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REVIEW
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Review of Clinical Trials of COVID-19 Vaccination Booster in SARS-CoV-2 Variants Era: To Take It or Not To Take It

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Since the COVID-19 outbreak in China in 2019, the pandemic has spread globally. There is no definitive cure, but vaccines have greatly protected humans from symptomatic infections and severe complications. However, vaccine efficacy has been greatly reduced by the advent of SARS-CoV-2 variants worldwide. The World Health Organization has classified the variants into two groups: variants of concern (Alpha, Beta, Gamma, Delta, Omicron) and variants of interest (Lambda, Mu). Clinical trials and modifications of vaccines are currently undertaken to improve their clinical efficacies. This is particularly worrying in immunocompromised patients since breakthrough infections with multiple lineages of variants can pose a continuous threat of severe diseases in these vulnerable subjects, though there is no evidence showing immunocompromised patients are at a higher risk of vaccine-associated adverse events. However, there is no consensus on the schedule, benefits, and risks as well as contraindications (both absolute and relative) of receiving booster vaccinations. This review looks into the efficacy and safety of COVID-19 vaccination booster to guide clinical decisions on when and who to receive booster vaccination.

Keywords: COVID-19, vaccinations, booster, risks analysis, review

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INTRODUCTION

Since the outbreak of COVID-19 infection in late 2019 in China, it has spread globally causing massive morbidity and mortality. It spreads through contact, droplets, and aerosol transmission (PriyankaChoudhary et al., 2020). The morbidity and mortality rates in developed countries slowed down because COVID-19 vaccines provided immune protection against SARS-CoV-2 (Arbel et al., 2021; Yan et al., 2021a). In spite of the high efficacy and safety profile of vaccines as reported in various studies, some patient groups are still undecided whether to receive vaccinations (Abu-Farha et al., 2021; Yigit et al., 2021a; Choudhary et al., 2021; Zhou et al., 2021). Previous studies and guidelines have documented the special considerations for different clinical special populations, and medical staff should assist in the risk–benefit analysis to make a proper clinical decision (Yan et al., 2021b; Furer et al., 2021; Powers et al., 2021; Soiza et al., 2021).

Worldwide, a significant portion of people in developed countries has completed COVID-19 vaccination schedule, while some in developing and under-developed countries have not completed basic vaccination schedules due to resources scarcity and income disparity (The Lancet Infectious

TABLE 1 | Summary of characteristics of SARS-CoV-2 variants by the WHO Classification (WHO, 2021a). a) Variants of concern.

WHO label	Pango lineage	GISAID clade	Nextstrain clade	Additional amino acid changes monitored	Earliest documented samples	Date of designation
Alpha	B.1.1.7	GRY	20I (V1)	+S: 484K +S: 452R	United Kingdom, September 2020	December 18, 2020
Beta	B.1.351	GH/501Y.V2	20H (V2)	+S: L18F	South Africa, May 2020	December 18, 2020
Gamma	P.1	GR/501Y.V3	20J (V3)	+S: 681H	Brazil, November 2020	January 11, 2021
Delta	B.1.617.2	G/478K.V1	21A	+S: 417N	India, October 2020	VOI: April 4, 2021 VOC: May 11, 2021
Omicron	B.1.1.529	GR/484A	21K	-	Multiple countries, November 2021	VUM: November 24, 2021 VOC: November 26, 2021

WHO label	Pango lineage	GISAID clade	Nextstrain clade	Earliest documented samples	Date of designation
Lambda	C.37	GR/452Q.V1	21G	Peru, December 2020	June 14, 2021
Mu	B.1.621	GH	21H	Colombia, January 2021	Aug 30, 2021

Pango lineage	GISAID clade	Nextstrain clade	Earliest documented samples	Date of designation
AZ.5	GR	-	Multiple countries, January 2021	VUM: June 2, 2021
C.1.2	GR	-	South Africa, May 2021	September 1, 2021
B.1.617.1	G/452R.V3	21B	India, October 2020	VOI: April 4, 2021 VUM: September 20, 2021
B.1.526	GH/253G.V1	21F	United States, November 2020	VOI: March 24, 2021 VUM: September 20, 2021
B.1.525	G/484K.V3	21D	Multiple countries, December 2020	VOI: March 17, 2021 VUM September 20, 2021
B.1.630	GH	-	Dominic Republic, March 2021	October 12, 2021
B.1.640	GH/490R	-	Republic of Congo, September 2021	November 22, 2021

VOC, variants of concern; VOI, variants of interest; VUM, variants under monitoring.
VOI, variants of interest; VUM, variants under monitoring.

Diseases, 2021; Van De Pas et al., 2022). Vaccination does not confer sufficient lifelong protection: post-vaccination humoral responses decrease after 3–6 months (Chemaitelly et al., 2021; Levin et al., 2021; Erice et al., 2022). Early studies on booster vaccination show that the infection rate in the booster cohort is lower compared with those without receiving a booster (Bar-On et al., 2021). Of even greater concern, vaccine efficacy dwindles when it comes to Delta- and Omicron-related variant infections, which is associated with higher viral load and transmissibility (Campbell et al., 2021; Torjesen, 2021). Patients without sufficient protective efficacy run a higher risk of symptomatic infection, severe hospitalization, mortality, and long COVID-19 syndrome (Yan et al., 2021c).

This prompts a key question: who should receive a booster 6 months after the last dose since vaccination per se may be associated with risks? This paper evaluates the risk and benefits of booster vaccination to assist clinical decision making. Literature data were retrieved from electronic databases (PubMed, Medline, Scopus, Cochrane, Google Scholar) on December 14, 2021, with the following keywords: COVID-19, Vaccine, Booster, and Variants. Related articles are reviewed to address the key question.

COVID-19 Variants

Since the outbreak in 2019, various variants have been identified worldwide. The transmissibility and mortality of SARS-CoV-2 have been changing with the new mutations. Various reports have shown the reduced efficacy of vaccines to neutralize SARS-CoV-2 variants. WHO has proposed the classification of SARS-CoV-2 variants into two major types: variants of concern (VOC) and variants of interest (VOI) (WHO, 2021a). Their characteristics are listed in **Table 1** (WHO, 2021a). In view of the emerging variants globally, vaccine efficacy against different variant strains are recorded in **Table 2**.

BENEFITS OF BOOSTER VACCINATION

Waning humoral responses have been reported worldwide 6 months after completion of vaccination (one to three doses, depending on vaccination design) (Levin et al., 2021; Chemaitelly et al., 2021; Shrotri et al., 2021). This is particularly evident in men, participants older than 65 years old, or people with immunosuppression (Levin et al., 2021) for BNT162b2 (Pfizer-BioNTech) recipients. In spite of the waning antibody titer after 6 months of completion of BNT162b2 (Pfizer-BioNTech) vaccination, the protection against hospitalization and death persists at a robust level. The estimated effectiveness of BNT162b2 (Pfizer-BioNTech) against SARs-CoV-2 infection peaked at 77.5% (95% CI, 76.4–78.6) in the first month after the second dose, but it progressively dropped to 20% 5 months after the second dose (Chemaitelly et al., 2021). Thus, reinfection by SARS-CoV-2 is possible (Cromer et al., 2021). Vaccine

TABLE 2 | COVID-19 vaccine efficacy against symptomatic infection 14 days after complete vaccination schedule (without booster) against variant strains 2 weeks after administration, stratified by region.

