



Review Article

COVID-19 Booster Vaccines Administration in Different Countries

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Abstract: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that resulted in the COVID-19 global pandemic had consequently led to the development of different types of COVID-19 vaccines, including the messenger RNA (mRNA) vaccines, inactivated virus vaccines, a protein subunit vaccine, and viral vector recombinant vaccines. Countries worldwide started their national vaccination program as soon as the COVID-19 vaccines got approved by the World Health Organization (WHO) under the emergency use listing. This includes COVID-19 vaccines by Pfizer-BioNTech, Moderna, AstraZeneca, Janssen, Sinovac, and Sinopharm. Findings suggested that protection against COVID-19 provided by these vaccines may be waning or that the protection reduces against variants of concern (VOC) or even inadequate protection of the primary vaccination for some risk groups. This led to the development of the COVID-19 booster vaccine that aims to improve and prolong the protection against COVID-19. This review aims to discuss the various COVID-19 booster vaccines that are being authorized and administered, the eligibility criteria for the different booster vaccines, and the extent of protection these booster vaccines provide in the United States (US), Israel, United Kingdom (UK), Singapore and Chile.

Keywords: SARS-CoV-2; COVID-19; vaccine; booster; waning

1. Introduction

COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This pandemic started in 2020 and has yet to end^[1, 2]. As of 13 December 2021, there had been 270,218,553 confirmed cases, and 5,308,045 deaths reported globally^[3]. COVID-19 has consequently led to the development of COVID-19 vaccines at an unprecedented pace.

These vaccines activate the immune response upon binding to the spike protein^[1, 4], and the primary goal of immunization against COVID-19 is to protect against severe disease, hospitalization, and death^[5]. Therefore, our hope now lies in getting the world fully vaccinated to quell this global pandemic.

The various COVID-19 vaccines developed include messenger RNA (mRNA) vaccines, inactivated virus vaccines, a protein subunit vaccine, and viral vector recombinant vaccines^[4, 6]. Vaccines that are approved by World Health Organization (WHO) under the emergency use listing (EUL) include mRNA vaccines by Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273); viral vector vaccines by AstraZeneca and Janssen; and inactivated virus vaccines by Sinopharm and Sinovac^[7]. When this review went to press, at least 56% of the world population had received at least one dose of the COVID-19 vaccine, and 8.47 billion COVID-19 vaccine doses have been administered globally (as of 12 December 2021)^[8]. However, despite the development of vaccines and the global initiation of immunization, the pandemic is still ongoing.

Recently, there have been findings that the protection COVID-19 vaccines provide against the infection may be waning^[9-12]. Hence, the further development of COVID-19 booster vaccines comes into place. In fact, in recent months, several countries have begun administering COVID-19 booster vaccines to eligible individuals that have completed their primary vaccine series. This review aims to discuss the COVID-19 booster vaccination program in a few countries, including the United States (US), Israel, United Kingdom (UK), Singapore, and Chile. We will also discuss the eligibility criteria for the various booster vaccines and the extent of protection they provide against COVID-19.

2. Administration of COVID-19 booster vaccine in various countries

The rationale for the administration of COVID-19 boosters includes (i) the waning protection against infection or disease, particularly severe disease, over time (i.e., waning immunity), (ii) reduced protection against variants of concern (VOC), or (iii) inadequate protection from the currently recommended primary series for some risk groups for which evidence from the Phase 3 clinical trials may have been lacking. Nonetheless, its rationale may differ by vaccine product, epidemiological setting, risk group, and vaccine coverage rates^[13].

COVID-19 booster vaccines aim to restore antibody levels^[14] and improve an individual's protection after their primary doses, allowing for longer-term protection^[15]. They are administered when, with time, the immunity and clinical protection have dropped below a rate deemed sufficient^[5]. In this review, some of the COVID-19 booster vaccines that will

be discussed includes mRNA vaccines- Pfizer-BioNTech/COMINARTY (BNT162b2)^[16], and Moderna (mRNA-1273)^[17], viral vector vaccines-Janssen BioTech Inc. (JNJ-78436735)^[18], and Oxford AstraZeneca (AZD1222)^[15], inactivated virus vaccines- Sinovac (CoronaVac)^[10], and Sinopharm (BBIBP-CorV)^[19] (Table 1) .

Table 1. COVID-19 vaccines and their respective manufacturers.

