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Review Article

Efficacy of COVID-19 Vaccines against the Omicron Variant of SARS-CoV-2: A Review

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variant of concern has been the dominant cause of worldwide COVID-19 cases since 2022. All Omicron sub-lineage viruses have demonstrated high transmissibility and an ability to escape vaccine-induced immunity. While first-generation vaccines, including monovalent vaccines, continue to provide protection against severe disease, hospitalization, and mortality, their efficacy against Omicron subvariants remains sparse. These vaccines have also been associated with rapidly waning protection against primary COVID-19 and COVID-19 reinfections conferred by evolving Omicron sub-lineages. This led to the development and deployment of updated vaccines and the introduction of the bivalent booster. Through this review, we highlight the brief journey of the variants of concern leading to the dominance of Omicron and the effectiveness of the key vaccines against these variants, including the updated (bivalent) boosters.

Introduction

The pathogenic agent of Coronavirus disease-2019 (COVID-19), severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is an enveloped virion that contains a positive sense single strand of ribonucleic acid (RNA).[1] Despite the unique feature of proof-reading polymerase activity during replication, the RNA virus is associated with a high mutation rate due to the uncontrolled viral replication facilitated by interferons of the infected host. With every round of infection, the absolute quantity of mutations increases and clusters within populations before spreading across populations by way of global travel and migration activities. According to the World Health Organization (WHO) and Center for Disease Control and Prevention, the declared variants of concern (VOCs) for SARS-CoV-2 include the Alpha, Beta, Gamma, Delta, and Omicron isolates of SARS-CoV-2. Lineage B.1.1.7, Alpha, was designated as the first VOC by the WHO, and continues to diverge into a monophyletic clade. In context to these aforementioned VOCs, SARS-CoV-2 has defied a ladder paradigm of viral evolution,[2] as these variants have not antigenically descended from another in a progressive fashion. The dominant consequences of emerging mutant variants of SARS-CoV-2 include the possibility of new variants that may potentially bypass the standard diagnostic investigation protocol, impact disease severity, have faster transmissibility, and alter vaccine effectiveness.

Immunization has been recognized as a key pillar of disease prevention since the advent of vaccines. The development of the first vaccine by Edward Jenner for prevention of smallpox is a historical landmark in immunology. Dr. Jenner's published case studies on inoculation in 1798 demonstrated that artificially induced pathogenic exposure can effectively prevent disease when the body encounters the same pathogen in the future.[3] Vaccination elicits a tailored adaptive immune response when the body encounters the target pathogen.[4] The adaptive immune response progresses via T and B lymphocytes. Helper T cells recognize presenting pathogens and activate memory B cells, which bring about rapid replication of existing antigen specific antibodies to target, contain, and signal for the destruction of the presented pathogen.[4] Building on this knowledge, disease prevention was quickly recognized as one of the key strategies in curtailing the COVID-19 pandemic, resulting in the development and eventual approval of

Keywords: Bivalent COVID-19 vaccine; COVID-19 vaccination booster; COVID-19; Omicron; SARS-CoV-2.

Abbreviations: ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease-2019; FDA, US Federal Drug Administration; mRNA, messenger RNA; RBD, receptor-binding domain; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; WHO, World Health Organization; VOCs, variants of concern; VOI, variants of interest; VBM, variant being monitored; VOHC, variant of high consequence.

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the first-ever messenger RNA (mRNA) vaccine, by the US Federal Drug Administration (FDA).[5] Some key vaccines that were developed for COVID-19 include:

1. mRNA vaccines: BNT162b2/Pfizer and mRNA-1273/Moderna;
2. SARS-CoV-2 spike protein and Matrix-M adjuvant vaccine: NVX-CoV2373 (Novavax);
3. Adenovirus vector vaccine: Janssen/Ad26.COV2.S, ChadOx1 nCoV-19/AZD1222 (Oxford/AstraZeneca).

These vaccines elicit a specific immune response against the spike protein of SARS-CoV-2 to prevent the virion from host cell binding, fusion, and entry.[6–8] In the case of mRNA vaccines, the Pfizer (BNT162b2) and Moderna (mRNA-1273) vaccine efficiencies were reported to show an overall reduction following the emergence of the Omicron variant (as compared to the Delta variant) for adults who completed the primary immunization series, consisting of two doses.[9] Additionally, both mRNA vaccines were found to have a continually decreasing rate of effectiveness over time, following the last administration of a booster dose.[9] Following the onset and spread of the Omicron variant, Andrews *et al.* found that subjects who received two doses of the viral vector vaccine, ChADOx1(Oxford/AstraZeneca) had significantly reduced protective effect following the administration of a booster dose against the variant. The recombinant protein nanoparticle vaccine developed by Novavax (NVX-COV2373) was shown to similarly display a progressive reduction in neutralization antibody titers in adults administered with two and three doses, as the variant waves of SARS-CoV-2 progressed from the Beta to Omicron variants.[10]

While the deployment of SARS-CoV-2 vaccines have significantly reduced the disease burden globally, efficacy of these vaccines has been steadily declining as new mutagenic sequences of the virus compete and spread. In this context, it is pertinent to understand viral evolution and its impact on vaccine efficacy.

