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REVIEW

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Current evidence on efficacy of COVID-19 booster dose vaccination against the Omicron variant: A systematic review

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Abstract

Coronavirus disease 2019 (COVID-19) is an ongoing pandemic, which affected around 45 million confirmed cases of COVID-19, including more than 6 million deaths. However, on November 24, 2021, the World Health Organization announced a new severe acute respiratory syndrome coronavirus 2 variant designated as the B.1.1.529, a variant of concern (VOC), and the variant has been named as "Omicron." Available preliminary evidence suggests that, as compared with previous VOCs, it has an increased risk of infectivity. Studies have shown that protection from various vaccines effectiveness against hospitalization and death from severe COVID-19 disease is decreasing slowly after a two-dose schedule of COVID-19 vaccines. In response to experiencing a new COVID-19 variant and ongoing resurgence of cases, the importance of COVID-19 vaccine booster dose and durability of the effect of the third dose of vaccine against COVID-19 Omicron variant is controversial yet. To address this, we conducted a systematic literature survey on effectiveness of the third or booster dose of COVID-19 vaccine against the Omicron variant. We have performed a systematic search in PubMed (Medline), Google Scholar, and MedRXiv database, from inception to January 2022 using the MeSH terms and keywords "Corona Virus Disease-2019 OR COVID-19 AND Omicron AND COVID-19 Booster Vaccine." We have identified a total of 27 published studies. We have reviewed all the eligible available studies on the effectiveness of the COVID-19 vaccine booster shots against the Omicron variant. This review may be helpful in accelerating the COVID-19 booster dose vaccination.

KEYWORDS
booster dose, COVID-19, COVID-19 vaccine, Omicron, SARS CoV-2

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an ongoing pandemic, which has so far affected 45 million confirmed cases and more than 6 million deaths.[1] However, on November 24, 2021, the World Health Organization announced the fifth new COVID-19 covariant designated as the B.1.1.529, a variant of concern (VOC), and has been named as "Omicron."[2] Available preliminary evidence suggests that, as compared with previous VOCs, it has increased

Abbreviations: B.1.1.529, Omicron variant; BNT162b2, Pfizer BioNTech Vaccine; ChAdOx1 nCoV-19, Oxford–AstraZeneca Vaccine; COVID-19, coronavirus disease 2019; mRNA-1273, Moderna vaccine; RT-PCR, real-time reverse-transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

transmissibility and increased resistance to vaccine-induced immunity.[3] The Omicron variant was initially confirmed from a specimen collected on November 9, 2021, and has a large number of mutations (>50 mutations), some of which are highly concerning; it has a high capacity for immune escape and the T cells, which destroy infected cells, also appear to not recognize the Omicron variant, which helps in preventing the severity of the disease, hospitalization, and deaths.[3] It was first to come into attention by an outbreak in the South African younger adults <30 years age at the province of Gauteng, an area of high infection-acquired immunity following a third Delta wave with low vaccine coverage in this age group, where only 44% of the adult populations have received at least one dose of COVID-19 vaccine. Till now, the new variant has been identified in almost more than 57 countries.[3] The most common symptoms shown by Omicron-affected patients were fever, severe fatigue, a scratchy throat, wet cough, runny nose, diarrhoea, headache, and other body aches. Current SARS-CoV-2 real-time reverse-transcription polymerase chain reaction (RT-PCR) diagnostics continue to detect this variant.[4] However, it was also found that, with a usual RT-PCR test, one of the three target genes called S gene is not detected (S gene dropout or S gene target failure) and this test can therefore be used as a marker for this variant, pending sequencing confirmation.[5] The first report from a hospital in Tshwane, the epicentre of the Omicron outbreak in South Africa, had shown that 42 patients in the ward on December 2, 2021, revealed that 29 (70%) patients were not on oxygen therapy, whereas 13 patients were dependent on supplemental oxygen, of which 9 (21%) had a diagnosis of COVID-19 pneumonia based on a combination of symptoms, clinical signs, chest X-ray, and inflammatory markers. The remaining four patients were on oxygen for other medical reasons (two previously on home oxygen, one for heart failure, and one with a confirmed diagnosis of pneumocystis pneumonia). There were only four patients in high care and one in the intensive care unit (ICU). The number of patients in high care on double oxygen, high-flow nasal oxygen, or on noninvasive ventilation was noticeably less in the present wave. All are being prescribed steroids as the mainstay of therapy. Of 38 adults in the COVID wards on December 2, 2021, 6 were vaccinated, 24 were unvaccinated, and 8 had unknown vaccination status. Of the nine patients with COVID pneumonia, eight were unvaccinated and one was a child. Only a single patient on oxygen was fully vaccinated but the reason for the oxygen was chronic obstructive pulmonary disease.[6] Recently, the Center for Disease Control recommended all persons aged ≥12 years receive a third dose (booster) of a messenger RNA (mRNA) vaccine 5 months after receiving the second mRNA vaccine dose and immunocompromised individuals to receive a third primary dose.

