HUMAN VACCINES & IMMUNOTHERAPEUTICS
2022, VOL. 18, NO. 5, e2065824 (9 pages)
https://doi.org/10.1080/21645515.2022.2065824

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COMMENTARY

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Need of booster vaccine doses to counteract the emergence of SARS-CoV-2 variants in the context of the Omicron variant and increasing COVID-19 cases: An update

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ABSTRACT

The emergence of different variants of SARS-CoV-2, including the Omicron (B.1.1.529) variant in November 2021, has resulted in a continuous major health concern at a global scale. Presently, the Omicron variant has spread very rapidly worldwide within a short time period. As the most mutated variant of SARS-CoV-2, Omicron has instilled serious uncertainties on the effectiveness of humoral adaptive immunity generated by COVID-19 vaccination or an active viral infection as well as the protection provided by antibody-based immunotherapies. Amidst such high public health concerns, the need to carry out booster vaccination has been emphasized. Current evidence reveals the importance of incorporating booster vaccination using several vaccine platforms, such as viral vector- and mRNA-based vaccines, as well as other platforms that are under explorative investigations. Further research is being conducted to assess the effectiveness and durability of protection provided by booster COVID-19 vaccination against Omicron and other SARS-CoV-2 variants.

ARTICLE HISTORY
Received 30 December 2021
Revised 25 March 2022
Accepted 7 April 2022

KEYWORDS
SARS-CoV-2; Omicron variant; B.1.1.529; vaccines; booster doses; enhancing immunity; protection

Introduction

The ongoing coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has posed high global health concerns and resulted about one-half billion confirmed cases and over 6 million deaths worldwide. Although our understanding of the virus is continuously improving, progressive vaccination drive is intense across the globe, and new vaccines are being developed, the pandemic has not ended given the continuous emergence of variants and the consequent COVID-19 epidemic waves.[1–6] Viral variants are emerging given the evolving nature of SARS-CoV-2, and acquired genomic mutations contribute to increasing transmissibility, disease severity, morbidity, mortality, and immune escape mechanisms. These changes allow the virus to evade the protection rendered by vaccine-induced antibodies, natural infection, and antibody-based therapies.[6–11]

The World Health Organization (WHO) has been labeling and classifying the variants as variants of concern (VOC), interest (VOI), or under monitoring (VUM), based on, among other factors, the data available on transmissibility and pathogenicity.[4] Among the existing SARS-CoV-2 variants, the Delta variant (B.1.617.2) is highly transmissible, the most virulent variant, and caused vaccine breakthrough infection.[9] Several countries have been experiencing continuous COVID-19 epidemic waves, which limits people movement and affects the economies.[1–3–12–14] More recently, a new VOC named Omicron (B.1.1.529) emerged in November 2021. Omicron, which is the most mutated SARS-CoV-2 variant, originated in South Africa and rapidly spread to many other countries, highly increasing COVID-19 cases worldwide.[3,15,16] Furthermore, Omicron has higher transmissibility and the ability to evade vaccine-induced immunity and antibody-based immunotherapies via its immune escape mechanisms.[17–20]

Omicron has become the dominant strain worldwide, resulting in a huge increase in COVID-19 cases and newer outbreaks and posing new challenges in the prevention and control of the COVID-19 pandemic.[6,21] In this context, Huang et al. (2022) reported seasonal predictions on Omicron development in 11 key countries.[22] The findings suggest that the pandemic due to Omicron had an initial exponential-like growth rate and may show small resurgences in the months of April and June in northern and southern hemisphere countries, respectively. Infectious virus neutralization assays revealed that the Beta and Delta variants were consistently cross-neutralized; however, Omicron neutralization is much reduced or nonexistent (up to a 34-fold decrease compared with that of the wild-type virus).[23] Such evolving scenario has

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emphasized the need for booster vaccine doses to increase the levels of protective antibodies in vaccinated individuals. Despite this, the current vaccines may not be efficient enough to avoiding breakthrough infection with SARS-CoV-2 variants, particularly Omicron. However, the current vaccines may confer sufficient immunity to minimize the severity of infection, reduce hospitalization days, and death. The present article highlights the necessity of booster vaccine doses and discusses the progress made in such direction to counter emerging SARS-CoV-2 variants, with a particular focus on Omicron.