Evolution of SARS-CoV-2 Variants

SARS-CoV-2, like other viruses, continues to evolve over time through genetic recombination or genetic mutations. While some of these changes do not affect the viral properties, other mutations affect the virulence, transmissibility, risk of reinfection, or other factors, including vaccine efficacy, immune evasion, and diagnosis. The global public health organizations WHO and SARS-CoV-2 Interagency group have been monitoring these viral mutations through viral genetic sequence-based surveillance and epidemiological investigations. They characterize these variants as VOC and variants of interest (VOI), variant being monitored (VBM), and variant of high consequence (VOHC) to prioritize monitoring, research, and response to the COVID-19 pandemic. The naming and tracking of the genetic variants for SARS-CoV-2 is based on the Greek alphabet and designated by the 'Technical Advisory Group on Virus Evolution', representatives from WHO COVID-19 reference laboratory network, Global Initiative on Sharing All Influenza Data (GISAID), Nextstrain, and Pango, as well as experts in virological, microbial nomenclature, and communication from several countries.

VOI is categorized by changes in genetic markers that affect the receptor binding and neutralization ability by antibodies from previous infection or vaccination. Currently no SARS-CoV-2 variants are designated as VOI. VOC is categorized for variants that exhibit increase in transmissibility, significant reduction in neutralizing antibodies generated during previous infection and vaccination, reduced effectiveness of therapeutics or vaccines, diagnosis evasion, and more severe disease. The Omicron variant is currently classified as a VOC. Previously circulating variants - Alpha, Beta, Gamma, Delta, and Epsilon were designated as VOC but later downgraded as a VBM based on emerging evidence suggesting that while being associated with severe disease and higher transmissibility, they are no longer detectable or circulating at very low levels, thus posing no risk to public health. VOHC is used to categorize strains with clear evidence of significantly reduced or failure in preventive and medical countermeasures compared to previous strains. Currently, no SARS-CoV-2 strain has been designated under this category.[3] The progression of the SARS-CoV-2 pandemic has been delineated by five dominant variants, driven by the Alpha (B.1.1.7 and Q lineages), Beta (B.1.351 and descendants), Gamma (P.1 and descendent lineages), Delta (B.1.617.2 and AY lineages), and Omicron (B.1.1.529, BA.1, BA.1.1, BA.2, BA.3, BA.4, BA.5, XBB.1.5, B.Q1.1, B.Q.1, XBB, C.H.1.1, B.N.1 lineages) variants.

Previous VOCs (Alpha, Beta, Gamma, and Delta)

The Alpha variant (B.1.1.7 and Q lineages) emerged in September 2020, became the dominant variant in the United Kingdom (UK) by the end of 2020, and was designated a VOC from December 2020 until March 2022.[11] The Alpha variant was found to be 24–33% more transmissible,[12] leading to 47–57% higher hospitalization and 44.74% higher mortality[12] than the wild-type SARS-CoV-2 (ancestral strain). It was found to have 17 mutations in the viral genome, eight of which manifest in the spike protein - characteristically N501K, D614G, P681H, mutations, resulting in screening failures, immune escape, and a greater receptor-binding domain (RBD) binding affinity to angiotensin-converting enzyme 2 (ACE2) host receptor cells.[13,14] The Alpha B.1.1.7 variant is a descendent of the early mutation D614G and was found early in the pandemic as it emerged from China, allowing higher infectivity and increased virion density.[15]

The Beta variant (B.1.351 and descendants) was originally documented in May 2020 in South Africa and designated a VOC from December 2020 until March 2022.[16] The variant was found to be 20–30% more transmissible,[11] with eight mutations in the spike regions, four of particular concern that enhanced the attachment of the variant virion to human cells. While the N501Y and D614G mutations were common across the Alpha variant as well, E484K, K417N, and A701V were associated with the Beta variant.[14,17]

A third Gamma variant (P.1 and descendent lineages) was designated a VOC around a similar timeline form January 2021, after being detected first in Brazil in November 2020, and was reclassified as a VBM by March 2022.[16] It was noted to have 17 mutations, 10 in the spike protein. Some notable mutations included the N501Y, D614G, and E484K common to the Beta strain and K417T and H655Y unique to the gamma variant.[14] There were higher transmission rates (29–48%) associated with this variant, including among previously recovered individuals,[11] and higher hospitalization and associated mortality relative to non-VOCs and the ancestral SARS-CoV-2 strain.[18] Of the four lineages of the Gamma variant, P.4 was found to host a L452R mutation in the spike RBD region, also key to the Delta variant.[19]