	BNT162b2 (Pfizer), 2-dose	mRNA-1273 (Moderna), 2-dose	ChAdOx1 nCoV-19 (AZD 1222), 2-doses	Ad26.COV2.S (Janssen), 1-dose	Coronavac (Sinovac), 2-dose
Alpha (B.1.1.7)	United Kingdom: 93.7% (Lopez Bernal et al., 2021) (95% CI, 91.6–95.3) Qatar: 89.5% (Abu-Raddad et al., 2021) (95% CI, 85.9–92.3) Canada: 89% (Nasreen et al., 2021) (95% CI, 87–90)	Canada: 92% (Nasreen et al., 2021) (95% CI, 88–95) France: 86% (Charmet et al., 2021) (95% CI, 81–90)	United Kingdom: 74.5% (Lopez Bernal et al., 2021) (95% CI, 68.4–79.4) Canada: 91% (Nasreen et al., 2021) (95% CI, 62–98)	Multinational: 69.7% (Sadoff et al., 2022) (95% CI, 60.7–76.9)	Not reported
Beta (B.1.351)	Qatar:75% (Abu-Raddad et al., 2021) (95% CI, 70.5–78.9) Canada: 82% (Nasreen et al., 2021) (95% CI, 65–91) France: 49% (elderly) (Lefevre et al., 2021) (95% CI, 14–69)	Canada: 89% (Nasreen et al., 2021) (95% CI, 21–98) France: 77% (Charmet et al., 2021) (95% CI, 63–86)	Canada: 41% (Nasreen et al., 2021) (95% CI, 12–60) US: 21.9% (Madhi et al., 2021) (95% CI, −49.9 to 59.8)	South Africa: 52% (Sadoff et al., 2021) (95% CI, 30.3–67.4) Multinational: 51.9% (Sadoff et al., 2022) (95% CI, 19.1–72.2)	Not reported
Gamma (P.1)	Canada: 82% (Nasreen et al., 2021) (95% CI, 65–91)	Canada: 89% (Nasreen et al., 2021) (95% CI, 21–98) France: 77% (Charmet et al., 2021) (95% CI, 63–86)	Canada: 41% (Nasreen et al., 2021) (95% CI, 12–60)	Multinational: 36.4 (Sadoff et al., 2022) (95% CI, 13.9–53.2)	Brazil:50.7% (Palacios et al., 2020) (95% CI, 35.6–62.2) Brazil:47% (Ranzani et al., 2021) (95% CI, 39–54) Turkey: 84% (Tanriover et al., 2021) (95% CI, 65.0–92.0) Chile: 66.6% (Jara et al., 2021) (95% CI, 65.4–67.8)
Delta (B.1.617.2 and AY lineages)	United Kingdom: 88% (Lopez Bernal et al., 2021) (95% CI, 85.3–90.1) Canada: 92% (Nasreen et al., 2021) (95% CI, 90–94) Israel: 88% (Reis et al., 2021) (95% CI, 85–90)	Canada: 95% (Nasreen et al., 2021) (95% CI, 1–97) Qatar:51.9% (Tang et al., 2021b) (95% CI, 47.0–56.4) US: 86.7% (Bruxvoort et al., 2021) (95% CI, 84.3–88.7)	United Kingdom: 67.0% (Lopez Bernal et al., 2021) (95% CI, 61.3–71.8) Canada: 87% (Nasreen et al., 2021) (95% CI, 69–95)	Multinational: 6.0 (Sadoff et al., 2022) (95% CI, −178.3 to 59.2)	Not reported
Omicron	South Africa: 70% (Collie et al., 2022) (95% CI, 62–76)	US: 30.4% (Tseng et al., 2022) (95% CI, 5–49)	Not reported	South Africa[a]: 63% (Gray et al., 2021) (95% CI, 31–81)	Not reported
Lambda (C.37)	Brazil: 66.5% (Zuckerman et al., 2021) (95% CI, 42.8–103.4)	Not reported	Not reported	Multinational: 10.0 (Sadoff et al., 2022) (95% CI, −39.5 to 42.0)	Not reported
Mu (B.1621; B.1.621.1)	Not reported	US: 90.4% (Bruxvoort et al., 2021) (95% CI, 73.9–96.5)	Not reported	Multinational: 35.8 (Sadoff et al., 2022) (95% CI, 1.5–58.6)	Not reported

[a]*Vaccine efficacy of two doses of Ad26.COV2.S (Janssen), 2 weeks after vaccination.*

protection against major variants of SARS-CoV-2 is summarized in **Tables 2–8**. One of the major concerns is that all vaccines express the ancestral SARS-CoV-2 spike protein, whereas currently circulating variants such as Delta variant possess several mutations to evade the response, resulting in a 4-fold lower neutralizing antibody response to Delta-variant infections (Kent and Juno, 2021).

Vaccination Efficacy Against Variants of Concern

VOC include Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529) variants. They have been associated with higher transmissibility and reduced vaccination efficacy. Despite being infected with B.1.1.7 (Alpha) and B.1.351

TABLE 3 | BNT162-b2 (Pfizer-BioNTech) vaccine efficacy (without booster) against different clinical severity in variant strain infection 2 weeks after administration.

Doses	Severity of illness	Alpha	Beta	Gamma	Delta	Omicron
1	Asymptomatic	38% (95% CI, 29–45) (Sheikh et al., 2021)	17% (95% CI, 10–23) (Abu-Raddad et al., 2021)	Not reported	30% (95% CI, 17–41) (Sheikh et al., 2021)	Not reported
	Symptomatic	27% (95% CI, 13–39) (Sheikh et al., 2021)	43% (95% CI, 22–59) (Chung et al., 2021)	43% (95% CI, 22–59) (Chung et al., 2021)	33% (95% CI, 15–47) (Sheikh et al., 2021)	Not reported
	Hospitalization	83% (95% CI, 62–93) (England, 2021; Stowe et al., 2021)	0% (95% CI, 0–19) (Abu-Raddad et al., 2021)	56% (95% CI, −9 to 82) (Chung et al., 2021)	94% (95% CI, 46–99) (England, 2021; Stowe et al., 2021)	Not reported
2	Asymptomatic	92% (95% CI, 90–93) (Sheikh et al., 2021)	75% (95% CI, 71–79) (Abu-Raddad et al., 2021)	Not reported	79% (95% CI, 75–82)	Not reported
	Symptomatic	92% (95% CI, 88–94) (Sheikh et al., 2021)	88% (95% CI, 61–96) (Chung et al., 2021)	88% (95% CI, 61–96) (Chung et al., 2021)	83% (95% CI, 78–87)	Not reported
	Hospitalization	95% (95% CI, 78–99) (England, 2021; Stowe et al., 2021)	100% (95% CI, 74–100) (Abu-Raddad et al., 2021)	100% (Chung et al., 2021) (95% CI not reported)	96% (95% CI, 86–99) (England, 2021; Stowe et al., 2021)	Not reported

TABLE 4 | mRNA-1273 (Moderna) vaccine efficacy (without booster) against different clinical severity in variant strain infection 2 weeks after administration.