Emergence of Omicron and the global health concerns

Omicron was initially discovered by South African scientists on 24 November 2021, in samples collected from South African and Botswana patients.[24] According to the WHO, Omicron has become the dominant strain worldwide; it has formally been discovered in nearly 150 countries across the world and has a doubling rate of 1.5 to 3 days, which is higher than that of previous SARS-CoV-2 variants.[9] Omicron has the greatest number of mutations of any SARS-CoV-2 variant, with more than 50 in its genome, including over 30 mutations in the viral spike (S) protein, which regulates infectivity and antigenicity.[25] Omicron has acquired new characteristics such as escape from PCR testing (S Gene Target Failure),[26] increased transmissibility[27]and infectivity,[28] and escape from natural or vaccine-induced immunity and antibody-based therapies.[17–20]According to epidemiological surveillance,[29] Omicron appears to greatly escape immunity from prior infection compared to other variants (Beta and Delta), which appeared to be more susceptible to natural immunity than the original strain. Natural immunity was 85%, 88%, 91%, and 75% successful at preventing reinfection with the original strain and the Beta, Delta, and Omicron variants, respectively.[30] The effective dose 50 (ED50) of serum samples from COVID-19 convalescent patients infected with the original SARS-CoV-2 strain against pseudotyped Omicron is 8.4-fold lower than that against the D614 G reference strain, whereas the ED50 against other pseudotyped VOCs (Alpha, Beta, Gamma, and Delta) and VOIs (Lambda, Mu) is only 1.2–4.5-fold lower.[31] According to a UTMB study, natural immunity in unvaccinated people provides minimal protection against Omicron, since the level of natural immunity in unvaccinated individuals against Omicron is 16 times lower than that against previous variants a month after infection, and much lower after six months.[32] However, natural immunity still confers some level of protection, and individuals with natural immunity are remarkably less likely to be infected with Omicron.[29]

The pediatric group (<18 years old) is more susceptible to vaccine breakthrough infections or reinfections due to Omicron. Chen et al. (2022) assessed neutralization susceptibility in pediatric serum specimens; the neutralizing antibody titer against Omicron was substantially lower than that against the ancestral virus.[33] Omicron is causing vaccine breakthrough infection and reinfection compared to other VOCs, which may lead to disease severity and death.[34,35] As high amounts of broadly neutralizing antibodies (bNAbs) have been detected against Omicron, highly efficacious Omicron-based vaccines eliciting long-term cross-protective immunity are recommended.[36] Fifteen out of 29 substitutions have been found in the receptor-binding domain (RBD) of the Omicron S protein, the primary target of monoclonal antibody (mAb)-based therapy. Hence, the mAbs approved by the US FDA may be less effective against Omicron.[37] Bagabir et al. (2022) highlighted that artificial intelligence (AI) applied on digital health can help develop preventives and therapeutic agents against the ongoing COVID-19 pandemic.[38]

COVID-19 vaccination and challenges posed by SARS-CoV-2 variants

The WHO, US FDA, and EU have approved several vaccines for emergency use with 65–95% efficacy, and most countries including the USA, UK, India, and EU countries have been rigorously vaccinating their citizens.[5] The Pfizer vaccine is licensed in the US, so not all vaccines are used under Emergency Use Authorization (EUA). Although vaccination was initiated throughout the world, the inequal distribution of vaccines among developed and developing nations may become a reason for further viral spread.[39,40] In addition, the vaccination process was severely affected by the hesitancy shown by people throughout the world.[41,42] This was mostly attributed to the novelty of the technology used to manufacture the vaccines as most vaccines were still under examination in clinical trials and the results of their efficacy and safety studies were not completely available to the common man.[43] The available vaccines consist of two doses whereby fully vaccinated people develop protective antibodies that can last for at least six months. In most vaccinated people, although infections cannot be restricted, severe illness and death may be avoided. However, neutralizing antibody responses and vaccine effectiveness vary by vaccine agent, decrease with increased time post-vaccination, and are negatively impacted by emerging SARS-CoV-2 variants.[44–46] The Delta variant was associated with breakthrough infections, where even fully vaccinated people suffered from SARS-CoV-2 reinfections. However, most breakthrough infections were either asymptomatic or resulted in mild symptoms. With the emergence of Omicron, which has more than 30 mutations potentially affecting the S protein, questions regarding vaccine efficacy have reemerged. Furthermore, Omicron may have emerged from a chronically infected COVID-19 patient vaccinated with an mRNA- or non-mRNA-based vaccine, allowing the virus to adapt and mutate to escape the immune response.[47] Therefore, the efficacy of existing vaccines manufactured using the S protein of previous viral variants has been questioned. Moreover, the increased transmissibility of the Delta and Omicron variants is evidenced by the reproductive number (R0), which is 2.5, 7, and >10 for the wild-type virus, Delta variant, and Omicron variant, respectively.[27] In vitro infectivity experiments have demonstrated that Omicron continues to rely upon the human ACE2 receptor for host cell entry and that it is nearly 4-fold and 2-fold more infectious than the wild-type and Delta pseudoviruses, respectively.[48] This shows that among the current SARS-CoV-2 variants, Omicron may have the highest transmissibility. Furthermore, compared to the Delta variant, Omicron replicates more than 70 times faster in the human bronchus, which could explain why Omicron may be transmitted faster between humans than other variants.[49] Despite