The Delta B.1.617.2 variant, first detected in Oct 2020 in India, was found to be highly transmissible (76–117%),[11] and remained as the globally dominant variant of the latter half of 2021, displacing previous VOCs in the majority of regions. It was designated a VOC by May 2021[16] and hosted at least 13 mutations, with four concerning mutations in the spike protein - L452R, P681R, D614G (shared with other highly transmissible VOCs) and T478K.[14] The

former two mutations significantly affected the viral attachment to the host cell, infectivity, and decreased recognition by the host immune system.[20] Studies from the UK (per the SPI-M-O Consensus statement on COVID-19) suggested 40–60% higher transmissibility compared to the Alpha variant and reduced vaccine efficacy. The Delta variant was downgraded as a previous VOC in June 2022 by the WHO.[16]

Current VOC (Omicron)

The Omicron variants (XBB.1.5, XBB, B.Q1.1, B.Q.1, C.H.1.1, B.N.1, BA.5, BA.7, BA.2, BA.5.2.6, BF.11, BA.2.75, BA.2.75.2, BA. 4.6, B.1.1.529, BA.2.12.1, BA.4, and BA.1.1 lineages), are currently designated VOCs with predominant worldwide circulation. Omicron is marked by a distinct clade from the ancestral branch of SARS-CoV-2, as its emergence did not evolve from the previously circulating Delta variant. It is characterized with increased transmissibility and significant immune evasion compared with the early wild-type strain and the four previously identified VOCs.[21] Five sub-lineages of Omicron have been identified, with the initial three sister lineages BA.1, BA.2, and BA.3, later followed by BA.4 and BA.5.[22] The Omicron variant was first identified as a unique mutagenic sequence of SARS-CoV-2 in South Africa in November 2021 and rapidly spread to over 140 countries within seven weeks.[23] It is the most antigenically divergent of all variants, carrying over 50 unique characteristic mutations, over 30 of which result in changes to the spike protein compared to the Alpha variant.[24,25]

The first dominant Omicron variant sub-lineage, B.1.1.529 (BA.1) is characterized by 37 mutations.[26] BA.1, BA.2, and BA.3 share 21 common mutations, 11 of which are contained in the RBD and theorized to contribute to a larger ACE2 affinity due to an overall increase in positive electrostatic surface potential.[27] BA.2 and BA.3 sub-lineages branch off the same node of the B.1.1 subvariant, and have gone on to mutate independently along separate branches.[22] The BA.2 sub-lineage genome contains 28 unique mutations not present in BA.1, four of which are located on the RBD.[28] BA.4 and BA.5, which contain identical spike proteins, are marked by similar deletion in the spike, also found in the Alpha and BA.1 lineage.[22] As of December 2022, the XBB 1.5 VOC has become a predominant variant, outcompeting the other Omicron subvariants. The relative effective reproduction number of XBB.1.5 is more than 1.2-fold higher than the parental XBB lineage.[29] Additionally, the binding affinity to host ACE2 and infectivity of XBB.1.5 was found to be 4.3-fold and 3.3-fold higher, by acquiring the S:F486P substitution to augment ACE2 binding affinity.[29] Overall, the immune resistance, infectivity, and transmissibility was enhanced with this variant.[29,30] The Omicron variant is associated with higher infectivity, antigenic changes that mediate antibody escape from an existing pre-immune population, and was found to have a transmission rate 3.4 times higher than that of the Delta variant and 2.1 times higher than other variants in the United States (US).[31] Interestingly, the Omicron sub-lineages are able to evade immunity in both convalescent and fully vaccinated individuals.[30,32] Convalescent sera from individuals infected with BA.1 showed significant reduction in neutralizing antibodies against the BA.4 and BA.5 strains.[33] They harbor the L452Q/R mutation that allows evasion from humoral immunity.[14,34]