Protection from various vaccines against hospitalization and death from severe COVID-19 disease is waning slowly after a two-dose schedule of a COVID-19 vaccine.[7] However, results from some studies have concluded that booster dose vaccination with any of the commonly used mRNA-based vaccination significantly reduces the chances of reinfection with COVID-19 and, even if infected also, the disease may be mild only.[8–11] However, booster-dose effectiveness and its durability against the new Covid-19 variant Omicron is not clear yet, as it is spreading globally. Hence, in the present systematic review study, we aim to review all the available evidence studies' findings on the effectiveness of the booster or third COVID-19 vaccine dose against the new COVID-19 variant Omicron.

2 | METHODOLOGY

We have performed a literature search of PubMed, Google Scholar, and MedRXiv database search was performed from inception to till January 2022, using the MeSH terms and keywords "Corona Virus Disease-2019 OR COVID-19 AND Omicron AND COVID-19 Booster Vaccine." The study search was limited to only original research studies with the aim of booster dose efficacy against the new COVID-19 variant Omicron. We have identified a total of 27 published studies (Figure 1).

3 | RESULTS

A total of 27 eligible studies were identified (in vitro studies: 5; prospective observational studies: 20; case series: 2) and were included for analysis. All 27 review studies' findings are summarized in Table 1.

4 | FINDINGS

A preliminary analysis by insurer Discovery, the largest private health insurance administrator, from the first 3 weeks of the Omicron wave in 211,000 positive PCR tests from adults covered by the insurer (41% of these adults had received two doses of the Pfizer vaccine), and 78,000 results were attributed to Omicron infections reported that the two-dose Pfizer-BioNTech vaccination provides 70% protection against hospitalization for those who have received the two-dose series compared with the unvaccinated. Protection against hospitalization was maintained across all people aged 18–79 years, with slightly lower levels of protection for those aged 60–69 (67%) and 70–79 (59%) years. Overall protection against infection fell to 33% for the two-dose series, down from the 80% seen during the Delta wave. The report also revealed that a total of 16% of ICU admissions were among the vaccinated individuals only. Additionally, the risk of reinfection with Omicron was significantly higher compared with prior variants. The insurer's data have shown that those who had been infected with the Delta variant had a 40% relative risk of reinfection with Omicron, those infected during the Beta wave had a 60% risk of reinfection, and those infected with the original viral strain identified in Wuhan during the first wave had a 73% risk of reinfection. The data suggest that, after adjusting for vaccination status, the risk of hospitalization among adults with a COVID-19 diagnosis was 29% lower with Omicron than it was during the first wave in early 2020. In addition, the analysis found that, hospitalized adults had shown a lower possibility of being admitted to