the high rates of transmissibility, Omicron was noted to cause milder infections as compared to the previous Delta variant and also its mortality rate is much lower.

Studies on antibody concentrations after two doses of vaccination with vaccines from Astra Zeneca, Pfizer-BioNTech, and Moderna have revealed 5.3–6.2-, 11.4-, 20-, 25-, 29.8-, 41-, and 49–84-fold reductions in neutralizing antibody titers against the Omicron variant compared to those against previous variants or the original strain.[48–50–53] Indeed, neutralizing antibody titers in sera from some double-vaccinated participants dropped to below the detectable threshold against the Omicron variant. Hence, when compared to those against the vaccine strain, the neutralizing antibody titers against some SARS-CoV-2 VOCs are lower. This is important because there is a relationship between neutralization and efficacy against viral variants.[54] Moreover, several studies have shown that antibody levels start falling 3–8 months after vaccination.[54,55] The UK Health Security Agency (UKHSA) has suggested that vaccine efficacy against symptomatic disease 25 weeks after full (two doses) COVID-19 vaccination may be lower than 10% for the Omicron variant, compared with 40% for the Delta variant.[27] Furthermore, the reduced serum neutralizing capacity against Omicron highlighted the diminished neutralizing ability of the mAbs, imdevimab and casirivimab, against the Omicron variant.[56] Although two vaccine doses are not strong enough to prevent infection, they may still protect from Omicron-derived severe disease, including hospitalization and death, because 80% of the epitopes in the S protein recognized by CD8+ T cells are not affected by the mutations in the Omicron variant.[32,48] Nevertheless, the emergence of Omicron has encouraged the use of booster doses. By 9 December 2021, most SARS-CoV-2 Omicron variant cases found in Denmark were fully (76%) or booster-vaccinated (7.1%), and 4.3% had a previous SARS-CoV-2 infection; most patients (76%) had symptoms, nine cases were hospitalized, one required critical care, and no deaths were reported.[32]

Dawood (2022) has discussed how changes in the S protein alter the S protein-ACE2 receptor interaction.[57] He also reported that Omicron stimulates the immune response more than the wild-type strain. The multiple S protein mutations in Omicron are responsible for the escape from antibody neutralization and the reduced vaccine efficacy to restrict infection. Keeton et al. (2022) assessed the ability of adaptive response such as those involving T cells to react with the Omicron S protein in vaccinated (with Ad26.CoV2.S or BNT162b2) and unvaccinated convalescent COVID-19 patients.[58] The study found that the magnitude of the cross-reactive T cell response against Omicron was similar to that against Delta and Beta. The production of safe and effective vaccines against SARS-CoV-2 and its VOCs will be the best approach to combat this ongoing pandemic. The RBD of the S protein is a major target for the development of vaccine candidates. In this context, Wang et al. (2022) have reported a self-adjuvanting lipoprotein conjugate composed of α-galactosylceramide (αGalCer), which activates a potent invariant natural killer T cell response, and the RBD; this conjugate induces potent immunity against SARS-CoV-2 VOCs.[59] The αGalCer-RBD conjugate was shown to induce stronger humoral and cellular responses than the unconjugated RBD/αGalCer mixture. Moreover, the conjugate vaccine displayed effective cross-neutralization of all VOCs including Delta and Omicron. Thus, this study will be helpful in the design of various subunit vaccines.