The SARS-CoV-2 virion is surrounded by a lipid bilayer, decorated with glycosylated protruding class fusion proteins called spike proteins that mediate virion profusion. The Omicron mutation has been found to exhibit a favorable epistasis in the RBD. The presence of both Q498R and N501Y mutations in the Omicron variant has been found to result in a 2-fold increase in spike protein binding affinity to the ACE2, as compared to the Alpha variant. Studies have shown that Omicron's structural gene variations affect infectivity. This assessment was made by analyzing all four structural proteins of the virion by developing SARS-CoV-2 virus-like particles (SC2-VLPs), indicating that the spike, nucleocapsid, membrane, and envelope structural proteins all contained notable mutations.[35,36] The VLP-mediated study found that the spike and nucleocapsid protein mutations of Omicron contribute to an increase in infectivity, while the membrane and envelope gene variants compromise infectivity relative to previous viral variants.[35,36] Viral immune evasion can occur through three mechanisms. A major ramification of the emergence and evolution of Omicron is the vaccine-elicited immune and anti-spike monoclonal antibody escape. The Omicron variant is characterized by a cluster of mutations resulting in alternate structural conformations of the spike protein, the primary target for monoclonal antibody therapeutics.[24] Monoclonal antibody therapeutics for SARS CoV-2 can be escaped by a single mutation, as they bind to a single epitope on the S protein of the virion. On the other hand, polyclonal antibodies are more resistant to mutation induced escape in principle, as they bind to multiple regions of the key viral proteins. Thus, the Omicron variant escaped the neutralization activity of convalescent plasma and two doses of vaccine-induced serum more easily than the ancestral strain and other VOCs, including Beta and Delta.[37]

Impact of Viral Evolution on Vaccine Efficacy

Currently 50 vaccines for COVID-19 have been approved worldwide (https://covid19.trackvaccines.org/vaccines/). The WHO has listed nine vaccines for emergency use and for travel to the US - *Comirnaty* (Pfizer-BioNTech), *Spikevax* (Moderna), *Vaxzevria* (AstraZeneca), *Covaxin*, *Covishield*, *BIBP*/Sinopharm, *CoronaVac* (Sinovac), *Nuvaxovid* (Novavax), and *Covovax*.[38] In the US, three major types of COVID-19 vaccines have been approved or authorized for use by the FDA – 1) mRNA vaccines: *Cominarty* (Pfizer-BioNTech) and *Spikevax* (Moderna); 2) protein subunit vaccine: *Novavax*; and 3) viral vector vaccine: Jannsen/J&J. The antigenic target for the vaccines is the spike protein RBD on the virus surface. The host generated antibodies can attach to this target thus preventing attachment to the host cell ACE2 receptor and neutralizing the virus.[39] The focus of vaccine development has been to prevent severe disease and mortality, and while many of the vaccines have shown robust seroconversion towards this effect, studies have shown that the immune response wanes over time and is affected by the evolving viral strains. For this review, we have only selected some key vaccines based on the available literature demonstrating the impact of viral evolution on vaccine efficacy.

Effectiveness of primary vaccination series

While conventional vaccines such as live attenuated, killed, and subunit vaccines have provided successful protection against a variety of pathogens, one of the obstacles associated with conferring protection against infectious agents is combating pathogens that have the ability to evade the adaptive immune system.[40] Additionally, the rapid development and large-scale deployment of new vaccines has been limited by conventional methodology, as witnessed during the early days of the COVID-19 pandemic, thus paving the way for mRNA vaccines.[41] mRNA based approaches had been promising alternatives, and the first published report of an mRNA vaccine showed that protein production could be detected in a mouse model.[42] However, subsequent animal studies

showed high innate immunogenicity, mRNA instability, and inefficient *in vivo* delivery leading to concerns for human application.[43]

Technological inventions over the past decade have led to promising developments in application of nucleic acid therapeutics in humans.[41] Research demonstrated that to achieve an antigen-specific immune response the synthetic mRNA in a vaccine would need to enter the cytosol through the plasma membrane, but that the exonuclease catalyzed decay of mRNA in the cytosol would be a challenge for mRNA vaccine development.[44] In recent years, the potential for exogenous mRNA or mRNA synthesized *in vitro* to become an expression vector for antigenic proteins have been recognized, but the mechanisms of mRNA delivery, immunity at the cellular level, and measurement of mRNA uptake into the cell have been ongoing subjects of study.[45] Designs proposed for mRNA vaccines were modeled after eukaryotic mRNA and an open reading frame with a cap, a poly(A) tail, and 5′ and 3′ untranslated regions, which all contribute to mRNA stability.[44] mRNA vaccines have some key advantages over live, attenuated and subunit vaccines. mRNA vaccines are non-integrating and non-infectious platforms with minimal insertional mutagenesis risk, as they are degraded by normal cellular processes. Additionally, the ease of delivery modifications can be used to modulate the safety profile and half-life of vaccines. mRNA vaccines have a key advantage for inexpensive, scalable production in short timelines due to high yields through *in vitro* transcriptional processes.[41] The COVID-19 mRNA vaccines are delivered to the deltoid muscle site, then transit to the myocyte cytosol and ribosomes to undergo translation to produce the spike protein which induces host antibody and cell mediated immune response, including neutralizing antibodies, after entering the circulation.[46,47] To ensure safe and successful delivery of the mRNA for intracellular uptake, they are encapsulated in lipid nanoparticles to facilitate the process.[48,49]