Doses	Severity of illness	Alpha	Beta	Gamma	Delta	Omicron
1	Asymptomatic	Not reported	Not reported	Not reported	Not reported	
	Symptomatic	61% (95% CI, 56–66) (Chung et al., 2021)	56% (Chung et al., 2021) (95% CI, −9 to 82)		77.0% (Bruxvoort et al., 2021) (95% CI, 60.7–86.5)	Not reported
	Hospitalization	59% (95% CI, 39–73) (Chung et al., 2021)				Not reported
2	Asymptomatic	98.4% (Bruxvoort et al., 2021) (95% CI, 96.9–99.1%)	Not reported	Not reported	86.7% (Bruxvoort et al., 2021) (95% CI, 84.3–88.7)	Not reported
	Symptomatic	90% (95% CI, 85–94) (Chung et al., 2021)	88% (Chung et al., 2021) (95% CI, 61–96)		94.1% (Bruxvoort et al., 2021) (95% CI, 90.5–96.3)	30.4% (Tseng et al., 2022) (95% CI, 5–49)
	Hospitalization	94% (95% CI, 59–99) (Chung et al., 2021)	100% (Chung et al., 2021) (95% CI not reported)		97.5% (Bruxvoort et al., 2021) (95% CI, 92.7–99.2)	100%[a] (Tseng et al., 2022)

[a]*No hospitalization case after receiving two doses of vaccine.*

TABLE 5 | ChAdOx1 nCoV-19 (AZD 1222) vaccine efficacy (without booster) against different clinical severity in variant strain infection 2 weeks after administration.

Doses	Severity of illness	Alpha	Beta	Gamma	Delta	Omicron
1	Asymptomatic	37% (95% CI, 32–42) (Sheikh et al., 2021)	10.4% (95% CI, −76.8 to 54.8) (Madhi et al., 2021)	33% (95% CI, 32–34) (Cerqueira-Silva et al., 2021)	18% (95% CI, 9–25) (Sheikh et al., 2021)	Not reported
	Symptomatic	39% (95% CI, 32–45) (Sheikh et al., 2021)	21.9% (95% CI, −49.9 to 59.8) (Madhi et al., 2021)	33% (95% CI, 26–40) (Hitchings et al., 2021)	33% (95% CI, 23–41) (Sheikh et al., 2021)	Not reported
	Hospitalization	76% (95% CI, 61–85) (England, 2021; Stowe et al., 2021)	61% (95% CI,−64 to 91) (Nasreen et al., 2021)	52% (95% CI, 50–53) (Cerqueira-Silva et al., 2021)	71% (95% CI, 51–83) (England, 2021; Stowe et al., 2021)	Not reported
2	Asymptomatic	73% (95% CI, 66–78) (Sheikh et al., 2021)	Not reported	70% (95% CI, 69–71) (Cerqueira-Silva et al., 2021)	60% (95% CI, 53–66) (Sheikh et al., 2021)	Not reported
	Symptomatic	81% (95% CI, 72–87) (Sheikh et al., 2021)	10% (95% CI, −77 to 50) (Madhi et al., 2021)	78% (95% CI, 69–84) (Hitchings et al., 2021)	61% (95% CI, 51–70) (Sheikh et al., 2021)	Not reported
	Hospitalization	86% (95% CI, 53–96) (England, 2021; Stowe et al., 2021)	Not reported	87% (95% CI, 85–88) (Cerqueira-Silva et al., 2021)	92% (95% CI, 75–97) (England, 2021; Stowe et al., 2021)	Not reported

(Beta) variants after mRNA-based vaccination, the protection against severe, critical, or fatal COVID-19 cases remains 96% in Qatar (Chemaitelly et al., 2021). The vaccine efficacy against symptomatic infection quickly drops from over 90% before the spread of Delta variant to 42–80% after the spread of the variant (Tang et al., 2021a; Pouwels et al., 2021; Sheikh et al., 2021). This

TABLE 6 | Ad26.COV2.S (Janssen) vaccine efficacy (without booster) against different clinical severity in variant strain infection 2 weeks after administration.

Doses	Severity of illness	Alpha	Beta	Gamma	Delta	Omicron	Lineage B.1
1	Mild	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
	Moderate to severe	70.2 (95% CI, 35.3–87.6) (Sadoff et al., 2022)	64% (95% CI, 41–79) (Alter et al., 2021) 51.9% (95% CI, 19.1–72.2) (Sadoff et al., 2022)	36.5% (95% CI, 14.1–53.3) (Sadoff et al., 2022)	–5.7% (95% CI, –177.7 to 59.2) (Sadoff et al., 2022)	Not reported	72% (95% CI, 58–82) (Zhukova et al., 2020)
	Severe to critical		64% (95% CI, 46–95) (Alter et al., 2021) 51.9% (95% CI, 19.1–72.2) (Sadoff et al., 2022)		71% (95% CI, 56–81) (CDC, 2021b)	Not reported	86% (95% CI, –9 to 100) (Zhukova et al., 2020)

TABLE 7 | Sputnik V COVID-19 Vaccine (Gam-COVID-Vac) vaccine efficacy (without booster) against different clinical severity in variant strain infection 2 weeks after administration.

Doses	Severity of illness	Alpha	Beta	Gamma	Delta	Omicron
1	Asymptomatic	Not reported	Not reported	Not reported	Not reported	Not reported
	Symptomatic	Not reported	Not reported	Not reported	Not reported	Not reported
	Hospitalization	Not reported	Not reported	Not reported	35% (95% CI, –21 to 65) (Barchuk et al., 2021)	Not reported
2	Asymptomatic	Not reported	Not reported	Not reported	Not reported	Not reported
	Symptomatic	Not reported	Not reported	Not reported	Not reported	Not reported
	Hospitalization	Not reported	Not reported	Not reported	81% (95% CI, 68–88) (Barchuk et al., 2021)	Not reported

TABLE 8 | Coronavac (Sinovac) COVID-19 vaccine efficacy (without booster) against different clinical severity in variant strain infection 2 weeks after administration.

Doses	Severity of illness	Alpha	Beta	Gamma	Delta	Omicron
1	Asymptomatic	Not reported	Not reported	16% (95% CI, 15–17) (Cerqueira-Silva et al., 2021)	Not reported	Not reported
	Symptomatic	Not reported	Not reported	Not reported	14% (95% CI, –60 to 55) (Li et al., 2021)	Not reported
	Hospitalization	Not reported	Not reported	27% (95% CI, 25–28) (Cerqueira-Silva et al., 2021)	Not reported	Not reported
2	Asymptomatic	Not reported	Not reported	54% (95% CI, 53–55) (Cerqueira-Silva et al., 2021)	59% (95% CI, 16–82) (Li et al., 2021)	Not reported
	Symptomatic	Not reported	Not reported	Not reported	Not reported	Not reported
	Hospitalization	Not reported	Not reported	73% (95% CI, 72–74) (Cerqueira-Silva et al., 2021)	100% (Kang et al., 2021) (95% CI not reported)	Not reported

efficacy also dwindles as time elapses (Barouch et al., 2021; Ciabattini et al., 2021; Naaber et al., 2021; Pegu et al., 2021).