Increased interest in terms of antibody-mediated immunity during SARS-CoV-2 infection is attributed to the exaggerated T cell responses, cytokine storm, and immune exhaustion that harm the patients during the acute phase of COVID-19.[60,61] The depletion of T cell immunity that is majorly due to immune exhaustion, and lack of memory T cells play a key role in the adaptive immune responses to SARS-CoV-2 infection, thereby shifting focus back onto the antibody facilitated immune responses.[62] It was also noted that the T cell responses are modulated by the conserved proteins (Orf3, Orf6) of the virus and therefore, IFN-α/β activation is affected. This causes unrestricted multiplication of the virus in the infected cells.[63] The coexistence of both suppression and activation of CD8+ T cells, T CD4+, and other cytokines are presumed to play a key role in the adaptive immune responses during SARS-CoV-2 infection which can result in restricting viral replication, and limiting virus spread. However, impaired lymphocyte proliferation, apoptosis, and immune exhaustion could limit the protective effect and increase disease severity.[64] Although the neutralizing antibodies decline after natural infection and vaccination, people may still be protected against the Omicron variant due to resilient T cell immune responses (CD4+ T cells and CD8+ T cells).[65–67] This may be attributed to the low clinical severity with the Omicron variant observed during its emergence from South Africa.

Importance of booster doses to counter Omicron

The emergence of the Omicron variant has emphasized the importance of COVID-19 booster shots.[27,28,53,68,69] The USA and the UK have already initiated booster dose vaccination among their citizens to control the spread of the Omicron variant. Fully vaccinated residents who received a booster dose had a 10 times lower risk of contracting COVID-19 than residents who had received the primary vaccination series or were unvaccinated.[69] Early research from the UK,[70] The UKHSA has indicated that booster shots are moderate to highly effective against symptomatic infection, providing 70–75% protection in the weeks following booster administration. Meanwhile, Pfizer-BioNTech, a vaccine manufacturer, has prescribed a booster dose of the existing vaccines, which may potentially protect against Omicron by inducing high neutralizing antibody titers. The researchers highlighted that the third dose (booster dose) induced a 25-fold increase in neutralizing antibody titers when compared to the titers elicited after two doses, and that the antibodies elicited after the third dose neutralized Omicron.[32,48] However, Ai and colleagues[71] reported that Omicron may escape vaccine-induced immune protection after the third dose more effectively than the prototype strain and other VOCs. The researchers investigated the immunogenicity of COVID-19 breakthrough infection, a third heterologous booster of a protein subunit vaccine primed with two doses of inactivated vaccines, and a third homologous booster of an inactivated vaccine against SARS-CoV-2 pseudotypes of the prototype strain and Beta, Delta, and Omicron variants. The geometric mean titers (GMTs) of neutralizing antibodies against

the prototype strain and Beta and Delta variants were 67.4, 8.8, and 35.1, respectively, 14 days after two doses of inactivated vaccines, but the neutralizing activity against Omicron was below the lower limit of quantification in 80% of the samples. The GMTs were significantly increased to 285.6, 215.7, 250.8, 48.7 against the prototype strain and Beta, Delta, and Omicron variants, respectively, 14 days after a third homologous booster vaccination, while the GMTs considerably increased to 1436.0, 789.6, 1501.0, and 95.8, respectively, 14 days after a third heterologous booster vaccination. Although all samples showed positive neutralizing activity against Omicron after booster vaccination, the neutralizing antibody titers against Omicron 14 days after homologous or heterologous vaccine booster administration were significantly lower (5.86- to 14.98-fold) than those against the prototype strain.

In a recent phase 4 single blind randomized study, it was has observed that heterologous boosting results in a more robust immune response than homologous boosting.[72] Geurtsvan Kessel et al. (2022) reported that after two mRNA-1273 immunizations or Ad26.COV.2 priming, BNT162b2 booster vaccination partially restored neutralization of the Omicron variant, although the neutralizing antibody titers against this variant were still up to 17-fold lower than those against the wild-type virus.[23] Pérez-Then et al. (2022) discovered that heterologous CoronaVac priming followed by a BNT162b2 booster regimen results in increased virus-specific antibody levels and robust neutralizing activity against the original virus and Delta variant, which is similar to the titers reported after two mRNA vaccine doses.[73] Omicron neutralization was undetectable in subjects who received a two-dose CoronaVac vaccine; however, it increased 1.4-fold after administration of the BNT162b2 dose when compared to that after two-dose mRNA vaccination. Despite this rise, neutralizing antibody titers for Omicron and Delta variants were 7.1 and 3.6 times lower, respectively, than those for the ancestral original strain.

