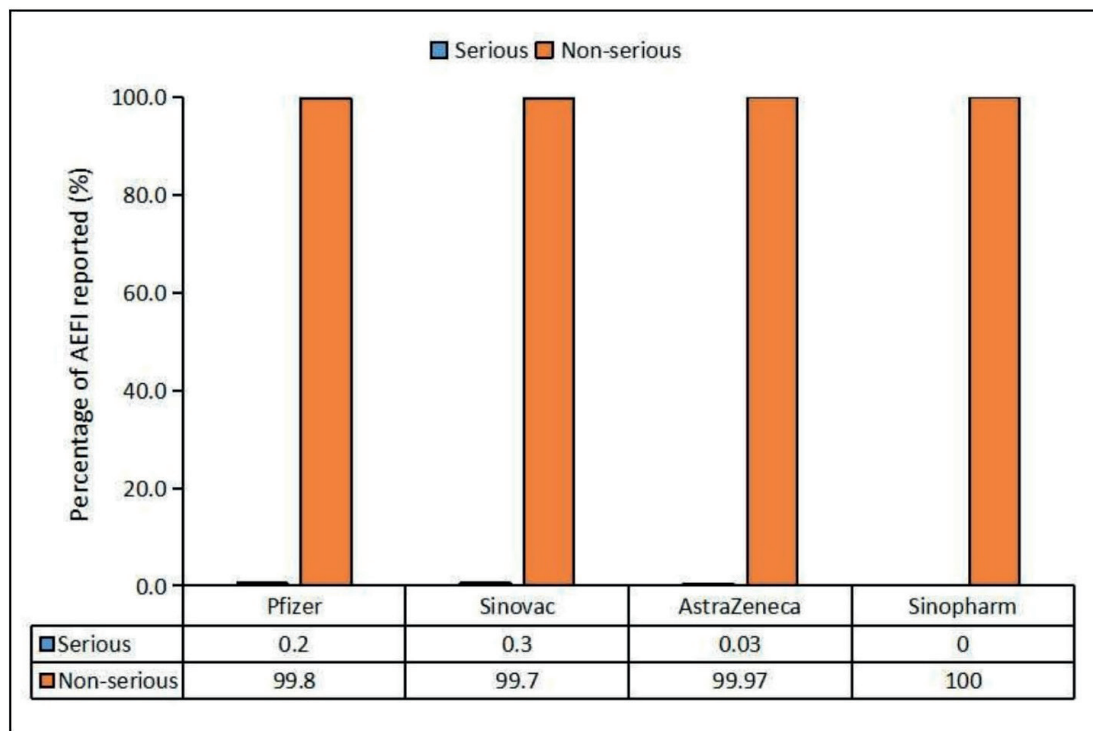


Figure 3. Serious and non-serious adverse effects following immunization (AEFI) according to the different types of vaccine. The graph represents the percentage of adverse effects reported against the total number of people that received the respective type of vaccine.

more than 1000 residents on June 7, 2021, at the Program Perumahan Rakyat (PPR) Kampung Muhibbah at Bukit Jalil⁷¹. The Malaysian government is applying mobile vaccination units to reach densely populated areas, where the residents may have a problem getting to the vaccination center due to mobility issues and traveling distance problems. On June 11, 2021, Malaysia continued its mobile vaccination campaign to speed up its inoculation drive by deploying four mobile vaccination trucks to vaccinate some 7200 residents of public housing projects in Kuala Lumpur⁷². This campaign was focused on the elderly and disabled people, where each truck will carry 600 vaccine doses daily. Furthermore, mobile vaccination centers under the Community Vaccine Mobilization (MOVAK) program also boost efforts to vaccinate 500,00 traders in Johor by July 6, 2021⁷³. As for now, the mobile vaccination program was one of the effective strategies that helped Malaysia increase the daily vaccination rate as half of its population at least had received their first jab.