Two mRNA vaccines were developed to combat the COVID-19 pandemic. Moderna's COVID-19 primary series monovalent vaccine (mRNA-1273) received emergency use authorization (EUA) from the FDA in December 2020, delivering 100 µg mRNA in each dose. The vaccination schedule is two doses given at a 28-day interval for individuals 18 years and older. Preliminary data from a phase 1, dose-escalation, open-label trial showed immune responses in all trial participants who were placed in three dosage groups (25, 100, and 250 µg).[50] CD4 T cell responses and expression of T helper 1 (Th1) cytokines were noted, and the authors concluded that the 100 µg dose had a better reactogenicity profile while still maintaining a high level of Th1-based CD4 T cell responses.[50] Notably, the preliminary report addresses the issue of sufficient mRNA uptake and some of its mechanisms of action. The efficacy and safety assessment published three months later demonstrated that the vaccine efficacy for various demographic subgroups ranged from 86.4% to 97.5% with a 95% confidence interval (CI).[51] Pfizer's primary series monovalent vaccine (BNT162b2) received EUA during the same timeline for individuals 12 years and older, delivering 30 µg mRNA in each dose with a vaccination schedule of two doses to be administered in a 21-day interval.[51] Both BNT162b2 and mRNA-1273 utilize lipid nanoparticles (LNPs) for the delivery of the full length spike proline substitutions.[51,52] According to the published data at the time for subgroups, vaccine efficacy for BNT162b2 ranged from 87.7% to 100% (95% CI).[53] T follicular helper cells and Th1-type CD4 T cell responses were reported in early experiments and data for BNT162b2, suggesting that a TH1-type CD4 T cell response may be a general effect of the mRNA COVID-19 candidate vaccines that use LNPs for delivery.[53] These two candidate monovalent vaccines were subsequently authorized for use in children younger than 12 years of age, with two doses recommended to be given in a 4–8 week interval.[54]

The immune response associated with these vaccines was initially thought to be largely humoral, triggering B cells to promote the production of neutralizing antibodies. Although, a significant body of research has since shown that these vaccines reprogram both the innate and adaptive immune responses, including CD4+ and CD8+ T cells against SARS-CoV-2.[55,56] Data from clinical trials of the primary series monovalent vaccination of mRNA-1273 and BNT162b2 showed 94.1% and 95% efficacy, respectively, in preventing symptomatic and severe COVID-19 disease.[51,52] However, this immune response was variable across different population groups (such as those with underlying immunocompromising conditions or treatments),[57] duration since last vaccination (waning immunity across all age groups over time),[58] and the new variants of SARS-CoV-2[9,59,60] that have evolved. Both vaccines were able to provide comparable efficacy (□91%) against the Alpha variant of the virus when sera from vaccinated individuals was studied through virus-neutralization assays.[59,61] Although there was a 6.4-fold reduction in neutralization antibody titers against the Beta variant against infection, but effectiveness has remained high against hospitalization or severe disease.[59] By August 2021, the Delta variant became predominant and vaccine effectiveness decreased to about 66%.[62–64] Studies show that a key feature of the new VOC was reduction in post-vaccination protection, as a factor of duration since the last vaccine dose, underlying immunocompromised status and others factors.[6,65] Based on a significant body of research, the Center for Disease Control and Prevention recommended a third and fourth dose for protection against breakthrough infections and severe disease owing to waning immunity associated with the aforementioned factors.[6]

Effectiveness of bivalent vaccines

In November 2021, the Omicron variant emerged as the most antigenically diverse and quickly dominated new infection worldwide.[66] In contrast to other variants, the Omicron variants and subvariants have outperformed and significantly evaded immunity induced by the monovalent vaccination; leading to a higher number of breakthrough infections.[67,68] A study from December 2021 suggested that vaccine efficacy against hospitalization for COVID-19 caused by the Omicron variant (B.1.1.529) decreased to 70% for the monovalent/primary two-dose dose series of BNT162b2.[69] Another study found that vaccine effectiveness of the monovalent/primary two-dose series of the BNT162b2 and a second (booster) dose of the Ad26.COV2.S vaccine against COVID-19-related hospitalization caused by the Omicron variant (B.1.1.529) was 70 and 72% respectively, 1 to 2 months after the vaccine was administered.[70] A recent study from October 2022, showed that effectiveness and durability of the BNT162b2 vaccine (monovalent/primary two-dose series plus a booster) against hospitalization caused by BA.1 or BA.2 and BA.4 or BA.5 COVID-19 was further diminished to 56.3%.[71] The study also noted that boosting with a third dose of the monovalent vaccine was effective against severe disease caused by all four sub-lineages at 1 to 2 months.[71]