Lu and coworkers[20] used the sera of BNT162b2 (25 samples) and CoronaVac (25 samples) vaccine recipients and revealed that neutralizing antibodies against the Omicron variant, either strain HKU691 or HKU344-R346K, were detected in less than 25% of BNT162b2 recipients and none of the CoronaVac recipients. The study, however, had several limitations; for example, the number of samples examined was rather low and serum collection was carried out 56 days after the first dose. Nevertheless, the results instilled doubts on the effectiveness of the two vaccines. It is tempting to speculate that the neutralizing antibodies elicited after vaccination with the BNT162b2 vaccine respond much better to the Omicron variant than the ones produced after the administration of CoronaVac. Having this in mind, it remains unclear whether the recipients of CoronaVac should receive booster vaccination from the same vaccine brand or other vaccine preparations such as BNT162b2 or mRNA1273. The answer will surely bring tremendous benefit to the people of 48 countries who used the vaccine.[74] Garcia-Beltran and coworkers[28] performed neutralization assays against the wild-type, Delta, and Omicron pseudoviruses using serum from four different types of vaccinated individuals, according to dose regimen: recent primary vaccination (<3 months), distant (6–12 months), distant plus previous SARS-CoV-2 infection, or recently boosted (<3 months). The participants received either S-encoding mRNA in lipid nanoparticles (BNT162b2 from Pfizer-BioNTech or mRNA1273 from Moderna) or an adenovirus-vectored vaccine (Ad26.COV2.S from Janssen/Johnson & Johnson). The neutralization of the Delta variant was lower than that of the wild-type in all individual categories, with undetectable levels in most individuals distantly vaccinated (>6 months). All three primary vaccination series (<3 months or >6 months) resulted in low to absent SARS-CoV-2 neutralization. In previously infected individuals, neutralizing antibody titers against Omicron were 9–17-fold lower than those against the wild-type. However, participants recently boosted exhibited potent neutralization of the Omicron variant, which was only moderately lower than that of the wild-type (6-fold for mRNA-1273, 4-fold for BNT162b, and 13-fold for Ad26.COV2.S), suggesting that booster shots enhance the cross-reactivity of neutralizing antibody responses. In another study that assessed the efficacy of BNT162b2 and ChAdOx1 vaccines, it was noted that two doses are insufficient to confer protection against infection and mild disease caused by the Omicron variant. However, it was confirmed that a booster dose with BNT162b2 significantly protected against mild and severe disease.[75] Moreover, the Moderna mRNA vaccine was found to be 50 times less protective against infection by the Omicron variant. However, a booster dose of the same vaccine showed improved efficacy in combating infection with the Omicron variant.[76] Individuals who received mRNA booster shots (BNT162b2 or mRNA-1273) had larger frequencies of Omicron RBD-binding B cells and higher levels of Omicron RBD-specific IgG1 antibodies than those who received booster shots using inactivated viral vaccines, independent of the kind of primary immunization. Thus, individuals who receive a booster dose of an mRNA vaccine after the initial two-dose regimens are more likely to be protected against SARS-CoV-2 infection, including the Omicron variant.[77]

Doria-Rose et al.[53] have evaluated the neutralizing antibody titers in serum samples from mRNA-1273 (Moderna) vaccine recipients against Omicron, and compared them with those against D614 G and Beta in a pseudovirus-neutralizing experiment conducted in two independent laboratories. When blood samples were taken four weeks after two standard vaccinations with 100 μg mRNA-1273, they discovered that Omicron was 49–84-fold less sensitive to neutralization than D614 G, and 5.3–6.2-fold less sensitive than Beta. A 50 μg booster dose improved Omicron-specific neutralizing antibody titers, potentially lowering the incidence of symptomatic vaccine breakthrough infections. Moreover, the amount of a third shot (booster dose) has a positive effect on neutralizing antibody titers, as the currently approved 50 μg booster with mRNA-1273 boosted neutralizing antibody levels against Omicron by approximately 37-fold compared to pre-boost levels, while a 100 μg dose of mRNA-1273 enhanced neutralizing antibody levels by about 83-fold.[78] Moreover, the neutralization of the Omicron variant could increase substantially after a booster dose of the mRNA-1273 vaccine.[79] Studies on the efficacy of two-dose vaccination and booster doses revealed the importance of a booster dose to protect against severe illness even among the susceptible populations such as people aged >60 years.[44,80,81]