Walk-in Vaccination

Another way to increase the immunization rate is by opening the COVID-19 inoculation for walk-ins without a vaccination appointment. It is

an initiative that can double the vaccination rate because it is more convenient by eliminating the need for an appointment and avoiding excessive waiting time⁷⁴. This has been proven in Singapore which opened up 37 vaccination centers for walk-in vaccination of the Pfizer-BioNTech from August 10, 2021⁷⁵. This effort aimed to increase the vaccination rates among the elderly at high risk of developing severe illness when infected with COVID-19. To date, Singapore has one of the best vaccination rates globally, with 79% of its population having received at least one dose. Moreover, Singapore has started to ease social distancing restrictions and restart parts of its economy⁷⁶.

In Malaysia, walk-in vaccination is efficient for those facing problems getting to vaccination centers, such as irregular migrants and refugees^{77, 78}. Vaccinating the millions of irregular migrants and refugees in Malaysia is a part of the country’s plan to control COVID19 infections. Malaysia also has one of the fastest vaccination rates in the world after walk-in vaccination started in the Klang Valley. It is also proven that walk-ins effectively increase immunization rates, as seen from the “Jab first, register later” initiative in Kapit, Sarawak in June, and the US walk-in vaccination in pharmacies in May.

Table V. Non-serious adverse effects following immunization (AEFI) reported in Malaysia according to the types of vaccines and dosage. The percentage was calculated based on the numbers of side effects reported against the total number of people receiving the respective vaccine.

Percentage (%)	Site pain		Site swelling		Site redness		Tiredness		Headache		Muscle pain		Joint pain		Weakness		Fever		Vomiting		Chills		Rash		
	1 st	2 nd	1 st	2 nd	1 st	2 nd	1 st	2 nd	1 st	2 nd	1 st	2 nd	1 st	2 nd	1 st	2 nd	1 st	2 nd	1 st	2 nd	1 st	2 nd	1 st	2 nd	
Doses																									
Pfizer	65.4	7.7	16.0	1.9	4.2	0.6	38.1	4.9	30.7	4.1	21.1	2.8	10.5	1.5	20.3	2.8	10.8	1.6	8.5	1.4	8.3	1.3	2.8	0.4	
Sinovac	43.5	3.2	5.2	0.4	2.6	0.3	46.8	2.7	39.6	2.5	20.1	1.3	12.8	0.8	24.3	1.5	12.3	0.6	10.8	0.7	10.2	0.5	4.3	0.3	
AZ	74.6	0.6	18.6	0.1	6.7	0.0	63.6	0.4	60.5	0.4	45.4	0.2	33.0	0.1	50.4	0.2	62.7	0.2	13.5	0.1	48.3	0.1	2.8	0.0	
Sinopharm	46.3	7.3	4.9	0.0	7.3	0.0	65.9	4.9	43.9	7.3	31.7	0.0	22.0	0.0	36.6	2.4	22.0	0.0	9.8	2.4	7.3	0.0	12.2	0.0	
Total	64.8	4.1	14.9	0.9	4.9	0.3	49.6	2.8	43.9	2.3	30.3	1.5	19.7	0.8	32.7	1.6	31.2	0.9	10.9	0.7	24.1	0.7	3.1	0.2	

Increasing the Number of Vaccination Centers

To increase the vaccination rate, we need to maximize the public health service, such as hospitals and pharmacies, to handle the rollout of COVID-19 vaccination programs. Globally, this has prompted the coordination of available services at a large scale, as well as the development and implementation of COVID-19 vaccination strategies to secure maximum inoculation over the shortest period. In Europe, pharmacists are being promoted as healthcare professionals handling injections at COVID-19 vaccination centers. Meanwhile, as a crucial part of the healthcare system, pharmacies play an important part in providing medicines, therapeutics, vaccines, and critical healthcare services to the public^{79,80}. This is important to ensure the continuous function of pharmacies during the COVID-19 pandemic.