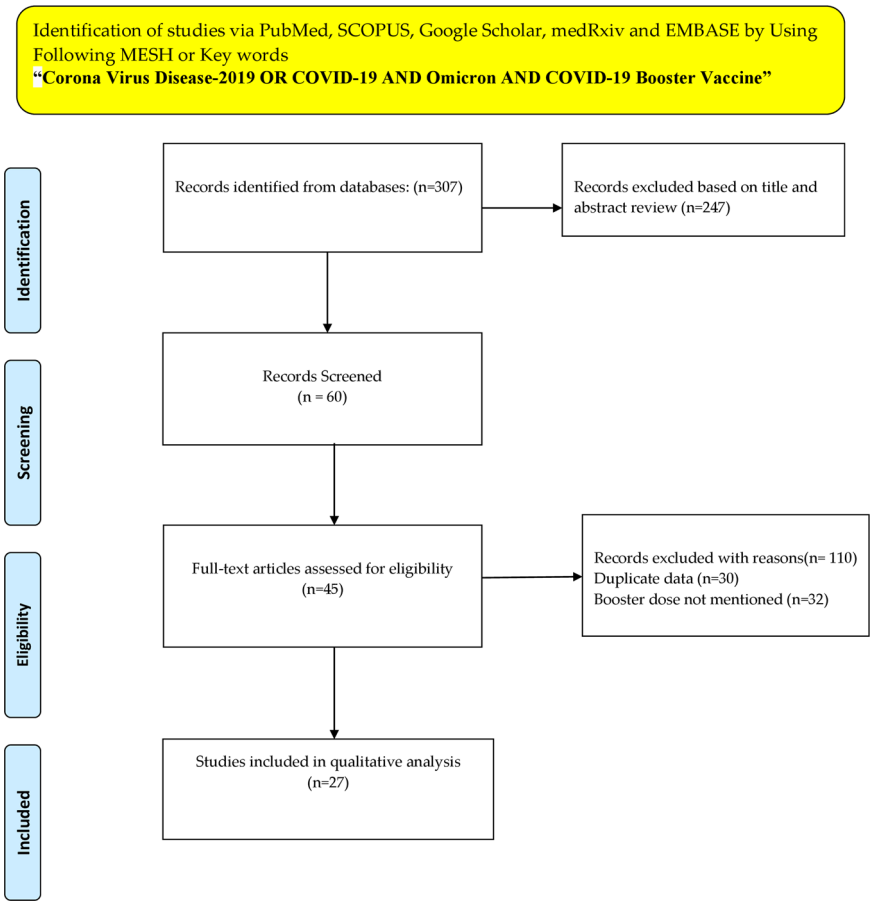

FIGURE 1 PRISMA flow diagram for the study selection. COVID-19, coronavirus disease 2019; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

high care or ICUs compared with prior waves and less number of hospitalized patients presented with less respiratory distress and a lower proportion required supplemental oxygen.[12]

Data of a study from the United Kingdom (UKHSA/MRC Biostatistics Unit, University of Cambridge) has been shown that the risk of hospitalization with Omicron variant infection was approximately half of that for the Delta variant (hazard ratio [HR] 0.53, 95% confidence interval [CI]: 0.50–0.57). The risk of hospitalization from the emergency departments with Omicron variant was approximately one-third of that for the Delta variant (HR 0.33, 95% CI: 0.30–0.37). These analyses were stratified on date of specimen and area of residence, and further adjusted for age, sex, ethnicity, local area deprivation, international travel, and vaccination status. In this analysis, the risk of hospitalization is lower for Omicron cases after the second and third doses of vaccine, with an 81% (77%–85%) reduction in the risk of hospitalization after three doses compared with unvaccinated Omicron cases.[13]

A test-negative case–control study by Andrews et al. investigated the efficacy of booster-dose vaccine against symptomatic illness caused by the Omicron and Delta variants (persons infected with the Omicron variant: 886,774; persons infected with the Delta variant: 204,154; test-negative control: 1,572,621). Vaccine efficacy was calculated after primary vaccination with two doses of BNT162b2 (Pfizer BioNTech), ChAdOx1 nCoV-19 (AstraZeneca), or mRNA-1273 (Moderna) vaccine and after a booster vaccination with BNT162b2, ChAdOx1 nCoV-19, or mRNA-1273. Findings of the study revealed that, among ChAdOx1 nCoV-19 primary-course population, effectiveness of vaccine increased to 62.4% (95% CI: 61.8–63.0) at 2–4 weeks after a BNT162b2 booster, and among BNT162b2 primary-course population, effectiveness of vaccine was increased to 67.2% (95% CI: 66.5–67.8) at 2–4 weeks after a BNT162b2 booster. However, vaccine effectiveness after a ChAdOx1 nCoV-19 primary course increased to 70.1% (95% CI: 69.5–70.7) at 2–4 weeks after an mRNA-1273 booster and after a BNT162b2 primary-course vaccination, the mRNA-1273 booster increased vaccine effectiveness to 73.9% (95% CI: 73.1–74.6) at 2–4 weeks. Overall, a BNT162b2 or mRNA-1273 booster dose vaccination after either the ChAdOx1 nCoV-19 or BNT162b2 primary course substantially increased protection. However, the protection waned over time.[14]

The COV-BOOST trial, a multicenter, randomized, controlled phase-2 trial, investigated the reactogenicity and immunogenicity of seven different COVID-19 vaccines as a third dose after two doses of ChAd (Oxford-AstraZeneca) or BNT (Pfizer-BioNtech). Findings of the trial revealed that all the seven vaccines in the study yielded a great escalation of antibodies and cellular immune responses after ChAd/ChAd initial course and all except one after BNT/BNT, with no safety concerns.[15]

