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REVIEW

Research progress on vaccine efficacy against SARS-CoV-2 variants of concern

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to circulate worldwide and a variety of variants have emerged. Variants of concern (VOC) designated by the World Health Organization (WHO) have triggered epidemic waves due to their strong infectivity or pathogenicity and potential immune escape, among other reasons. Although large-scale vaccination campaigns undertaken globally have contributed to the improved control of SARS-CoV-2, the efficacies of current vaccines against VOCs have declined to various degrees. In particular, the highly infectious Delta and Omicron variants have caused recent epidemics and prompted concerns about control measures. This review summarizes current VOCs, the protective efficacy of vaccines against VOCs, and the shortcomings in methods for evaluating vaccine efficacy. In addition, strategies for responding to variants are proposed for future epidemic prevention and control as well as for vaccine research and development.

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Introduction

Novel coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Expanding vaccination and building an immune barrier are the best strategies to combat the SARS-CoV-2 epidemic. In the past year, the number and speed of COVID-19 vaccine approvals have reached an unprecedented level. According to WHO statistics, there are 334 COVID-19 vaccine candidates worldwide as of 18 January 2022, of which 194 are in the preclinical stage and 140 are in clinical trials.[1] In the WHO guidance updated on November, 2021, 24 vaccines were in the WHO EUL/PQ evaluation process, and the Comirnaty vaccine is the first and the only COVID-19 vaccine to receive official approval for marketing.[2]

A number of SARS-CoV-2 variants have emerged and spread worldwide.[3,4] Some of the variants are characterized by increased infectivity, pathogenicity, or immune escape, resulting in a resurgence of the pandemic and possible failure of the immune barrier established by first-generation vaccines and previous infections.[5–9] These variants pose a global threat to health and safety and are listed as variants of concern (VOCs) by the WHO. By the end of 2021, the major variants designated as VOCs include Alpha (Pango lineages: B.1.1.7), Beta (Pango lineages: B.1.351), Gamma (Pango lineages: P.1), Delta (Pango lineages: B.1.617.2), and Omicron (Pango lineages: B.1.1.529).[10] Delta caused a resurgence of the pandemic in India and neighboring countries beginning in mid-2021, leading to a new wave of outbreaks worldwide, even in countries with high vaccination rates, such as the United Kingdom (UK) and Israel.[11] In UK, effectiveness of two doses of BNT162b2 against infection with Delta was 88%, compared to 94% for Alpha.[12] Just a few months after Delta became the dominant strain, the Omicron variant, which was added to the VOC list on 26 November 2021, started to cause a new wave of SARS-CoV-2 circulation.[10]

The spread of VOCs has affected the actual protective efficacy of current first-generation vaccines to various degrees. The results of Phase III clinical trials of the Novartis (NVX-CoV2373), Johnson & Johnson (Ad26.COV2.S), and Oxford-AstraZeneca (ChAdOx1) vaccines in South Africa have shown that the vaccine efficacy (VE) against the local Beta variant is reduced to various degrees.[13–15] For example, the protective efficacy of the ChAdOx1 vaccine against mild to moderate illness with Beta is only 10%.[13] Data from Qatar showed that the Pfizer/BioNTech (BNT162b2) vaccine confers 87% protection against infection with Alpha and 72% against Beta.[16] In Israel, the overall efficacy against infection of vaccines fell from 95% to 39% with the emergence of the Delta variant, with continued recent declines.[17,18] During the period in which Omicron was dominant, the effectiveness of two doses of the BNT162b2 vaccine against hospitalization for Covid-19 was significantly reduced from 93% in the previous non-Omicron period to 70% in South Africa.[19] This decrease in the efficacy of emergency authorized vaccines against VOCs has raised concerns about the efficacy of these vaccines and the possibility of reinfection. Although approved COVID-19 vaccines are less effective against infection of VOCs, they remain highly effective in preventing severe illness and death. In this review, the properties of VOCs reported to date as well as the effects of the major variants on the protective efficacy of vaccines are summarized. Furthermore, strategies are proposed to deal with these variants.