According to the guidelines from the CDC, pharmacies can also provide adult vaccination based on local conditions. It should also be considered for adult vaccination because it can be brought during a visit with zero additional risks to the patient and healthcare provider. In addition, consideration should be given to prioritizing older adults with underlying conditions for vaccination to prevent the increased risk of complications or side effects. In Europe, pharmacists have also been historically involved in the supply and inoculation of vaccines prior to the COVID-19 pandemic, such as influenza, human papilloma, and pneumococcal viruses⁸¹. Given their expertise, professional pharmacists in many countries have been lobbying the government to secure pharmacist involvement in their COVID-19 vaccination drive; thus, speeding up vaccination in the populations. A previous study reviewed vaccination programs led by pharmacists, which are widely accepted by patients and helped improve the rate of vaccination⁸¹.

The US is one of the best-performing countries in COVID-19 vaccination. This is driven by many contributing factors, one of which is administering the COVID-19 vaccine by shipping vaccine doses directly to pharmacies. A total of 36 states permitted vaccine inoculation by pharmacists in the US⁸². The pharmacists also have been classified as sources of immunization information, hosts of immunization sites, and immunizers by the American College of Physicians and the American Society of Internal Medicine. More than 17 million COVID-19 vaccines doses have

been administered at community pharmacies in Britain. Similarly, in Australia, pharmacists are permitted to administer vaccines recently. In France, the government began to engage all health professionals, including pharmacists, in their national mass vaccination drive⁸².

In Malaysia, we currently have 5,000 pharmacists and 21,000 active registered pharmacists who are willing to help in boosting the COVID-19 vaccination program. These strategies might hasten the vaccination rate in the population⁸².

Drive-Through Vaccination

The COVID-19 pandemic causes the decline of non-urgent, face-to-face routine medical visits, including those for routine vaccination. However, it is not recommended to postpone or cancel the COVID-19 inoculation for a person because it will leave these individuals more vulnerable to COVID-19. Hence, drive-through or curb-side vaccination clinics are effective ways to be applied and ensure the continuity of people receiving the COVID-19 vaccine jabs⁸³.

According to Reid et al⁸³, the advantages of drive-through vaccination can decrease the risk of exposure to healthcare workers and patients at the clinics since patients could decrease their exposure via social distancing by staying “encapsulated” in their vehicles. Furthermore, by staying in their vehicles, they can avoid further infection that might occur in indoor walk-in clinics⁸⁴.

In Malaysia, the drive-through vaccination program is one of the additional initiatives that will be implemented by the government to increase the capacity and speed up the provision of vaccines to the people under the National COVID-19 Immunization Program, for example, drive-through vaccination centers (VC) at public universities and drive through VC for those with disabilities⁸⁵. The drive-through program for the public has also been rolled out after the success of the pilot project for the drive-through COVID-19 vaccinations at the Universiti Sains Malaysia.

Vaccination Program at School

As restrictions are being lifted and students are returning to school, it is important to increase and speed up COVID-19 vaccination rates among young people, especially in Asian countries⁸⁶. School districts are consistently a large part of the daily life of many children and students, which makes them a very strategic place to deliver the vaccine. The CDC has provided action steps to set up COVID-19 vaccination clinics at schools

because it can provide a very convenient location for eligible students and teachers to get vaccinated⁸⁷. It can potentially serve other people in the surrounding area, especially the family members of the students. Schools may also offer the vaccination on weekdays and weekends with the right planning and communication by the government.

The immunization program in Malaysia has been held since 1950 and has offered free vaccination for all children. Some vaccines are delivered through the school health service (mobile school team)⁸⁸. Vaccines that have been offered include the Bacillus Calmette–Guérin (BCG) vaccine that gives protection against tuberculosis and MMR, which is the combination of measles (M), mumps (M), and rubella (R)⁸⁹. The program aims to sustain and strengthen the health system⁹⁰.