Recently, a micro neutralization assay study with wild-type SARS-CoV-2 virus and B.1.351 (Beta), B.1.617.2 (Delta), and Omicron

TABLE 1 Summary of the studies related to booster dose efficacy against Omicron variant

S.No	Findings	References
1.	The risk of hospitalization is lower for Omicron cases after the second and third doses of vaccine, with an 81% (77%–85%) reduction in the risk of hospitalization after three doses compared with unvaccinated Omicron cases.	https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1044481/Technical-Briefing-31-Dec-2021-Omicron_severity_update.pdf.[13]
2.	A booster dose of BNT162b2 (Pfizer BioNTech) or mRNA-1273(Moderna) vaccine after either the ChAdOx1 nCoV-19 (Oxford–AstraZeneca) or BNT162b2 primary course substantially increased protection against Omicron.	Andrews et al.[14]
3.	COV-BOOST is a multicenter, randomized, controlled phase 2 trial of third-dose booster vaccination against COVID-19. All the seven vaccines in the study yielded a great escalation of antibodies and cellular immune responses after ChAd/ChAd (Oxford–AstraZeneca) initial course and all, except one, after BNT/BNT (Pfizer BioNTech), with no safety concerns.	Munro et al.[15]
4.	The higher neutralization efficiency (by a factor of 100) against the Omicron variant after the third dose than after the second dose.	Nemet et al.[16]
5.	Booster-dose vaccine effectiveness was evaluated at least after 7 days of receiving the third dose, compared with receiving only 2 doses 5 months ago, was estimated to be 93% (231 events for 2 doses vs. 29 events for 3 doses; 95% CI: 88–97) for hospitalization, 92% (157 vs. 17 events; 82–97) for severe COVID-19 disease, and 81% (44 vs. 7 events; 59–97) for COVID-19 mortality.	Barda et al.[17]
6.	Following a booster dose, a 14-fold reduction in neutralizing activity against the Omicron variant and over 90% of booster-vaccinated population had shown neutralizing activity against the Omicron variant	Edara et al.[18]
7.	Individuals who had received a booster dose (mRNA vaccine) had shown potent neutralization antibodies against Omicron.	Garcia-Beltran et al.[19]
8.	An increased estimates of vaccine effectiveness against the COVID-19-associated emergency and/or urgent care department encounter or hospitalizations during both Delta- and Omicron-predominant time duration among adults who have been administered with a third or booster-dose vaccination (mRNA vaccine).	Thompson et al.[20]
9.	Persons who had received the booster dose of mRNA COVID-19 vaccine (compared with unvaccinated and those who received of two doses) were less likely among cases with symptomatic SARS-CoV-2 infection compared with test-negative controls.	Accorsi et al.[21]
10.	Booster doses with BNT162b2 (Pfizer BioNTech) in those with two doses of either BNT162b2 or CoronaVac provided acceptable neutralizing immunity against Omicron variant at 1 month postbooster dose. However, three doses of BNT162b2 (Pfizer BioNTech) elicited higher levels of $PRNT_{50}$ antibody to Omicron variant, suggesting longer duration of protection.	Peiris et al.[22]
11.	Antibody titers against Omicron were low or undetectable after two immunizations and in most convalescent sera. A booster vaccination significantly increased titers against Omicron to levels comparable to those seen against the ancestral (D614G) variant after two immunizations. Neither age nor sexes were associated with differences in postvaccination antibody responses.	Lusvarghi et al.[23]
12.	Neutralization of Omicron was undetectable in participants that had received a two-dose regimen of CoronaVac vaccine, BNT162b2 booster resulted in a 1.4-fold increase in neutralization activity against Omicron, compared with a two-dose mRNA vaccine.	Pérez-Then et al.[24]
13.	mRNA booster immunizations in vaccinated and convalescent individuals resulted in a significant increase of serum-neutralizing activity against Omicron.	Gruell et al.[25]
14.	Immune boosting through three vaccine shots significantly improved the convalescents' immunity against the Omicron variants.	Ma et al.[26]

TABLE 1 (Continued)