Vaccine brands/ Research name	Manufacturer	References
Pfizer-BioNTech (Before FDA approval)/COMINARTY (After FDA approval) (BNT162b2)	Pfizer, Inc., and BioNTech	[16]
Moderna (mRNA-1273)	ModernaTX, Inc	[17]
JNJ-78436735	Janssen BioTech, Inc., a Pharmaceutical Company of Johnson & Johnson	[18]
CoronaVac	Sinovac BioTech Ltd.	[20]
BBIBP-CorV	Beijing Bio-Institute of Biological Products Co., Limited. (BIBP), placed under the China National Pharmaceutical Group Corporation (Sinopharm)	[19]

2.1. United States (US)

The US's authorized and recommended COVID-19 booster vaccines are from Pfizer-BioNTech, Moderna, and Janssen^[11, 21]. As of 22 November 2021, 196.4 million people have been fully vaccinated and 36.1 million have received a booster dose^[22]. The Centers for Disease Control Prevention (CDC) has allowed for a mix and match dosing; thus, individuals can choose any COVID-19 vaccines for their booster shot regardless of their previous vaccines^[11, 17]. However, mixing products for an initial two-dose series or additional doses is not recommended^[17].

On 12 August 2021, the US Food and Drug Administration (FDA) amended the authorizations for both mRNA COVID-19 vaccines (Pfizer–BioNTech's BNT162b2 and Moderna's mRNA-1273) to allow for the use of an additional dose in immunocompromised patients^[23, 24]. On 22 September 2021, the Pfizer-BioNTech booster vaccine authorization was extended to include individuals aged 65 years or older and 18-64 with a high risk of severe COVID-19 or whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk^[23, 25]. The FDA then made similar booster recommendations for Moderna in October 2021^[11] and the inclusion criteria are the same as those for Pfizer-

BioNTech^[11, 21]. Later, on 19 November 2021, the US FDA amended the use of Pfizer-BioNTech and Moderna COVID-19 vaccines, authorizing the single-use of COVID-19 boosters for individuals aged 18 and above who completed their primary vaccination series with any COVID-19 vaccines authorized or approved by the FDA^[21]. The administration of booster doses for both vaccines have to be at least six months after completing Pfizer-BioNTech or Moderna's COVID-19 primary vaccination series or at least two months after the completion of Janssen's COVID-19 primary vaccination series^[21]. Regarding the COVID-19 vaccine by Janssen, the FDA advisory panel is also recommending their single booster dose COVID-19 vaccine of Janssen or Pfizer BioNTech or Moderna to all adults 18 and above, 2 months after Janssen's primary vaccination^[11].

In terms of booster vaccine effectiveness, on 21 October 2021, Pfizer-BioNTech announced their phase 3 randomized, controlled COVID-19 vaccine booster trial data, which consists of 10,000 participants 16 years and above. The results showed that the booster doses administered to individuals who received Pfizer-BioNTech primary two-dose series had vaccine protection restored and showed relative vaccine efficacy of 95.6% compared to those who did not receive a booster dose^[26]. Besides that, the FDA also analyzed the immune response data from around 200 participants aged 18 through 55 who received a single booster dose about 6 months after their second dose. The antibody response against the SARS-CoV-2 virus in the same individual showed booster response 1 month after receiving a booster dose of Pfizer-BioNTech, compared to the response 1 month after the two-dose primary series^[21].

Moderna's booster vaccine is a reduced dose that is to be administered at least 6 months after its primary vaccination series^[11]. This reduced dose is shown to reactivate the immune memory and increase the worldwide vaccine supply^[27]. The FDA analyzed the immune response data from 149 participants ≥ 18 years of age from the original clinical studies who received a booster dose at least 6 months after their second dose and compared it to the immune responses of 1,055 study participants after completing their two-dose series. Results show that booster response was demonstrated from the antibody response against the SARS-CoV-2 virus 29 days after a booster dose of the vaccine^[11].