A study by Szilagyi et al⁹⁰ demonstrated that the vaccination rates in school-located influenza vaccination (SLIV) were higher than in education-only schools^{90,91}. The study also stated that although it is challenging to implement and conduct flu vaccine clinics at school, it might increase the vaccination rates. This approach can also promote vaccine confidence due to information and misinformation about COVID-19 vaccines. Thus, we need to address the questions and misinformation about the COVID-19 vaccine among vaccinated students and their families.

More Exposure to Vaccines

Most people are reluctant to take the COVID-19 vaccines due to the lack of information and misinformation. People may also have previous experiences that affect their trust and confidence in taking vaccines in general, affecting their decision to get vaccinated⁹². According to the CDC, strong confidence in the vaccines within communities leads to more people getting vaccinated, leading to fewer COVID-19 illnesses, hospitalization, and death.

Trust in vaccines is important and critically dependent on the ability of the government to disseminate information regarding the benefits, safety, and effectiveness of the vaccines. Although the development of COVID-19 vaccines has been an amazing success story, there is still much that needs to be done to gain the trust in the vaccination program. Governments also need to understand the citizen's specific vaccine concerns, historical experiences, religious or political affiliation, and socioeconomic status. For instance, African Americans in the US are not interested in being vaccinated⁹². These issues may be related to the negative history of the healthcare system,

as well as historical abuse of power like the lack of informed consent toward these specific groups.

Improving Vaccine Delivery

To date, the delivery of the vaccines is only limited to intramuscular injection. Although intramuscular injection is safe and effective, the mucosal injection could enhance the local immune responses that inhibit the spread of pathogens. However, the understanding of mucosal immunity combined with the urgent need for the COVID-19 vaccine has resulted in only intramuscular vaccinations⁹³. Future research should explore the most effective route of COVID-19 vaccine administration and the mechanism that determines the efficacy of different delivery routes. Instead of intramuscular injection, another mucosal vaccine route delivery is using a nasal spray.

SARS-CoV-2 mainly infects the upper respiratory tract; thus, the microenvironment of the nasal passage is crucial for immunity and protection. Several trials using intranasal vaccinations have received favorable results because they can prevent nasal shedding due to the COVID-19 virus infection. However, other trials also gave different outcomes from intranasal vaccinations as results showed that the DNA vaccine did not reduce the viral load in the nasal turbinate. According to the CDC, the nasal spray vaccine comprised of inactivated influenza vaccine is very effective against influenza B and influenza A (H3N2)⁹⁴. Therefore, further study is needed to decide the most effective route for immunization.

Due to the recent and rapid mutations of the virus, current vaccination efficacy has shown to drop even though it is still the best method against having severe implications from COVID-19 infections. Having a vaccine that could act against all variants of COVID-19 is necessary to maintain their high efficacy rate. A recent study had found a novel approach that utilizes the systemic priming of the mRNA lipid nanoparticles (LN-P)-based vaccine via the intranasal passage⁹⁵. This is an important finding because it does not require adjuvants, just a straight nasal challenge. Intranasal vaccination could be more effective than the common intramuscular injection because the local immune microenvironment is important for immunity against infection and viral shedding prevention. It provides efficacious protection that has not been observed in any of the current vaccines given. Also, this is crucial to bring down cases that will then be able to further protect the vulnerable or those who could not be vaccinated.

Oral Antiviral Therapeutic Drugs

Instead of the COVID-19 vaccination, some studies have been initiated to develop an antiviral therapeutic agent that can treat COVID-19 infection. In March 2021, Pfizer Inc. has announced that they had designed a novel oral antiviral therapeutic, PF-07321332, against SARS-CoV-2. The PF-07321332 is a protease inhibitor that will bind to an enzyme called protease, inhibiting the virus from replicating. It has demonstrated a potent *in vitro* antiviral activity against SARS-CoV-2 and other coronaviruses, suggesting its potential use as a treatment for COVID-19 infection and future coronavirus threats⁹⁶. Protease inhibitors also have been used successfully in treating HIV and Hepatitis C, either alone or combined with other antivirals. This class of molecules may likely be developed as a treatment for COVID-19 infection since targeted viral protease therapeutics are not related to any toxicity.