S.No	Findings	References
15.	Booster vaccination increased the nAb NT_{50} titer against all variants.	Zeng et al.[27]
16.	Booster recipients exhibited dramatically increased nAb titers and generation of a stronger and much broader neutralization against the Omicron variant after the booster vaccination.	Zeng et al.[28]
17.	A booster dose of BBIBP-CorV (Sinopharm Beijing Institute of Biological Products COVID-19 vaccine) led to a significant rebound in neutralizing immune response against SARS-CoV-2, while the Omicron variant showed extensive but incomplete escape from booster-enhanced neutralization.	Yu et al.[29]
18.	A homologous inactivated vaccine booster or a heterologous booster with a protein subunit vaccine (ZF2001) significantly increased neutralization titers to both WT and Omicron variant.	Wang et al.[30]
19.	Comparing with those who received a booster and those who received two doses, there was an estimated odds ratio of 0.14 (95% CI: 0.13–0.15) 28–65 days following receipt of the booster (86% reduction in the odds of testing positive for SARS-CoV-2).	Patalon et al.[31]
20.	A booster dose of mRNA-1273 vaccine was associated with neutralization titers against the Omicron variant that were 20.0 times higher than those assessed after the second dose of vaccine.	Pajon et al.[32]
21.	A 50 μg of mRNA-1273 (Moderna) boost increased Omicron neutralization titers and may substantially reduce the risk of symptomatic vaccine breakthrough infections.	Doria-Rose et al.[33]
22.	At all four time intervals after the second mRNA vaccine dose, very minimal neutralizing antibody titers were detected against Omicron, including for a majority of patients who had SARS-CoV-2 breakthrough infections. Neutralizing antibody titers against all other variant spike protein-bearing pseudoviruses declined dramatically from 1 to 6 months.	Evans et al.[34]
23.	Homologous and heterologous booster vaccines had an acceptable safety profile and were immunogenic in adults who had completed a primary Covid-19 vaccine regimen at least 12 weeks earlier.	Atmar et al.[35]
24.	Heterologous boosting with Convidecia elicited significantly increased GMTs of neutralizing antibody against SARS-CoV-2 than homologous boosting with CoronaVac in participants who had previously received one or two doses of CoronaVac.	Costa Clemens et al.[36]
25.	The third heterologous dose was of either a recombinant adenoviral vectored vaccine (Ad26.COV2-S), an mRNA vaccine (BNT162b2, Pfizer BioNTech), or a recombinant adenoviral-vectored ChAdOx1 (Oxford–AstraZeneca) nCoV-19 vaccine, compared with a third homologous dose of CoronaVac. All four vaccines administered as a third dose induced a significant increase in binding and neutralizing antibodies, which could improve protection against infection. Heterologous boosting resulted in more robust immune responses than homologous boosting and might enhance protection.	Li et al.[37]
26.	Heterologous ChAdOx1 (Oxford–AstraZeneca):mRNA-1273 (Moderna) prime-boost immunization induces significantly broader and more potent serum-neutralizing antibody and MBC responses against WT SARS-CoV-2 and VOCs relative to homologous ChAdOx1 vaccination, and this difference appears to be driven by both the magnitude and quality of the early secondary B-cell response.	Kaku et al.[38]
27.	Recipients of both vaccine types had a ~9- to 10-fold increase in IgG and neutralizing titers within 2 weeks of vaccination, and an 8-fold increase in live Omicron VOC neutralization, restoring titers to those measured after the third vaccine dose.	RegevYochay et al.[39]

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; GMTs, geometric mean titers; mRNA, messenger RNA; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VOCs, variants of concern; WT, wild type.

variant isolates were performed by Nemet et al.[16] with the use of serum samples obtained from 2 groups of 20 health care workers. A group comprising participants who had received two doses of the BNT162b2 vaccine (mean, 165.6 days since receiving the second dose) and the second group comprising those who had received three vaccine doses (mean, 25 days since receiving the third dose) found higher neutralization efficiency (by a factor of 100) against the Omicron variant after the third dose than after the second dose; however, even with three vaccine doses, neutralization against the Omicron variant was lower (by a factor of 4) than that against the Delta variant.[16]