Although no significant differences in vaccine effectiveness was observed with the Delta variant after two doses, absolute differences in vaccine effectiveness were observed with one

dose. Hence, the authors suggested that vulnerable groups receive two vaccine doses.[82] To confirm the safety, immune response, and side effects of various COVID-19 vaccines, the Cov-boost trial involving AstraZeneca, Johnson & Johnson (Janssen), Curevac, Moderna, Pfizer, Novavax, and Valneva was conducted. Booster doses are safe and effective, but the antibody boost varies substantially.[83,84] However, the study had several limitations such as dose interval and limitation to younger age groups. Another recent Israeli study suggested that the rate of infection and disease severity were substantially lowered in people aged over 60 who received a booster (third) dose of the Pfizer-BioNTech COVID-19 vaccine.[44,85] Therefore, "for more antibodies, a booster seems key."[86]Individuals who have been vaccinated and boosted have sufficient titers of neutralizing antibodies, which are needed for long-term protection against not only Omicron but also other variants. Interestingly, in a recent analytical study on monkeys, it was revealed that an Omicron-specific booster is no different from the standard booster of Moderna after two doses of the Moderna vaccine, suggesting that a new booster specific for a new variant is not necessary.[87] However, it is currently difficult to ascertain this due to the immunity that lasts after the COVID-19 vaccination.[88,89] We may need an annual vaccine boost as for the influenza virus. Globally, 197 countries and territories are vaccinating their citizens, and still only a few people are fully vaccinated (Figure 1).[90] Recently, the government of Israel declared that it will provide a fourth COVID-19 vaccine dose to its citizens.

There is emerging evidence indicating that mix-and-match mRNA-based vaccines may potentially improve immunogenicity and contribute to increasing the concentrations of neutralizing antibodies among vaccinees. In a previous study, mix-and-match vaccines using a first dose of Oxford (AZD1222), Pfizer (BNT162b2), or Moderna (mRNA-1273), followed by a second dose of Novavax (NVX-CoV2373), CoronaVac (DB15806), Janssen (JNJ -78,436,735), or CanSino (AD5-nCOV) vaccines revealed improved serum neutralizing abilities with reference to both the Delta and Omicron variants; however, further extensive research is required to understand the potential adverse effects.[91] The rate of COVID-19-related hospital admissions were found to be significantly lower among people vaccinated with the Pfizer BNT162b2 than among unvaccinated people;[92] more than 70% of the unvaccinated people needed hospitalization, while less than 10% of fully vaccinated (two doses) people needed hospitalization. Furthermore, there was a 25% increase in the RT-PCR positivity rates among fully vaccinated people during the period of the emergence of the Omicron variant. This points to the fact that, although vaccines fail to protect against Omicron-related clinical infection, they significantly minimize the chances of hospitalization.

Recently, the Israeli authorities recommended a fourth dose for the population aged 60 years and above. The fourth dose was also suggested among healthcare workers, which was previously confined to immunocompromised people. These decisions were based on observations of breakthrough infections during the upsurge of the Delta variant in July 2021. However, the emergence of Omicron has further highlighted the significance of booster vaccination doses among susceptible populations.[93] Moreover, Petrelli et al. (2022) analyzed the safety and efficacy of a third vaccine dose in the general population.[94] The reduction in the risk of infection in the general population ranged from 88% to 92%. Moreover, the conversion rates for anti-S IgG ranged from 95% to 100%. The third vaccine dose (booster dose) as well as wearing the mask are essential measures to protect against COVID-19 severity and death, and may be the best strategies to prevent the emergence of new variants.[35–96–97]