Moreover, viral RNA-dependent RNA polymerase inhibitors, such as Molnupiravir are presently undergoing clinical trials conducted by the giant biopharmaceutical company, Merck, to treat COVID-19 patients. Although the company was scrapping two experimental COVID-19 vaccines after the results showed a disappointing immune response, Molnupiravir is the latest effort by Merck in developing COVID-19 countermeasures⁹⁷. Molnupiravir is an investigational oral antiviral in the form of a potent RNA analog that prevents the replication of multiple RNA viruses, including the SARS-CoV-2. It is also effective against prophylaxis, treatment, and prevention of transmission in several coronaviruses, such as SARS-CoV-2, SARS-CoV-1, and MERS. Merck also announced a deal to supply courses on the experimental treatment of Molnupiravir to the US. Although the results in non-hospitalized patients are promising, the use of Molnupiravir is yet to be approved⁹⁸. The drug is still in phase III testing, and Merck is expected to request emergency authorization with positive results.

With the continued global impact of COVID-19 due to mutations of the SARS-CoV-2 virus, it appears that we need to have access to other therapeutic options either now or after the pandemic. The PF-07321332 and Molnupiravir are potential oral antivirals that could be authorized at the first sign of infection. Both Pfizer and Merck are actively trying in multiple ways to make PF-07321332 and Molnupiravir available globally.

Combination of Vaccine and Oral Antiviral Therapeutic Drugs

While COVID-19 vaccines have been developed within a short time, there are also a significant number of people who could not be vaccinated due to pre-existing medical conditions, such as immunocompromised immune system and allergy history. Moreover, many people are unwilling to get vaccinated. Therefore, limited curing options have been developed and available to those infected. Undoubtedly, we need to maximize the authorization of COVID-19 vaccines and treatments to tackle the COVID-19 outbreak.

However, based on a survey conducted published in Nature, most scientists, immunologists, and virologists working on the coronavirus stated that it could not be eradicated and would become endemic⁹⁶. It will continue to circulate in communities of the global population for years to come. To control and tackle this COVID-19 outbreak, we need two-pronged strategies, i.e., to protect against severe disease via vaccines and treatments for those infected and those who could not take the vaccine due to pre-existing medical conditions.

Nevertheless, the failure to eliminate the coronavirus from the population does not mean that death, illness, or social isolation will continue. The future will rely heavily on the type of immunity that people acquire through infection or vaccination and how the coronavirus evolves⁹⁹. Influenza and other human coronaviruses that usually cause the common cold are also endemic. However, combinations of vaccines and acquired immunity mean that societies can reduce seasonal deaths and severe illness without the need to implement lockdown, masks, and social distancing.

Most countries that have started distributing COVID-19 vaccines expect to see a reduction in the severity of illness upon infection. However, it will be time-consuming to observe the effectiveness of the vaccines to reduce viral transmission. The results from clinical trials showed that vaccines that prevent symptomatic infection might also prevent a person from passing the virus. If the COVID-19 vaccines can block the transmission and remain effective against newer variants, it might be possible to eradicate the virus in certain regions where enough population is vaccinated to protect those who are not vaccinated⁹⁶. However, the rate of transmission increases in the latest variants, such as the Delta variants that renders a high infection rate, either in vaccinated or unvaccinated people.

Although the medications for COVID-19 are still being developed, the COVID-19 vaccines are the initiative that the world can rely on to reduce the severity of the disease. As of now, preventive measures such as social distancing, wearing masks, and sanitizing your hands still need to be followed. Both antiviral drugs and COVID-19 vaccines are the best approaches to address the problem.