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Etiological basis of the effects of VOCs on VE

The spike (S) protein is the most critical SARS-CoV-2 surface protein. Its *N*-terminal S1 domain contains a receptor-binding domain (RBD, 319–541 aa), of which 17 amino acids are in direct contact with human angiotensin I-converting enzyme 2 (hACE2) on the plasma membrane of target cells and mediates receptor recognition.[20] Three loops (N1, N3, and N5) in the *N*-terminal domain (NTD, 13–305 amino acids) constitute the supersite, to which all known anti-NTD antibodies bind.[21,22]

Given its key role in SARS-CoV-2 infection and adaptive immunity, the S protein is an important target site for neutralizing antibodies and the key target for vaccine design. Most of the vaccines listed by the WHO that are completed or undergoing clinical research are designed based on the genes encoding the S/RBD protein.[23] VOCs contain mutations at multiple sites in the RBD of the S gene, raising concerns about the protective efficacy of these vaccines. A crystal structure analysis of the B.1.351 triple mutant (417N-484K-501Y) RBD complexed with the monoclonal antibody P2C-1F11 by Zhang et al.[24] demonstrated that the K417N, E484K, and N501Y mutations in the RBD are the molecular determinants of antibody neutralization and receptor interactions. The lysine residue at position K417 forms a salt bridge with D30 in hACE2B;[20] this interaction is abolished in the K417T and K417N mutants. These results suggest that mutations at this site result in a decreased affinity for hACE2 in addition to escape from neutralizing antibodies.[25–27] The E484K mutation has received widespread attention owing to its ability to prevent neutralizing antibody binding.[28–31] *In vitro* neutralization assays of vaccine-induced immune sera and convalescent sera have confirmed that this mutation site is associated with immune escape.[29,32,33] Greaney et al.[34] found that E484K reduces the neutralizing potency of convalescent sera from some donors by 10-fold. After the coincubation of SARS-CoV-2 with convalescent plasma, the virus completely escapes neutralization on day 73 due to the E484 mutation.[35] The L452 R mutation in the RBD region is not only present in Delta but is also a key mutation in Epsilon (B.1.427/B.1.429) variants. This mutation decreases the neutralization potency of 14 of 34 RBD-specific monoclonal antibodies.[36] Computational and Cryo-EM structural analyses of the Omicron spike proteins have revealed that Q493K, G496S, Q498 R, and N501Y mutations increase the ACE2 binding affinity by forming new salt bridges and hydrogen bonds.[37–40] Current research and the design of modified vaccines for variants have focused on the mutation sites in the RBD region. Further preclinical and clinical studies are needed to determine the effects of modifications at these sites on the immunogenicity and cross-protection of the new generation of vaccines.

Introduction to VOCs designated by the WHO

Alpha variant

The Alpha variant was discovered in the UK in the fall of 2020 and became the dominant strain in the region in early 2021.[28] As of July, 2021, as many as 182 countries and regions reported the detection of Alpha, and the earliest positive samples can be traced back to September, 2020.[11,41] Alpha contains 17 amino acid mutations compared to the wild-type (WT) sequence, of which eight are located in the spike protein.[42] The N501Y mutation in the receptor binding domain may strengthen binding to the hACE2 receptor,[27,43] whereas the deletion within the NTDs (Δ69/70 HV) may increase infectivity.[44] The transmission rate of Alpha is approximately 43–90% higher than that of its predecessor lineage,[28] and its effective reproductive rate in the UK has increased by .4–.7.[45] Further analysis of contact tracing data suggested that infection with Alpha results in a 30–50% higher secondary attack rate than those of other variants.[46]