The efficacy of a third or fourth dose of monovalent vaccine was much reduced and limited primarily to protection against severe disease, while Omicron specific breakthrough infections were observed in a significant number of individuals.[72,73] In a study of 274 healthcare workers, a fourth dose of the monovalent mRNA vaccine yielded similar seroconversion and comparable levels of Omicron-specific neutralizing antibodies in contrast to the peak

response one month after the third dose. These results suggest that mRNA vaccines confer optimal humoral immunogenicity after three doses and that antibody titers can be restored by a fourth dose.[72]

The primary series of vaccinations have largely been ineffective against the Omicron variants and sub-lineages. The Omicron variants also showed reduced neutralization by sera of individuals vaccinated with triple doses of ChAdOx1 (Oxford/AstraZeneca) and Ad26.COV2.S (Johnson & Johnson), among other primary series vaccines.[74,75] Studies have shown that across vaccine types either primary homologous vaccination or heterologous boosting does not seem to affect the breakthrough infection incidence associated with Omicron; although a heterologous boosting, when having received a primary live vector or attenuated vaccine, may allow for more robust humoral immune responses and better protection against severe disease.[73,76–79]

SARS-CoV-2 has a propensity to rapidly mutate and compete against the host immune system to evade neutralization and transmission.[80] While the primary series of vaccines have been able to drive a robust immune response against the previous VOC, including being boosted by a third or fourth dose (homologous or heterologous) in some individuals, the Omicron variants have largely evaded this conferred protection. The BA.4 and BA.5 sub-lineages were also seen to evade neutralizing immunity when sera from BA.1 infected vaccinated and unvaccinated individuals was tested.[81] This low neutralization gap could significantly affect the unvaccinated and immunocompromised populations against symptomatic and severe disease.[81] This prompted adjustments to the antigenic target in the monovalent mRNA vaccines that encodes the spike protein of the ancestral SARS-CoV-2 (Wuhan-HU-1 isolate), to address the mutational changes associated with the newer viral variants.[82]

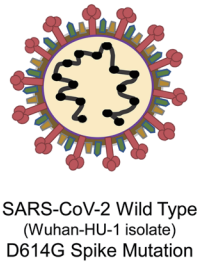
A first version of the bivalent booster containing the gene encoding the spike protein for BA.1 (25 ug) and the ancestral strain (25 ug) was authorized for use in multiple countries. It elicited strong neutralizing antibody responses against BA.1 and the epidemiologically dominant BA.4 and BA.5 subvariants.[83] Another study showed robust neutralizing antibody response against the BA.2.75 subvariant, regardless of previous SARS-CoV-2 infection.[84] By August 2022, the FDA had authorized Moderna and Pfizer's modified bivalent vaccines, with equal amounts of the mRNA encoding the original/ancestral strain and Omicron BA.4/BA.5 strains of SARS-CoV-2, to provide broader, durable, and potent protection (https://www.fda.gov/news-events/fda-newsroom/press-announcements). This strategy can help incur greater combined protection against both earlier variants and the current VOCs including its sub-lineages, even as the virus continues to evolve, in contrast to the monovalent booster that targeted only the original viral strain.[85] Muik *et al.* demonstrated that sera from triple mRNA vaccinated individuals with subsequent breakthrough infection through Omicron BA.4/BA.5 showed cross-neutralizing activity against previous Omicron variants BA.1, BA.2, BA.2.12.1, and BA.4/BA.5 itself. Additional studies in mice showed that when the BA.4/BA.5-adapted mRNA booster was administered after the primary series mRNA vaccine, a broader cross-neutralizing activity was noted compared to a BA.1-adapted booster.[86] Further, in naïve mice, primary immunization with the modified bivalent vaccine induced strong cross-neutralizing activity against Omicron VOCs and previous variants.[86] At the time of writing this review, a few papers have elucidated the efficacy of this updated/modified booster in humans. Tenforde *et al.* estimated the effectiveness of the updated booster in preventing severe disease among immunocompetent adults. The study found that in the described study cohort, administration of this booster dose provided additional protection against COVID-19 associated emergency department/urgent care encounters and hospitalizations in persons who previously received 2, 3, or 4 monovalent vaccine doses. Additionally, the study indicated that the effectiveness of the bivalent vaccine was evident relative to the waned immunity associated with previous monovalent vaccine doses (either 2 or 3 or 4 doses).[87] In a phase 2/3 clinical trial, Chalkias *et al.* studied the safety and immunogenicity of 50 µg of the updated bivalent vaccine compared against 50 µg of the mRNA-1273 (monovalent vaccine) as a second booster in healthy adults, after having received the two dose primary series monovalent vaccination.[88] They found that the neutralizing titer achieved against BA.4/BA.5 and ancestral strain at day 29 post-boost was higher in participants who received the updated bivalent booster compared to the monovalent booster.[88] Additionally, a random subset of participants were selected from the updated bivalent booster group who exhibited cross-neutralization against the emerging Omicron variants BQ.1.1 and XBB.1.[88] Kurhade *et al.* studied the effectiveness of the 2, 3, 4 dosed monovalent and updated bivalent vaccinated individuals in neutralizing the BA.4, BA.5 and newly emerged BA.2.75.2, BQ.1.1, or XBB.1.[89] The study found that while the sera from individuals receiving the updated bivalent vaccine was effective in producing high titers of neutralizing antibodies for BA.4/BA.5 (contrasting the monovalent vaccinated sera), they did not produce robust neutralization against the newer emerging variants BA.2.75.2, BQ.1.1, or XBB.1.[89] While further human studies will be required to confirm the robustness of the updated bivalent booster, it is pertinent to understand the unpredictability of viral evolution and its effect on vaccine efficacy. However, current data support a vaccine upgrade strategy that matches newer emerging SARS-CoV-2 variants, bolstering protection against future VOC. Table 1 summarizes the effectiveness of key COVID-19 vaccines described above[9,70,71,86,90-95], and a summary of the VOCs, key spike mutations, and their effects and vaccine efficacy is described in Figure 1.