One-Shot Vaccines

To provide effective protection against diseases, most traditional vaccines need to be injected twice, resulting in a costly and inconvenient regimen that often leads to logistical challenges and poor patient compliance¹⁰⁰. These drawbacks have encouraged the development of single-dose vaccines that can provide similar protection as double shot vaccines. Single-dose COVID-19 vaccines that have been developed are the Convidecia vaccine developed by CanSino Biologics Inc. from China and the Jansen vaccine developed by Johnson & Johnson/Janssen from the US. Both vaccines are viral vector types like the Oxford-AstraZeneca. However, the CanSino vaccine used adenovirus serotype 5 (Ad5) as the vector, while the Johnson & Johnson/Janssen vaccine used adenovirus serotype 26 (Ad26) to deliver the genetic instruction into the cell¹⁰¹.

Interestingly, single-dose vaccines have a great advantage as they only require a single injection. This is a huge saving in terms of costs to administer the vaccines and the resources required, as patients do not need to come twice for vaccinations. With similar efficacy and effectiveness results as double shot vaccines, single-dose vaccines can also be used for those concerned with the side effects¹⁰¹.

However, most countries have offered single-dose vaccines as a tremendous boost for outskirt and rural areas, which are difficult to reach as rural people are also classified as vulnerable populations to get infected with COVID-19. There are also high-risk populations, such as the homeless or the chronically ill and bed-bound populations that can be offered single-dose vaccines. As for now, there have been no reported cases of unusually rare blood clots for the CanSino vaccine. Advisors to the US FDA recommended the emergency use approval of the single-dose vaccine that can be stored and transported at a typical temperature. These factors made it the perfect option for rural areas and hard-to-reach communities, including those who are hesitant to take the vaccine^{102,103}.

On August 20, 2021, Malaysia received its first batch of the single-dose COVID-19 vaccine developed by CanSino Biologics Inc. from China¹⁰⁰. The government is considering offering single-shot vaccines for those living in rural and interior areas after looking into logistics and the location of rural populations. The government also stated that those who live in interior areas might have a problem and difficulties coming again for a second vaccine shot. It may be used during the phase two COVID-19 vaccination program, which has recorded a low sign-up rate from the outskirt areas.

Conclusions

The current SARS-CoV-2 pandemic is a continuing predicament that is the starting point toward a global crisis on an unpredictable scale. This review mainly discusses the effectiveness of the current COVID-19 vaccines that have been administered in many countries and the strategies for future protection against severe COVID-19 complications. Several companies have conducted preclinical and clinical trials for single drugs or combinations that are still in progress. The development of new vaccines that may have a higher affinity or specific targeting against the COVID-19 virus is underway¹⁰⁴. While we wait for an official report on the effectiveness and availability of the antiviral treatments, the COVID-19 vaccine is the best initiative that we can rely on to reduce the severity of the disease. Moving forward, vaccine development should consider targeting specific groups, such as elderly, and those with chronic diseases as they are the most vulnerable to having severe reactions to COVID-19 infections¹⁰⁵. As for now, the most effective preventive measures for COVID-19 are still early detection, quarantine, and supportive medications for positive patients.

The increase in the vaccination rate in many countries has proved to reduce the infection rate among vaccinated people. COVID-19 vaccination also reduced the severity, and the number of complications due to COVID-19 infection as the number of patients admitted to the ICU showed a descending trend since the national vaccination program began. The government has stated that we need to prepare for an endemic phase due to the emergence of new variants that are highly transmissible and contagious, resulting in a high number of daily cases. It has been reported that even with the newly emerging variants of

COVID-19, the efficacy of the vaccine remains high and vaccinating the mass population is still the finest option in managing the danger of new variants¹⁰⁶. The experience gained from global efforts in managing COVID-19 should move Malaysia to be prepared in controlling the disease as an endemic in the future. The vaccination rate needs to be increased as preparation because the virus will continue to circulate in the population for years to come.

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Conflicts of Interest

The authors declare no conflicts of interest.

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