A study from Israel on evaluation of the effectiveness of a third dose of the BNT162b2 mRNA vaccine for preventing severe COVID-19 outcomes (n = 1,158,269) found that a third dose of the BNT162b2 mRNA vaccine is effective in protecting individuals against severe COVID-19-related outcomes, compared with receiving only two doses at least 5 months ago. Vaccine effectiveness was evaluated at least after 7 days of receiving the third dose, compared with receiving only two doses after 5 months ago, and was estimated to be 93% (231 events for 2 doses vs. 29 events for 3 doses; 95% CI: 88–97) for hospitalization, 92% (157 vs. 17 events; 82–97) for severe COVID-19 disease, and 81% (44 vs. 7 events; 59–97) for COVID-19- mortality.[17]

A study by Edara et al.[18] investigated an authentic live virus neutralization assay to examine the neutralizing activity of the SARS-CoV-2 Omicron variant against mRNA vaccine-induced antibody responses in double-vaccinated and booster dose-vaccinated individuals, and found, following a booster dose, a 14-fold reduction in neutralizing activity against the Omicron variant and over 90% of booster-vaccinated population had shown neutralizing activity against the Omicron variant.[18]

Another study by Garcia-Beltran et al.[19] investigated the neutralization potency of sera from 88 mRNA-1273, 111 BNT162b, and 40 Ad26.COV2.S vaccine recipients against wild-type, Delta, and Omicron SARS-CoV-2 pseudoviruses. We included individuals that received their primary series recently (<3 months), distantly (6–12 months), or an additional "booster" dose, while accounting for prior SARS-CoV-2 infection, and found that individuals who had received a booster dose with mRNA vaccines had shown a potent neutralization antibodies against Omicron variant and only 4- to 6-fold lower than the wild type, suggesting enhanced cross-reactivity of neutralizing antibody responses.[19]

The VISION Network, USA, has done an investigation among adults who have received a third or booster dose of mRNA vaccine in 222,772 encounters from 383 emergency departments and urgent care clinics, and 87,904 hospitalizations from 259 hospitals among adults aged ≥ 18 years across 10 states from August 26, 2021, to January 5, 2022, and has found an increased estimate of vaccine effectiveness against the COVID-19-associated emergency and/or urgent care department encounter or hospitalizations during both the Delta- and Omicron-predominant time duration among adults who have administered the third dose of mRNA vaccine.[20]

Recently, a study from the United States assessed the association between receiving of three doses of BNT162b2 (Pfizer BioNTech) or mRNA-1273 (Moderna) vaccine and symptomatic SARS-CoV-2 infection from Omicron and Delta variants (cases [n] = 23,391 [13,098 Omicron and 10,293 Delta]; controls [n] = 46,764), and has found that individuals who have received three doses of mRNA COVID-19 vaccine (compared with unvaccinated and with those who received two doses) were less likely among cases with symptomatic SARS-CoV-2 infection compared with test-negative controls.[21]

In addition to above reviewed studies, few other studies have also shown the effectiveness of booster dose vaccination, significant increase in neutralizing immunity, and higher levels of antibody titers against the new COVID-19 variant Omicron.[22–32] Furthermore, in vitro studies on effectiveness of booster dose vaccination against Omicron have also revealed increased titers of neutralizing antibodies against Omicron variant compared with other SARS-CoV-2 lineages following the third or booster shot of vaccination.[27,33,34] Booster-dose vaccination of either homologous and/or heterologous vaccines was safe and produces significant immunogenicity against Covid-19 variants.[35–38] However, a preliminary study from Israel has shown that although the level of antibodies increased with the fourth booster shot of BNT162b2 mRNA vaccine, they were insufficient to prevent Omicron infection.[39]

5 | DISCUSSION AND CONCLUSION

To address the present ongoing pandemic with new variants, currently both Delta and Omicron increasing a rapid surge in the number of new COVID-19 infections, hospitalization, and mortality, all the findings reviewed from currently available studies support the evidence for booster-dose vaccine efficacy against SARS-CoV-2 variants, including Omicron. Hence, we suggest that every country should impliment policy changes to start booster dose vaccines to at least those who are immunocompromised, have concomitant comorbidities, and to vulnerable individuals, to decrease the COVID-19 severity and mitigate the healthcare and economic impacts. In addition, strict vigilance on following all the preventive measures should be continued by every individual to curtail the spreading of the SARS-Co-2 virus.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Santenna Chenchula conducted the literature search and data extraction, and drafted the manuscript. Padmavathi Karunakaran, Sushil Sharma, and Madhavrao Chavan revised the final manuscript. All authors reviewed and approved the final version of the manuscript.

DATA AVAILABILITY

The data used in this systematic review are available from the corresponding author with a reasonable request.

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