Future perspectives and conclusions

Multiple vaccines that were developed in response to the COVID-19 pandemic and were based on the spike protein of the ancestral strain of SARS-CoV-2 have proven effectiveness at protecting against severe disease caused by previous VOCs such as the Alpha, Beta, Gamma, and Delta strains of SARS-CoV-2. However, a reduction in effectiveness was observed with the Delta variant, prompting recommendation of a booster dose of the primary homologous or heterologous vaccine to circumvent the waning immune response associated with evolving viral strains, duration since last vaccine, and individuals who are immunocompromised, among others. With evolution of the Omicron variant, immune evasion and significantly decreased vaccine effectiveness has become a key issue for effective disease management. While there have been no newer variants of concern, there is a prevailing pattern of the virus becoming milder, largely due to improved vaccine-induced immune responses. The bivalent vaccines evenly target the ancestral strain of SARS-CoV-2 and Omicron strains BA.4 and BA.5, which were predominant circulating VOCs when the vaccines were first introduced. However, as of April 2023, the FDA announced a rescind of use order for both Pfizer-BioNTech and Moderna's monovalent vaccines, stating that only the bivalent

Table 1. Efficacy of some key COVID-19 vaccines against the BA.1 and BA.2 Omicron subvariants in adults

Vaccine Classification	Vaccine and Manufacturer	Effectiveness range against infection/symptomatic for two-dose series	Effectiveness range against infection/symptomatic two-dose series, followed by a booster dose	Effectiveness range against hospitalization	Advantages/Limitations
mRNA	BNT162b2 (COMIRNATY/ Pfizer BioNTech)	65.5% 2–4 weeks after 2nd dose of Pfizer 8.8% 25 weeks after 2nd dose of Pfizer.[90] Pfizer-BioNTech BA.4/BA.5 bivalent vaccine effectiveness was 83% 7–29 days after vaccination, and 81% 60–89 days after vaccination.[91]	65.5–74% respectively, 2 weeks to 2 months after mRNA (either Moderna or Pfizer) booster.[70,71] 45–64% for 5–10 weeks after mRNA (either Moderna or Pfizer) booster.[90]	BNT162b2 vaccine (monovalent/ primary two-dose series plus a booster) against hospitalization, caused by BA.1 or BA.2 and BA.4 or BA.5 COVID-19, was found to be 56.3%.[71]	*Advantage*: Production platform for mRNA based vaccines is flexible. *Limitation*: Half-life stability of mRNA is short, lack of thermostability has been observed. Shelf life is up to 9 months at ultra-cold storage and transportation of −80 °C to −60 °C (Per CDC's Vaccine Storage and handling toolkit).
	mRNA-1273 (SPIKEVAX/ Moderna)	75.1% for 2–4 weeks after second dose of Moderna.[71,90] 14.9% 25 weeks after 2nd dose of Moderna.[90]	65–66% for 2–4 weeks after mRNA (either Moderna or Pfizer) booster.[90]	Vaccine effectiveness after one bivalent booster, against severe infections resulting in hospitalization caused by omicron BA.4.6, BA.5, BQ.1, and BQ.1.1 was found to be 61.8%.[92]	Effectiveness of the vaccine is reduced against infection with BA.2, BA.2.12.1, BA.4 and BA.5, 14–30 days post fourth dose, disappearing beyond 90 days for all sub variants.[93]
Adenovirus vector (Recombinant)	Ad26.COV2.S/ Janssen			Ad26.COV2.S with homologous booster administered 6–9 months after primary single dose vaccination provided more than 80% protection against hospitalization.[94] 55%- 74%, effectiveness within 2 weeks to 2 months after the second dose administration.[95] Effectiveness against hospitalization after the booster dose of homologous 2nd dose of Janssen vaccine and heterologous mRNA booster shot was 54% and 79%.[95]	*Advantages*: A single dose vaccine provided significant protection with earlier VOC. *Limitation*: The FDA determined that the risk of thrombosis with thrombocytopenia syndrome warranted limiting the authorized use of the vaccine (https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-limits-use-janssen-covid-19-vaccine-certain-individuals).
Adenovirus vector	ChadOx1	39.2–57.1% for 2–4 weeks after 2nd dose of ChAdOx1 nCoV-19.[9]	44.4–64.6% 2–4 weeks after booster dose of ChAdOx1 nCoV-19. 34.3–56.7% for 5–9 weeks after booster dose of ChAdOx1 nCoV-19.[9]		*Advantage*: Viral vector-based vaccine follows the natural pathway of infection elicited immunity *Limitation*: Administration may be redundant for previously infected individuals, with existing antibodies
Adenovirus vector	nCoV-19/ AZD1222 (Oxford/ AstraZeneca)	After the second vaccine shot: 64 or 67% effectiveness.[86]			*Limitation*: Shelf life is up to 6 months at cold storage and transportation of 2 °C to 8 °C (Per CDC's Vaccine Storage and handling toolkit).