In terms of Janssen's (a pharmaceutical company of Johnson and Johnson (J&J)) vaccine efficacy in the US, those who received a single dose of the Janssen vaccine were only 73%, while those who received the booster shot vaccine efficacy increased to 94%^[18]. In addition, J&J announced on 21 September 2021 that their real-world evidence and phase 3 studies confirmed the strong and long-lasting protection of the single-shot J&J vaccine against COVID-19 related hospitalization. Data from the Phase 3 trial further ensures

protection against COVID-19 related death. According to J&J, they have also generated evidence that a booster shot can further increase protection against COVID-19 and is expected to significantly extend the protection duration of protection greatly^[28]. According to J&J's Phase 3 study, the booster shot administered 56 days after the single shot provided 100% protection against severe/critical COVID-19 (≥ 14 days post-vaccination), 75% protection against symptomatic moderate to severe/critical COVID-19 globally and 94% protection against symptomatic moderate to severe/critical COVID-19 in the US. Furthermore, compared to the single vaccine shot, the booster shot administered after 2 months, showed antibody levels rose 4-6 times higher than after the single shot. When the booster shot was administered 6 months after the single shot, antibody levels rose 9-fold 1 week after the booster. They continued to increase to 12-fold higher 4 weeks after the booster, in which the increase was irrespective of age^[18, 28]. Hence, booster shots may induce the humoral immune response and possibly boost the immune response, further increasing the vaccine efficacy against symptomatic infection^[18].

2.2. Israel

Israel is one of the countries that vaccinated their population very early and widely. By the end of March 2021, >50% of Israel's population had been fully vaccinated with two doses of Pfizer-BioNTech COVID-19 vaccine^[8, 29], while other countries were still struggling for their first dose. Even with 55% of the population completing two Pfizer-BioNTech vaccination doses, Israel is still struck with a fourth pandemic wave^[23]. Recently with COVID-19 booster shots authorized for use, Israel is the first country in the world to administer the COVID-19 booster vaccine^[4, 30]. The Israeli Ministry of Health announced a campaign to administer the third dose Pfizer-BioNTech COVID-19 vaccine, which started with immunocompromised individuals on 13 July 2021. It then extended to individuals ≥ 60 years of age on 30 July 2021. After that, it extended to those 50 years of age (12 August), 40 years (19 August), 30 years (24 August), and the entire population above 12 years of age on the 30 August. Within the first 2 weeks, more than half the population ≥ 60 years of age were vaccinated with the booster dose^[23].

The effect of Pfizer-BioNTech booster doses on COVID-19 is demonstrated in a study involving 1,137,804 Israelis that are ≥ 60 years old and had received two doses of Pfizer-BioNTech at least five months earlier. They found that at least 12 days after the booster dose, the booster group showed a lower rate of infection than the non-booster group by 11.3 while the rate of severe illness was lower by a factor of 19.5^[29]. Similarly, another observational study using mass vaccination data in Israel (1,158,269 Israelis) also found that the Pfizer-BioNTech booster vaccine effectively prevents severe COVID-19 associated

outcome. Compared to two doses of vaccines administered at least 5 months earlier, the vaccine effectiveness after at least 7 days of receiving the booster dose was estimated to be 93% effective in preventing COVID-19 associated hospital admission, 92% in preventing severe disease, and 81% in preventing COVID-19 associated death^[23].

2.3. United Kingdom (UK)

Since the launch of the COVID-19 vaccine program in December 2020, by mid-September 2021, 89.1% of the UK population had received their first dose, while 81% received both doses. The booster vaccine program started in September 2021^[31], with the Joint Committee on Vaccination and Immunization (JCVI) stating that the decision was “precautionary” and that, on balance it was preferable to maintain a high level of protection in vulnerable adults throughout winter^[32]. Booster vaccines available in the UK include Pfizer-BioNTech, Moderna, and AstraZeneca. They are given to high-risk individuals that are age ≥ 50 , individuals who live or work in care homes, frontliners or social care workers, individuals aged 16 and above with underlying medical conditions or a carer of a high-risk individual or living in a high-risk setting. Eligible individuals can receive their booster doses 6 months after their second vaccine dose^[15]. The JCVI advised that the Pfizer-BioNTech booster doses be preferred regardless of which vaccine brand an individual received for their primary doses. This follows data from COVID-19 Booster (CoV-boost) trial that indicates the Pfizer-BioNTech vaccine is well tolerated as a third dose and provides a strong booster response^[32]. Alternatively, it can be a half dose of the Moderna vaccine. For individuals who cannot have the mRNA vaccines, booster doses of Oxford AstraZeneca will be offered^[15, 31]. As of 1 November 2021, the government reported that 8.1 million UK people had received their booster shot^[33]. Nonetheless, on the same day, John Roberts from the Covid-19 Actuaries Response Group reported that approximately 5.8 million eligible individuals have not yet had their booster^[33].