However, recent studies have shown that the mRNA-based booster vaccine still induces a robust immune response to variants, though weaker when compared with its prototype. The mRNA-based booster vaccination is safe and well tolerated (Ebinger et al., 2021). It boosts antibody production to neutralize variant strains especially wild-type D614G ($p < 0.0001$). The neutralization titers against B.1.351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta) are either low or undetectable 1 month after vaccination (Ebinger et al., 2021). The vaccine-mediated protection against variants in the respiratory tract is durable but delayed (Gagne et al., 2021). It is dependent on anamnestic antibody responses which can be maximized by a booster dose (Gagne et al., 2021).

Upon receiving BNT162b2 (Pfizer-BioNTech) booster vaccination, the infection and severe illness rates are lower, compared with those without booster vaccination in Israel (Bar-On et al., 2021). A third-dose booster vaccine in Israel

showed a significant reduction of confirmed infection and severe illness by a factor of 11.3 and 19.9, respectively (Bar-On et al., 2021). This finding is consistent with another serological study which showed that the occurrence of breakthrough infection with SARS-CoV-2 correlated with neutralizing antibody titers during the peri-infection period (Bergwerk et al., 2021). Therefore, an elevated titer is protective against breakthrough infections. This is particularly important in ambulatory and inpatient settings in less developed countries where the resources are scarce and the hospital wards are usually crowded to favor transmission. A similar booster recommendation is recommended in recipients of CoronaVac since over one-fifth of recipients become seronegative 2 months after the second dose of vaccination (Yigit et al., 2021b). Vaccination protects patients in ambulatory and inpatient care settings (Thompson et al., 2021). A full-dose mRNA-based vaccination (even without booster) is associated with 90% (95% CI, 86–93) effectiveness against intensive care unit (ICU) admission and 91% (95% CI, 89–93) effectiveness against emergency care visits. The effectiveness of Ad26.COV2.S is 68% (95% CI, 50–79) against hospitalization and 73% (95% CI, 59–82) against emergency care visits.

Various studies show a close association between infection rate and serological titer of circulating antibody levels after vaccination (Bergwerk et al., 2021; Khoury et al., 2021). The vaccination regimen of ChAdOx1 nCoV-19 also recommends a booster regime since it induces multifunctional antibody responses, including antibody-dependent neutrophil/monocyte phagocytosis, complement activation, and natural killer activation (Barrett et al., 2021).

Some special populations are at high risks of breakthrough infections. The incidence risk ratio in the immunocompromised patient is 1.66 (95% CI, 1.17–2.35) even after full-dose mRNA-based vaccination. An increased incidence is observed over time, showing the decreasing protective efficacy as time elapsed. However, among those with COVID-19 infection, vaccination significantly reduces the risk of death (hazard ratio 0.20, 95% CI, 0.08–0.49) (Liu et al., 2021a).

Vaccination Efficacy Against Variant of Interest

VOI include Lambda (C.37) and Mu (B.1.621) variants. A study using a micro-neutralization assay following mRNA vaccine demonstrated a 1.6-fold reduction of neutralizing titers compared with the wild-type virus, increasing the likelihood of infection and disease transmission after vaccination (Zuckerman et al., 2021). The Lambda variant harbors two key mutations in the receptor-binding domain (RBD), L452Q and F490S, changing the antigenicity and infectivity. Cell line studies show that the convalescent and vaccine-based sera recorded 1.3- to 2.5-fold lower neutralizing antibody titers (Wang et al., 2021). The reason of partial escape from neutralizing antibodies in vaccinated individuals behind is closely related to the increased affinity between RBD and angiotensin-converting enzyme 2 (ACE2) binding, leading to increased processing of spike protein to yield a higher fusion activity and syncytium formation in these variants (Moghaddar et al., 2021). The antibody titer drop after 6 months against Lambda variant is 3-fold, leading to breakthrough infections (Liu et al., 2021b). The rapidly dropping antibody titers against Lambda and Mu infections can be countered by a third-dose booster to cope with the surge of variants transmission.

The Mu variant demonstrates a remarkable resistance to antibodies by convalescent plasma and vaccine-induced protection (Uriu et al., 2021). Pseudovirus model serological assay was performed on Mu variant infection. It was 9.1 times as resistant as the parenteral virus in response to mRNA-based vaccination (BioNTech), 2.0 times as resistant to neutralization by convalescent serum, and 1.5 times as resistant to neutralization by vaccine serum as the Beta variant. Similar resistance has been reported in inactivated vaccine-elicited antibodies (Xie et al., 2021).

RISKS OF BOOSTER VACCINATION

A booster vaccination is not without risks. Myocarditis has been reported worldwide, particularly in young male recipients after receiving the second dosage of BNT162b2 (Pfizer-Biotech) vaccine (Mevorach et al., 2021). The risk ratio 30 days after the second dose in fully vaccinated recipients (without booster) is 2.35 (95% CI, 1.10–5.02), while the risk ratio rises to 8.96 (95% CI, 4.50–17.83) in male subjects between 16 and 19 years old. It is uncertain whether the third dose will trigger further myocardial damage. However, severe complications such as myocarditis or allergy from the first two doses of BNT162b2 are relatively rare (Barda et al., 2021). Guillain–Barre syndrome has also been reported in adenovirus-vectored COVID-19 vaccines (WHO, 2021b). For the majority of fully vaccinated recipients who have no significant associated complications, a booster vaccination may be safer.

The booster may greatly safeguard the effect offered by the first two dosages. When serum antibody titer drops below the protective threshold, a "start over" vaccination may still be necessary, which may also trigger complications. Studies also reveal that antibody levels in the aged population are relatively lower after full vaccination, though no severe complications are observed (Wei et al., 2021). Therefore, a booster vaccination may be necessary for this population.

Overall, vaccination is very safe, though common transient side effects happen, and a booster is a good option that significantly consolidates the protective effect to fight against this long-term pandemic. It is recommended that the earliest time to receive a booster is 6 months after the initial vaccination (Chemaitelly et al., 2021; Levin et al., 2021). A future study evaluating long-term serum antibody titer and booster clinical trials are needed for guidance on booster vaccination.

WHETHER TO ADVOCATE BOOSTER VACCINATION

Though booster vaccination is associated with both benefits and risks, overall it is safe and effective. The BNT162b2 third-dose booster vaccination in Israel showed that the side effects were

mild and self-limiting, including immunocompromised patients and senior citizens (Shapiro Ben David et al., 2021). The most common side effects were fatigue (19.6%), myalgia (9.2%), and fever (8.1%) in immunocompromised patients and fatigue (21.3%), myalgia (9.9%), and fever (9.2%) in senior citizens. Over two-thirds of the recipients developed a better or similar response compared to the second dose. This is consistent with the study in the United Kingdom which showed that although there were numerous local or systemic side effects in the short term, the vaccine efficacy exceeded 60% within 2–3 weeks (Menni et al., 2021).