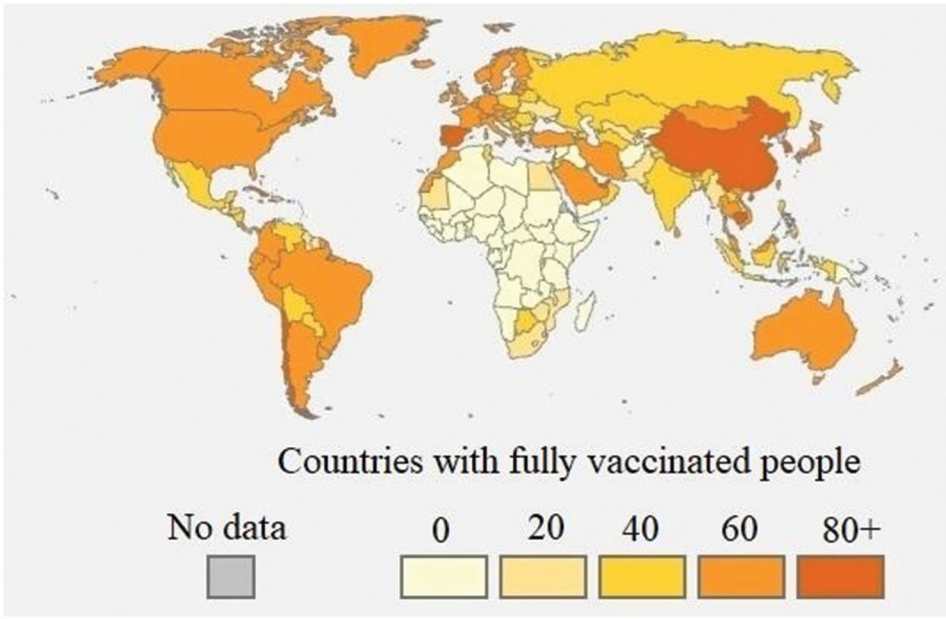

Figure 1. Worldwide COVID-19 vaccination data (ref. 92) as on 7 February 2022. (nearly 53% world population is fully vaccinated).

Conclusions and future prospects

Because of the greater transmissibility and potential for reduced susceptibility to antibody neutralization, the Omicron variant is causing great concern. Strong evidence and research on the efficacy of current vaccines against this variant are currently missing. Two vaccine doses are insufficient to protect against Omicron infection. The neutralizing antibodies induced by current vaccines must be broadened and of a much higher titer to prevent severe disease and death by this variant, especially considering the lack of an Omicron-specific vaccine. A two-dose vaccination plus booster shot program results in the induction of much higher neutralizing antibody titers, and is effective against Omicron. Therefore, in countries with high levels of circulating virus, vaccination and booster shots are critical for reducing the impact of future Omicron waves. Based on the currently available data, it seems that different vaccine platforms provide distinct protection against the Omicron variant. At present, mRNA-based vaccines seem to provide higher adaptive humoral protection than other platforms. In addition, mRNA-based booster vaccination in individuals primed with two doses of either mRNA or inactivated viral vaccinations develop significant antibody responses against the Omicron variant. Nevertheless, since data supporting this notion are still limited, it is important to be careful when making decisions. In addition, a thorough investigation of the activity of adaptive cellular immune responses such as T cells (cytotoxic and helper) in response to Omicron infection might provide insights on this matter. Whether the activated cellular adaptive immunity obtained via vaccination or previous infection plays a crucial role in the prevention of infection or severe disease by Omicron remains unclear. Vaccinated individuals may retain T cell immunity (CD4+ or CD8+) against the SARS-CoV-2 Omicron variant for up to 6 months, perhaps compensating for the lack of neutralizing antibodies. More research is urgently needed to determine how effective vaccination is at preventing symptomatic and asymptomatic disease by the Omicron variant, and which platforms provide the best protective adaptive signatures once used as booster shots because without a booster dose, there is no immunity against Omicron.

Acknowledgments

All the authors acknowledge and thank their respective Institutes and Universities.

Author contributions

All the authors contributed significantly to this manuscript. RKM, VK, AKS, NAE and KD conceptualized the manuscript. RKM wrote the first draft with input from KD, VK, AKS, RT, NAE, FN, TAM, CC. Authors RKM, NAE, FN, KD, CC, TAM, VK and PAD reviewed and updated the manuscript. All authors contributed to revisions and approved the final manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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