2.4. Singapore

As part of Singapore’s National Vaccination Program (NVP), the Health Sciences Authority (HSA) under the Pandemic Special Access Route (PSAR) has authorized the Pfizer-BioNTech, Moderna, and Sinovac COVID-19 vaccines for use in Singapore to prevent COVID-19^[34, 35]. It was only until 23 October 2021 that the Multi-Ministry Taskforce (MTF) announced that the Sinovac vaccine would be included in Singapore's NVP for those ≥ 18 years of age and unable to be vaccinated with mRNA vaccine. The administration for Sinovac vaccination will start on 30 October 2021^[34].

On 14 September 2021, Singapore started its Vaccination Booster Program, including COVID-19 booster mRNA vaccines by Pfizer-BioNTech, and Moderna^[34]. The eligibility criteria for booster vaccination are those ≥ 30 years of age or healthcare or frontliners ≥ 18 years of age who have received two doses 5 months ago^[36]. Singapore allows for a mix and match vaccine concept for booster doses as individuals need not receive the same vaccine as their previous two doses^[34]. Although Sinovac-CoronaVac was later added into the NVP on 23 October 2021^[34], it's used as a booster vaccine for individuals who cannot receive the third dose of the PSAR-authorized mRNA vaccines due to valid medical reasons^[37]. As of 22 November 2021, 86% of Singapore's total population has received one dose of the COVID-19 vaccine, while 85% of the total population had two doses of the COVID-19 vaccine, and 24% of Singapore's total population has received the COVID-19 booster shot^[36].

To study the effectiveness of vaccination boosters, Singapore's Ministry of Health studied the COVID-19 positive infection rates of individuals who have received their booster doses vis-à-vis fully vaccinated individuals who have not yet received their booster doses. The study included 685,083 fully vaccinated individuals above 60 years eligible for booster doses and had received their second vaccination dose >180 days before 15 September 2021. They found that with the administration of booster doses, the risk reduction against COVID-19 conferred roughly a further 70%, while against severe infections is 90% compared to those who did not receive a booster dose. There is indeed more protection with the addition of booster doses because two doses of mRNA vaccines already provided 40-60% effectiveness against COVID-19 infection when comparing those vaccinated versus unvaccinated individuals and $>90\%$ against severe illness. To sum up, based on estimates of combined data from different sources, individuals who are fully vaccinated and boosted benefit from vaccine effectiveness of about 80% or more against COVID-19 infection and about 99% against severe illness^[34].

2.5. Chile

The authorized COVID-19 vaccines in Chile are from Sinovac, Pfizer-BioNTech, AstraZeneca, CanSino^[38], Janssen, and Gamaleya^[39]. Based on Chile's vaccination plan, healthcare personnel was vaccinated first, followed by an age-descending strategy, in addition to teachers and school staff, and essential workers. Even individuals aged 12–17 years are eligible for vaccination^[38]. Chile's mass COVID-19 vaccination campaign started in February 2021^[40]. By October 2021, 91.6% of individuals had received a single vaccine dose, and 88.84% of its target population had been fully vaccinated. The COVID-19 booster vaccination started on 11 August 2021, which took into consideration recommendations from

the National Immunization Program, the Vaccines and Immunizations Advisory Committee (CAVEI), the COVID-19 Advisory Council, national scientific societies, and international experts with whom the President and Health Ministry authorities have met during the past few months. The administration of booster doses was first given to individuals who received the Sinovac vaccine, and during the first 8 weeks, 3,547,177 individuals received the booster dose ^[41].

In early October 2021, the President of Chile, Sebastián Piñera stated that vaccines administered in the country are safe and effective, can decrease infections and hospitalizations significantly, and have saved many lives^[41]. At the same time, the government of Chile reported preliminary results on the effectiveness of booster doses based on some 2 million individuals who have received two doses of Sinovac and the third dose of Sinovac, Oxford AstraZeneca, or Pfizer-BioNTech vaccines^[10]. The vaccine effectiveness, Sinovac, increased from 56% to 80.2%, while AstraZeneca rose from 56% to 93%, and Pfizer-BioNTech increased from 56% to 90%. Overall, all three booster vaccines effectively reduced the need for hospitalization^[41].