Variant of Concern & PANGO Lineage	VOC Designation Timeline	Characteristic Spike Mutations	Consequential Effects	Primary Vaccine (based on SARS-CoV-2 Wild Type) Efficacy
Alpha (B.1.1.7)	December 2020 – March 2022	N501Y, D614G,P681H	24-33% more transmissible, 47-57% higher hospitalization than Wuhan strain. Higher infectivity, increased virion density	Minimal reduction in vaccine efficacy – infection prevention, severe disease and mortality
Beta (B.1.351)	December 2020 – March 2022	N501Y, D614G, E484K, K417N, A701V	20-30% more transmissible. Enhanced attachment to host ACE2	Minimal to some efficacy reduction against severe disease
Gamma (P.1)	January 2021 – March 2022	N501Y, D614G, E484K, K417T, H655Y, L452R	29-48% more transmissible. Higher hospitalization and mortality in non-vaccinated, vulnerable groups	Minimal to some efficacy reduction against severe disease
Delta (B.1.617.2)	May 2021 – June 2022	N501Y, P681R, L452R, T478K	40-60% higher transmissibility than alpha. Higher hospitalization and mortality. Increased viral attachment, infectivity and immune evasion	Efficacy reduction against infection prevention and severe disease in individuals with waning immunity and vulnerable groups
Omicron (XBB. 1.5, BQ.1.1, BQ. 1, XBB, CH. 1.1, BN.1, BA.5, BA.7, BA.2, BA. 5.2.6, BF. 11, BA. 2.75, BA. 2.75.2, BA. 4.6, B.1.1.529, BA. 2.12.1, BA. 4, BA.1.1 lineages)	November 2021 – Current	N501Y, D614G, K417N, P681H, T478K, L452R, S477N, N440K,& others	3.4 times higher transmissibility than delta. Higher infectivity. Significant immune evasion	Efficacy reduction against symptomatic disease. Reduced immunogenicity against newer variants.

Fig. 1. Summary of the SARS-CoV-2 VOCs characteristic spike mutations and efficacy of primary immunization series.

booster should be administered.

Development of bivalent vaccines has marked the beginning of a new paradigm towards pandemic response. This strategy to regularly update the vaccine ingredient that target antigens to match the dominant circulating strain parallels an influenza-like situation with yearly effective vaccines. This approach can help overcoming issues with fading immunity and create robust protection particularly in vulnerable populations. Pan-variant vaccination and combination vaccines (COVID+Flu or COVID+Flu+RSV) are other strategies that can provide broad protection and are being explored by various major pharmaceutical pipelines, such as Pfizer (https://www.pfizer.com/science/drug-product-pipeline) and Moderna (https://www.modernatx.com/en-US/research/product-pipeline?slug=research%2Fproduct-pipeline). To achieve optimal immunization and achieve vaccine development that parallels viral evolution, there will be a need for continued variant and seroprevalence surveillance and real-world vaccine effectiveness monitoring.

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Conflict of interest

K.S.R has a patent pending based on disease surveillance and disease severity monitoring for COVID-19. All other authors declare no competing interests.

Author contributions

Manuscript concept and design (MR, KSR), acquisition of data (KSR, MS), analysis and interpretation of data (KSR, MS, MR), drafting of the manuscript (KSR, MS), critical revision of the manuscript for important intellectual content (MR, MS, KSR), administrative, technical, or material support (KSR, MR), and study supervision (MR, KSR). All authors have made a significant contribution to this study and have approved the final manuscript.

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