One concern of advocating booster vaccination is related to equity (The Lancet Infectious Diseases, 2021). The income disparity between developed countries and developing countries results in a competition for gaining access to vaccinations. Up to August 9, 2021, over 80% of the vaccines were distributed to high-income countries, while only 20% were in low-income countries with only 3% of the African population fully vaccinated (without a booster) (Kherabi et al., 2021; The Lancet Infectious Diseases, 2021). This results in increasing reporting of variants in different countries, in particular from low-income countries (see **Supplementary Appendix** with reports of different variants reported internationally). Vaccines thus should be made available to other countries before offering domestic booster vaccinations to reduce variants transmission and new variants from evolving (Dyer, 2021; Schaefer et al., 2021).

The vaccination schedule should be individualized for different populations, such as healthy individuals without previous SARS-CoV-2 infection and COVID-19 survivors with prior SARS-CoV-2 infection. The underlying reason is related to the waning trajectory of antibody titers in different populations. After a two-dose schedule of mRNA-based vaccination, healthy subjects developed similar antibody levels to COVID-19 survivors who recover from the infection for 1 year and receive single-dose mRNA-based vaccination (Gluck et al., 2021). None of the study participants experienced reinfection. The half-life of anti-SARS-CoV-2 IgG antibody ranges between 85 and 158 days (Lumley et al., 2021; Dan et al., 2021; den Hartog et al., 2021), while some studies also show the immunity may last over 300 days (Gluck et al., 2021; Lee et al., 2021). There is uncertainty about the booster schedule for different populations, and this may create a burden on healthcare service and spark controversy on vaccine equity between developing countries and developed countries (The Lancet Infectious Diseases, 2021). Overall, vaccine boosters quickly increase antibody levels since the large number of memory B cells and plasma cells derived from previous immunity drives rapid antibody productions after booster vaccination (Ebinger et al., 2021; Gobbi et al., 2021; Liao et al., 2021; Turner et al., 2021). Booster vaccination thus is protective against SARS-CoV-2 infection, but the booster schedule requires further studies.

Though vaccine recipients may have more persistent nasopharynx-homing SARS-CoV-2-specific T cells compared to infection-naïve subjects (Neidleman et al., 2021), a further booster vaccination still induces a stronger immune response while giving manageable side effects (Ebinger et al., 2021).

CURRENT RECOMMENDATION ON BOOSTER VACCINATION

The US Center for disease Control and Prevention and French National Authority of Health have recommended prioritization of booster vaccination for high-risk groups, subjects aged over 65 years, subjects between 50 and 64 years with underlying medical conditions, healthcare workers, and residents of long-term care facilities (Burki, 2021; Kherabi et al., 2021). The United Kingdom is currently considering a third-shot booster vaccination for all adults (Burki, 2021).

Healthcare workers are at high risk of infection. The British study of BNT162b2 vaccine showed vaccine effectiveness of 70% (95% CI 55–85) 21 days after the first dose and 85% (95% CI 74–96) 7 days after two doses in healthcare staff when the dominant variant was Alpha (B.1.1.7) (Hall et al., 2021).

The timing to receive booster vaccination is subject to debate. A study focusing on the immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) recommends a 3-month interval to receive a booster since a high protective efficacy is maintained until 3 months (Voysey et al., 2021). Efficacy was higher with a 12-week prime–boost interval (vaccine efficacy 81.3%, 95% CI 60.3–91.2), compared with a 6-week interval (vaccine efficacy 55.1%, 95% CI 33.0–69.9). Meanwhile, BNT162b2 (Pfizer) vaccine recommends a 6-month interval to receive a booster (CDC, 2021a).

Whether subjects with previous SARS-CoV-2 should receive a three-dose vaccination schedule and when they should receive the booster vaccination as antibody titers drop are still under debate. The antibody responses to the first vaccine dose in individuals with pre-existing immunity are equal to or exceed the titers found in naïve individuals after the second dose of BNT162b2 (Pfizer-BioNTech). The antibody titers against VOC, Delta variant (1.617.2), in COVID-19 recoverers (at least 11 months after complete resolution of the previous infection) receiving one-dose ChAdOx1 nCoV-19 vaccine are similar to or higher than the counterparts receiving two-dose BNT162b2 (Pfizer-BioNTech) (Havervall et al., 2021). BBV152 (Bharat Biotech) vaccine of India also induces a similar response in COVID-19 recoverers, suggesting one-dose vaccinations can give similar antibody levels as two-dose vaccinations (Kumar et al., 2021). Their adverse reaction to vaccination is higher than those of healthy adults (Krammer et al., 2021). COVID-19 recoverers receiving a second-dose vaccination show no additional benefits since they have reached the peak of their immunity after the first dose (Lozano-Ojalvo et al., 2021). These studies suggest that one-dose vaccinations in COVID-19 recoverers is sufficient to confer protection non-inferior to healthy individuals with two-dose vaccinations (Cavalcanti et al., 2021; Vicenti et al., 2021), and they should be put lower on the vaccination priority list (Saadat et al., 2021). Despite the similar efficacy, the post-vaccine symptoms are more prominent for those with prior infection after the first dose (Ebinger et al., 2021).

TABLE 9 | Absolute contraindications of vaccinations.

Absolute contraindications	Type of vaccine	Recommended actions
Severe allergic reaction, e.g., anaphylaxis	All (USCDC, 2021a)	1. Do not vaccinate 2. Referral to allergy immunologist 3. Consider other vaccine alternatives
Immediate allergic reaction	All (USCDC, 2021a)	1. Risk assessment 2. Referral to allergy immunologist 3. Prolong observation period after vaccination (e.g., 30 min)

TABLE 10 | Common relative contraindications of vaccinations reported in literatures and guidelines.

Relative contraindications	Type of vaccine	Recommended actions
Acute PCR-confirmed COVID-19 infection	All	Delay vaccination schedule until recovered from acute illness and the criteria for ending isolation have been met (WHO, 2021c)
With fever more than 38.5°C	All	Postpone vaccination until fever subsided (WHO, 2021c)
High thrombosis and thrombocytopenia risk	AstraZeneca/COVISHIELD and Janssen	Cautious for patients with history of heparin-induced thrombocytopenia, antiphospholipid syndrome, or major venous or arterial thrombosis with thrombocytopenia after viral vector COVID-19 vaccine (EMA, 2021a; USCDC, 2021b)
Capillary leak syndrome (CLS)	AstraZeneca COVISHIELD	Patients with history of CLS should not receive AstraZeneca vaccine. Vaccination with alternative vaccine is recommended (NACI, 2021)
Myocarditis and pericarditis	Pfizer and Moderna	Defer the second dose schedule if patients developed myocarditis or pericarditis after the first dose. Choice of alternative vaccine or continue with mRNA vaccine should be discussed with medical workers (cardiologist if possible) (WHO, 2021d; NACI, 2021)
Pregnancy, planning for pregnancy or breastfeeding	Viral-vector vaccines	USCDC recommends safe administration of viral-vector vaccine in all trimesters of pregnancy and breastfeeding. (as of August 11, 2021) (USCDC, 2021c) Canadian NACI recommends viral-vector vaccines should be avoided in pregnancy due to elevated risk of VITT (NACI, 2021). Vaccination is safe during breastfeeding (NACI, 2021)

NACI, National Advisory Committee on Immunization; USCDC, United States Center for disease Control and Prevention; VITT, vaccine-induced immune thrombotic thrombocytopenia.