3. Conclusion

With studies showing waning immunity against COVID-19^[9, 10], reduced protection against VOC, and that primary vaccination itself may be inadequate to protect some against COVID-19 infection, booster doses are introduced^[13]. The additional administration of a booster dose will restore high antibody levels^[14], further improving and prolonging the protection against COVID-19^[15]. Booster vaccines mentioned in this review include Pfizer-BioNTech, Moderna, Janssen, AstraZeneca, Sinovac, and Sinopharm. Based on the few countries discussed above that have started administering booster vaccines to their population, they seem to demonstrate positive results in protecting against COVID-19. Although the authorized brand of the booster vaccine and the eligibility criteria of booster vaccines may differ depending on countries, findings appear to be consistent that the administration of booster doses further increases vaccine effectiveness, decreases risk of infection, severity of disease, hospitalization, and death (Table 2).

Table 2. Summary of booster vaccination programs in different countries

Country	United States (US)	Israel	United Kingdom (UK)	Singapore	Chile
Population fully vaccinated (Primary vaccination)	196.4 million (as of 22 November 2021) ^[22]	>50% of the population (by end of March 2021) ^[8, 29]	81% of the population (by mid-September 2021) ^[31] .	85% of the total population (as of 22 November 2021) ^[36]	88.84% of its target population (by October 2021) ^[41]
Population vaccinated with booster vaccine	36.1 million (as of 22 November 2021) ^[22]	Within first two weeks >50% of those ≥ 60 years of age ^[23]	8.1 million (as of 1 st November 2021) ^[33]	24% of the total population (as of 22 November 2021) ^[36]	3,547,177 individuals (during the first 8 weeks) ^[41]
Type of booster vaccine	Pfizer-BioNTech, Moderna and Janssen ^[11, 21]	Pfizer-BioNTech ^[23]	Pfizer-BioNTech, Moderna, AstraZeneca ^[15]	Pfizer-BioNTech, Moderna, Sinovac ^[34, 37]	Sinovac, Oxford AstraZeneca, Pfizer-BioNTech ^[10]
Eligibility criteria for booster vaccine	≥ 18 years old after primary vaccination (6 months after Pfizer-BioNTech or Moderna) (2 months after Janssen's) ^[11, 21]	>12 years old after primary vaccination ^[23]	- High risk individuals age ≥ 50 - Individuals living or working in care homes - Frontliners/ social care workers - ≥ 16 years old with underlying medical conditions - Carer of a high-risk individual/ living in high risk setting	Above 30 years old, and healthcare or frontliners ≥ 18 years old after primary vaccination 5 months ago ^[36]	N/A

			*6 months after primary vaccination ^[15]		
Findings on booster vaccine effectiveness	<i>Pfizer-BioNTech</i>	- (≥ 12 days after booster)	N/A	Vaccine effectiveness of about 80% or more against COVID-19 infection, and about 99% against severe illness ^[34]	Sinovac increased from 56% to 80.2%; AstraZeneca rose from 56% to 93%; Pfizer-BioNTech increased from 56% to 90% ^[41]
	Vaccine efficacy of 95.6% ^[27] ;	Rate of infection lowered by a factor of 11.3 while rate of severe illness lowered by a factor of 19.5 ^[29]			
	Positive booster response after 1 month boosted ^[21]				
	<i>Moderna</i>	Positive booster response 29 days after booster dose ^[11]			
	<i>Janssen</i>	Vaccine efficacy increased from 73% to 94% ^[18] ;	- (≥ 7 days after booster)		
	Antibody levels rose 4–6 times higher than after the single shot (post 2 months);	antibody levels rose 9-fold 1 week after the booster and continued to increase to 12-fold higher 4 weeks after the booster (post 6 months) ^[18, 28]	93% effective in preventing COVID-19 associated admission to hospital, 92% in preventing severe disease and 81% in preventing COVID-19 associated death ^[23]		

Nonetheless, there are also debates on the waning of immunity^[12, 14]. The increase in disease severity could result from waning immunity or vulnerable individuals being vaccinated first. Nevertheless, we believe that getting vaccinated with the additional booster dose could be one of the strategies to decrease the risk of infection, hospitalization, the

severity of illness, and death, allowing for better control of the pandemic and a return to normalcy. It may even help improve people's quality of life, including mental health. Nonetheless, even after being fully vaccinated or vaccinated with an additional booster dose, other preventive measures should continue to be practiced. This includes physical distancing, wearing a face mask, and handwashing, while the government should also continue with mass vaccination, testing campaigns, contact tracing, and restricting large gatherings^[4, 42-47].

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