CONTRAINDICATIONS FOR VACCINATION

The absolute and relative contraindications of vaccination are documented in **Tables 9** and **10**. Absolute contraindications include mainly severe allergic reactions to its constituents shown in **Table 9** (USCDC, 2021a). Relative contraindications and recommended actions are listed in **Table 10**. Subjects with relative contraindications are recommended to discuss individual risk profiles to plan their vaccination decision. Counseling should include risk factors, relative contraindications, benefits and risks of vaccinations, alternative vaccines, and risks of without vaccinations. **Table 11** documents the ingredients of 24 COVID-19 vaccines with emergency use authorizations by national regulatory authorities (as of October 26, 2021).

RECOMMENDATIONS FOR BOOSTER VACCINATION

Heterologous vaccination (Com-COV study) is safe and induces robust immunity without serious adverse events (Borobia et al., 2021; Liu et al., 2021c; Moghnieh et al., 2021). This has been performed in subjects receiving "BNT162b2 (Pfizer/BioNTech) plus ChAdOx1 nCoV-19 (AZD1222)" and "BNT162b2 (Pfizer/BioNTech) plus BBIBP-Cor-V (Sinopharm)." The interim analysis documents that heterologous ChAdOx/BNT immunization regimen with 10–12 weeks vaccination interval is well tolerated and slightly more immunogenic compared to homologous BNT/BNT vaccination with 3-week intervals. A recent randomized controlled trial showed that heterologous vaccination with other vaccines after the initial two doses (either two-dose ChAdOx-1 or BioNTech) yields a higher SARS-CoV-2 anti-spike IgG titer and stronger cellular response (Munro et al., 2021). This may be a viable choice for countries without a stable source of vaccines or in immunocompromised patients who could not produce sufficient protective antibodies (Borobia et al., 2021; Liu et al., 2021c; Hillus et al., 2021; Moghnieh et al., 2021). Initial SARS-CoV-2 vaccination response can predict booster response; thus, reassessment of antibody response may be a viable choice whether to receive homologous or heterologous vaccination (Perkmann et al., 2021).

Timing of vaccinations is vital in certain patients after specific treatments. Suboptimal immunological response has been found in patients receiving BNT162b2 (Pfizer-BioNTech) after rituximab administration (Kant and Geetha, 2021). Delaying vaccination for 6 months after rituximab administration or B-cell reconstitution has been suggested

TABLE 11 | Components of 24 COVID-19 vaccines with emergency use authorizations by national regulatory authorities (as at October 26, 2021).

Type of vaccine	Active ingredient	Inactive ingredients
Pfizer (mRNA) (USFDA, 2021a), the United States	Nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2	1. 2-Polyethylene glycol (PEG)-2000-N, N-ditetradecyclacetamide 2. Cholesterol 3. 1,2-Distearoyl-sn-glycero-3-phosphocholine 4. (4-Hydroxybutyl) azanediyl)bis (hexane-6,1-diyl)bis (2-hexyldecanoate) 5. Sodium chloride 6. Monobasic potassium phosphate 7. Potassium chloride 8. Dibasic sodium phosphate dihydrate 9. Sucrose
Moderna (mRNA) (USFDA, 2021b), the United States	Nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2	1. PEG2000-DMG: 1,2-dimyristoyl-rac-glycerol,methoxypolyethylene glycol 2. 1,2-Distearoyl-sn-glycero-3-phosphocholine 3. Cholesterol 4. SM102: heptadecane-9-yl 8- ((2-hydroxyethyl) (6-oxo-6 (undecyloxyl)hexyl)amino) octanoate 5. Tromethamine 6. Tromethamine hydrochloride 7. Acetic acid 8. Sodium acetate 9. Sucrose
Janssen (viral vector) (USFDA, 2021c), the United States	Recombinant, replication incompetent Ad26 vector encoding a stabilized variant of the SARS-CoV-2 spike (S) protein	1. Polysorbate-80 2. 2-Hydroxypropyl-beta-cyclodextrin 3. Citric acid monohydrate 4. Trisodium citrate dihydrate 5. Sodium chloride 6. Ethanol
Sinovac/Coronavac (Vero cell) (Ltd SLSC, 2021), China	Inactivated SARS-CoV-2 virus (CZ02 strain)	1. Aluminum hydroxide 2. Disodium hydrogen dodecahydrate 3. Sodium dihydrogen phosphate monohydrate 4. Sodium chloride
Oxford-AstraZeneca Vaxzevria (EMA, 2021b), the United Kingdom	Chimpanzee adenovirus encoding the SARS-CoV-2 spike (S) protein ChAdOx1-S	1. L-Histidine 2. L-Histidine hydrochloride monohydrate 3. Magnesium chloride hexahydrate 4. Polysorbate 80 (E 433) 5. Sucrose 6. Disodium edetate (dihydrate)
Serum Institute of India Covishield (Oxford-AstraZeneca formulation) (Jeewandara et al., 2021); Ramasamy et al., 2021), India	Recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 spike (S) protein in genetically modified human embryonic kidney 293 cells	1. L-Histidine 2. L-Histidine hydrochloride monohydrate 3. Magnesium chloride hexahydrate 4. Polysorbate 80 (E 433) 5. Sucrose 6. Ethanol 7. Sodium chloride 8. Disodium edetate dihydrate (EDTA)
Sinopharm-BBIBP (inactivated virus in Vero cells) (Wang et al., 2020a), China	Inactivated SARS-CoV-2 virus (HB02 strain) in Vero cells culture	1. Aluminum hydroxide adjuvant 2. Beta-propiolactone 3. Disodium hydrogen phosphate 4. Sodium dihydrogen phosphate 5. Sodium chloride
Sputnik V (viral vector) (Logunov et al., 2021), Russia	Modified replication-deficient Ad26 and Ad5 encoding the SARS-CoV-2 spike (S) protein	1. Tris-(hydroxymethyl)-aminomethane 2. Sodium chloride 3. Sucrose 4. Magnesium chloride hexahydrate 5. Disodium EDTA dihydrate 6. Polysorbate 80 7. Ethanol

(Continued on following page)

TABLE 11 | (*Continued*) Components of 24 COVID-19 vaccines with emergency use authorizations by national regulatory authorities (as at October 26, 2021).

Type of vaccine	Active ingredient	Inactive ingredients
Abdala (Reuters, 2021; RPCEC, 2021; Vie Pce, 2021), Cuba	Protein subunit vaccine containing COVID-19-derived proteins	No clinical results and information on ingredients found on electronic databases (PubMed, Google Scholar, Medline, Scopus, embase)
Chinese Academy of Medical Sciences Covidful (ClinicalTrials.Gov, 2021a; ClinicalTrials.Gov, 2021b), China	Inactivated virus vaccine	No clinical results and information on ingredients found on electronic databases (PubMed, Google Scholar, Medline, Scopus, embase)
Cansino Convidecia (Wang et al., 2020b; Wu et al., 2021), China	Recombinant replication-deficient adenovirustype 5-vectored vaccine expressing full-length spike gene based on Wuhan-Hu-1 (Genebank accession number YP_009,724,390)	Detailed inactive components were not listed
Covaxin (BIOTECH, 2021; Sapkal et al., 2021), India	Whole-virion inactivated SARS-CoV-2 antigen (strain: NIV-2020770)	1. Aluminum hydroxide 2. Imidazoquinolinone 3. 2-Phenoxyethonol 4. Phosphate buffer saline
COVIran Barakat (Asghar Abdoli et al., 2021; Mallapaty, 2021), Iran	Inactivated SARS-CoV-2 virus with Vero cell culture	1. Aluminum hydroxide 2. Modified Egg's medium 3. Fetal bovine serum
CoviVac (ClinicalTrials.Gov, 2021c; Kozlovskaya et al., 2021; EMA, 2021b), Russia	Inactivated SARS-CoV-2 virus (strain:AYDAR-1) with Vero cell culture	1. Beta-propiolactone 2. Aluminum hydroxide 3. Disodium phosphate dihydrate 4. Sodium dihydrogen phosphate dihydrate 5. Sodium chloride
EpiVacCorona (Ryzhikov et al., 2021; Рыжиков ЕАР et al., 2021), Russia	Chemically synthesized peptides (short fragments of viral spike protein) conjugating to a carrier protein containing nucleocapsid proteins and maltose-binding proteins	1. L-Histidine 2. Aluminum hydroxide
FAKHRAVAC (IRCT, 2021a; IRCT, 2021b), Iran	Inactivated SARS-CoV-2 virus-based with cell culture	Detailed ingredients not published
Medigen (ClinicalTrials.Gov, 2021d; ClinicalTrials.Gov, 2021e; Hsieh et al., 2021), Taiwan	Recombinant S-2P spike protein adjuvanted with CpG 1,018	1. CpG 1,018 2. Aluminum hydroxide 3. Phosphate buffer solution
Minhai (ClinicalTrials.Gov, 2021f; ClinicalTrials.Gov, 2021g; ClinicalTrials.Gov, 2021h), China	Inactivated SARS-CoV-2 virus-based with Vero cell culture	Detailed ingredients not published
QazCovid-in (ClinicalTrials.Gov, 2021i; ClinicalTrials.Gov, 2021j), Kazakhstan	Inactivated SARS-CoV-2 virus-based with cell culture	Detailed ingredients not published
Sinopharm-WIBP (Xia et al., 2020; Al Kaabi et al., 2021; Xia et al., 2021), China	Inactivated SARS-CoV-2 virus (strain WIV-04) in Vero cell culture	1. Aluminum hydroxide 2. Disodium hydrogen phosphate 3. Sodium dihydrogen phosphate 4. Sodium chloride
Soberana (Malik et al., 2021; Mega, 2021; Valdes-Balbin et al., 2021), Cuba	Receptor binding domain of SARS-CoV-2 spike protein conjugated chemically to tetanus toxoid	Detailed ingredients not published
Sputnik light (ClinicalTrials.Gov, 2021k; ClinicalTrials.Gov, 2021l), Russia	Recombinant replication-deficient Ad26 encoding the SARS-CoV-2 spike (S) protein	1. Tris-(hydroxymethyl)-aminomethane 2. Sodium chloride 3. Sucrose 4. Magnesium chloride hexahydrate 5. Disodium EDTA dihydrate 6. Polysorbate 80 7. Ethanol
Zifivax (Yang et al., 2021; Zhao et al., 2021), China	Recombinant tandem repeat dimeric receptor binding domain-based protein subunit vaccine	1. Aluminum hydroxide Detailed ingredients not published
ZyCoV-D (Dey et al., 2021; Momin et al., 2021) (DNA plasmid vactor), India	DNA plasmid vector carrying the gene encoding the spike protein (S) of the SARS-CoV-2 virus	Detailed ingredients not published

The first seven vaccines in the table have been approved for emergency or full use by at least one WHO-recognized stringent regulatory authority (Pfizer, Moderna, Janssen, Sinovac, Oxford-AstraZeneca, Serum Insitute of India Covishield, and Sinopharm-BBIBP). The remaining vaccine candidates are arranged in alphabetical order.

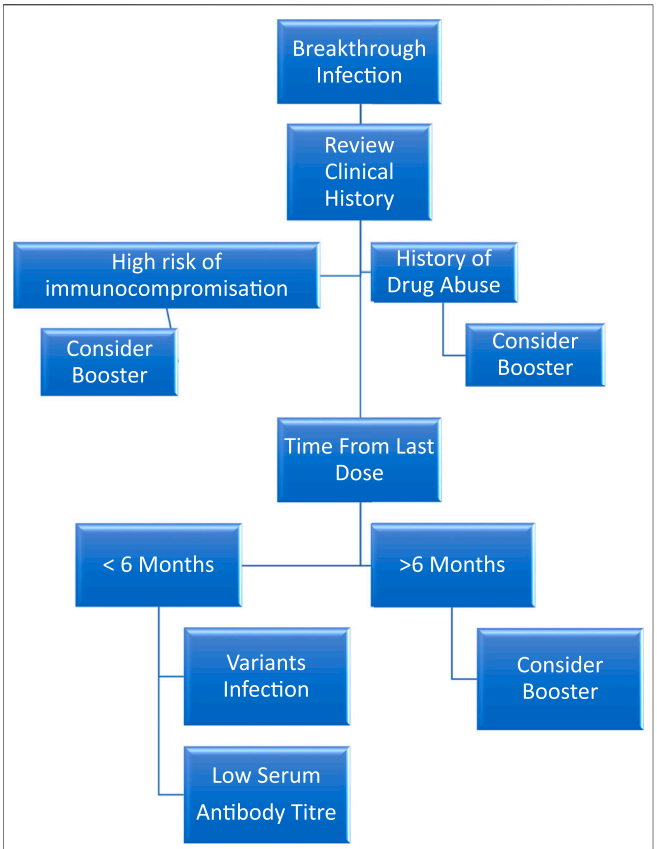

FIGURE 1 | Management algorithm for COVID-19 breakthrough infection. Common reasons include the following: **(A)** Abuse of drugs. **(B)** Baseline multiple comorbidities. **(C)** Changing strains. **(D)** Decreasing antibody level. **(E)** Elderly.

in previous studies (Kant et al., 2021). Vaccine booster schedule should be individualized according to the half-life of immunity decline. A British study shows that an extended interval before the second dose of ChAdOx1 nCoV-19 leads to increased antibody titers, while a third dose of ChAdOx1 nCoV-19 induces antibody that correlates with higher efficacy after second dose due to robust T-cell responses (Flaxman et al., 2021).

Patients receiving immunosuppressants or with chronic kidney impairment receiving renal replacement therapy also have suboptimal anti-SARS-CoV-2 antibodies after the second dose (Boyarsky et al., 2021a; Boyarsky et al., 2021b; Bensouna et al., 2021; Kamar et al., 2021; Peled et al., 2021; Werbel et al., 2021). A booster dose of mRNA-1273 vaccine induces serological response in 49% of renal recipients who are refractory to produce antibodies after two doses (Benotmane et al., 2021). This is similar in patients receiving solid organ transplants on immunosuppressants and with negative antibody titers before the third dose: 25% of them develop high-positive antibodies after a third dose, while over two-thirds of them remain negative (Werbel et al., 2021). A significant proportion of patients who fail to develop immunity after a third-dose booster is on triple immunosuppressants (Benotmane et al., 2021). The SENCOVAC study shows that an absence of antibody protection is associated with kidney transplant recipients due to their immunosuppression therapy (odds ratio 20.56, $p < 0.01$), while receiving BNT162b2 increases the chance of antibody response (odds ratio 6.03, $p = 0.02$) (Quiroga et al., 2021). These patients are advised to adopt persistent isolation measures and consider booster vaccines to optimize protection against COVID-19 infection (Quiroga et al., 2021). Use of rituximab is common in cancer or autoimmune disease treatments leading to failure of immunological response (Yahav et al., 2021). Heterologous vaccination leads to stronger induction of antibodies and CD4 T cells in immunocompromised patients: SARS-CoV-2-specific antibodies and T-cells response after second vaccination were induced 100% and 70.6% in transplant recipients (Baker et al., 2021; Schmidt et al., 2021).

A recent systematic review compared the relative likelihood of non-responders (Galmiche et al., 2021). The proportion of non-responders is higher among solid organ transplant recipients (range 18–100%), hematological malignancy (range 14–61%), cancers (2–36%), and dialysis usage (2–30%). Risk factors of failure of antibody induction include older age, use of corticosteroids, immunosuppressants, and anti-CD20 agents.

Currently, a new approach is consideration of immunosuppressant dosage adjustment or additional booster to maximize immunological response induction (Albach et al., 2021; Yan et al., 2021b; Connolly et al., 2021; Mackintosh et al., 2021; Yahav et al., 2021). With vaccination-refractory in immunocompromised subjects (solid organ transplant recipients) (Chavarot et al., 2021), recommendation of an additional dose is encouraged since a third vaccine dose increases the seropositivity prevalence from 40% to 68% (Husain and Argyropoulos, 2021). The seropositivity is protective against symptomatic infection, while it is unlikely to carry a significant risk of adverse events (Husain and Argyropoulos, 2021).

Cancer patients benefit from third-dose vaccinations since they run a high risk of failed induction of immune memory (Peeters et al., 2021). The CANVAX Cohort Study shows that immune responses to SARS-CoV-2 vaccines are moderately impaired in patients with cancer, while antibody testing may be effective to identify immune-inert patients to receive booster vaccinations (Naranbhai et al., 2021). A third-dose BNT162b2 (Pfizer/BioNTech) vaccination demonstrated a median 3-fold increase of neutralizing antibody response with mild adverse events (Shroff et al., 2021). This should be similarly considered in cancer patients with active anti-neoplastic treatment (Peeters et al., 2021). In view of the breakthrough infections with multiple lineages of variants, immunocompromised patients are at risk of severe diseases (Deng et al., 2021; D'Amelio et al., 2021). In terms of safety, immunocompromised patients are not at an increased risk of vaccine-related adverse events (Mackintosh et al., 2021).

RECOMMENDATION FOR BREAKTHROUGH INFECTION

Breakthrough infections have been reported worldwide. Breakthrough infections are mild in healthy adults (Abbasi, 2021). Thus, management of breakthrough infections should include a thorough clinical history review to determine the presence of risk factors and appropriate actions (**Figure 1**).

Common reasons related to this include: 1) infection of variant strains (Bosch et al., 2021); 2) low circulating antibody levels as time elapsed from the previous second dose (Chemaitelly et al., 2021; Levin et al., 2021); 3) insufficient induction of antibody due to multiple comorbidities or immunocompromised state (Albach et al., 2021; Arya et al., 2021); 4) history of substance abuse (Wang et al., 2022); and 5) old age (Butt et al., 2021; Glatman-Freedman et al., 2021).

Within 6 months after the last dose of mRNA-based vaccination, the antibody is still protective against COVID-19 disease (El Sahly et al., 2021; Thomas et al., 2021). Consideration of vaccine-resistant variant strain infection should be the top priority. Low serum antibody level leading to insufficient protective efficacy is the common reason for breakthrough infections. Booster vaccination after 6 months, regardless of antibody level, should be considered (Ebinger et al., 2021; Gobbi et al., 2021; Liao et al., 2021; Turner et al., 2021), though there is evidence suggesting breakthrough infections do not necessarily correlate with lack of vaccine-induced immunity (Duarte et al., 2021).

Patients with multiple comorbidities leading to the immunocompromised state should consider booster vaccination, with either homologous or heterologous vaccines (Baker et al., 2021; Schmidt et al., 2021). The multiple comorbidities include solid organ transplant patients on immunosuppressants (Werbel et al., 2021), autoimmune diseases with failed induction of antibody despite full-dose vaccination schedule (Yahav et al., 2021), chronic kidney disease with renal replacement therapy (Boyarsky et al., 2021a; Boyarsky et al., 2021b; Bensouna et al., 2021; Kamar et al., 2021; Peled et al., 2021; Werbel et al., 2021), poorly controlled hypertension, diabetes mellitus (Brosh-Nissimov et al., 2021), and cancers (Peeters et al., 2021).

CONCLUSION

This paper provides an updated evaluation of booster vaccination: its necessity, concerns, and benefits on variant strains. It gives a detailed description of the efficacy and safety of vaccination on variant strains. However, there are limited data on the effect of booster vaccination on Omicron strains at the time of writing, and Omicron-strain vaccination has been under development by vaccine manufacturers; thus, clinical trials of newly modified vaccines have not started. Booster vaccination brings benefits to the waning immunity and protective efficacy of COVID-19 vaccines. Booster vaccination induces immunological memory by elevating circulating anti-SARS-CoV-2 antibody level. Its associated risk is manageable, while risk–benefit analysis should be evaluated by medical health staff to manage comorbidities and rule out contraindications for vaccinations. Special populations should have an alternative vaccination schedule to boost their protective antibodies against multiple lineages of SARS-CoV-2 variants. These patients are not at a higher risk of vaccine-associated adverse events. More research is required on the schedule of booster vaccination and the type of booster vaccine for special populations.

CHECKLIST DECLARATION

1) Not in contravention of the European Respiratory Society (ERS) policy on tobacco
2) No funding on this project, and therefore no issue of copyright transfer
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AUTHOR CONTRIBUTIONS

Literature search, study designs, figures, data collections, data analysis, data interpretation, and manuscript writing were done by MZY, MY, and C-LL. MZY and MY contributed equally to this work. All authors have read and agreed to the published version of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fddsv.2022.858006/full#supplementary-material

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