Breakthrough infections with Alpha in vaccinated individuals have been reported, emphasizing the need for caution regarding the protective efficacy of the authorized vaccines. Immune responses to SARS-CoV-2 reach to peak levels within 1–4 weeks after infection or vaccination and persist within 3–8 months.[47–50] Novazzi et al.[51] reported that two patients naturally infected with Alpha were reinfected with the same variant after 45–90 days. Loconsole et al.[52] reported that medical workers who received two doses of the BNT162b2 vaccine developed breakthrough infections, and their serum had high titers of specific IgG against the Alpha variant at the time of diagnosis. Nonetheless, clinical studies have reported that high vaccination rates with BNT162b2, ChAdOx1, NVX-CoV2373, and other vaccines in many countries confer >70% protection against symptomatic COVID-19 with Alpha.[53,54] During the Alpha outbreak in Israel, the efficacy of vaccines against SARS-CoV-2 infection in people aged 16 years and over was 95% (95% CI; 95–96%), and the efficacies against severe cases and deaths were 98% (95% CI; 97–98%) and 97% (95% CI; 96–97%), respectively.[17] Another widely used vaccine, ChAdOx1, reduces the *in vitro* neutralization activity against Alpha but still exhibits good efficacy, with overall rates of protection against symptomatic COVID-19 with Alpha and non-Alpha variants of 62% (95% CI; 37–77%) and 77% (95% CI; 65–85%), respectively.[53]

Beta variant

In December 2020, South Africa announced the detection of the Beta variant. As of July, 2021, 131 countries and regions have reported this variant, and the earliest samples can be traced back to October, 2020.[11,55] The three RBD mutations in Beta (K417N, E484K, and N501Y) may cause substantial functional changes including changes associated with pathogenicity. N501Y is also present in Alpha, whereas *in vitro* studies have confirmed that K417N and E484K are associated with immune escape of the Beta variant and can lead to the partial loss of monoclonal antibody neutralizing activity and decreased immune serum neutralizing activity.[25,26,28,29] Similarly, Beta has resulted in the emergence of superinfections and vaccine breakthrough infections. Staub et al.[56] reported four cases of Beta infection among healthcare workers who had been infected with non-Beta variants, with serum antibody titers of 25.2–131.0 U/mL before reinfection. Saha et al.[57] reported two cases of non-Beta infection among healthcare workers in Bangladesh who were reinfected with Beta as well as two cases of Beta infection after vaccinations with ChAdOx1; all four cases were mild.

The Beta variant poses a more serious threat to VE than Alpha, Gamma, and Delta.[58] In a Phase III clinical trial of the NVX-CoV2373 vaccine conducted in the UK, the effectiveness against symptomatic COVID-19 with Alpha was 89%,[59] whereas in a Phase 2a-b clinical trial conducted in South Africa, the effectiveness was 60% in HIV-negative populations and 49% in the general population.[15] The efficacies of the Ad26.COV2.S vaccine against moderate to severe COVID-19 are 72% in the United States and only 57% in South Africa.[60] In South Africa, a phase 1b-2 trial reported that the ChAdOx1 vaccine confers a relatively poor protection rate of only 10% against Beta, which is a significant decline from the previous overall efficacy of 68% against the early epidemic strain in the UK, Brazil, and South Africa.[12,55] In Qatar, individuals who received two doses of the BNT162b2 vaccine have a 75% lower probability of COVID-19 caused by Beta and an approximately 90% lower probability of COVID-19 caused by Alpha.[16] Although the actual efficacies of various vaccines against Beta vary, most vaccines in the EUL can still provide good protection, especially against critical illness and death.[61]

Gamma variant

Gamma is derived from the B.1.1.28 lineage and was first discovered by researchers from the Japanese National Institute of Infectious Disease in four travelers from Brazil. This variant emerged in northern Brazil in December 2020 and has been reported in 81 countries and regions.[11] The earliest sample can be traced back to November, 2020.[62] The RBD of Gamma contains the same three mutations observed in Beta (E484K, K417N/T, and N501Y), and its affinity for hACE2 is similarly increased.[63] Accordingly, Gamma has raised concerns worldwide owing to its potential to escape natural and vaccine-induced immunity. Faria et al.[64] integrated genomic and mortality data using a two-category dynamical model and estimated that the transmissibility of Gamma may be 1.7 to 2.4 times that of local non-Gamma strains.

As with other variants, the efficacy of vaccines against Gamma is a concern. Early infection with non-Gamma strains may only provide a protective efficacy of 54–79% against Gamma.[64] The neutralizing activity of Pfizer BNT162b2 and ChAdOx1vaccine immune sera against Gamma is better than that against Beta and similar to that against Alpha.[9,65] Chen et al.[66] systematically analyzed 56 studies evaluating the cross-neutralization ability of immune sera against VOCs and found that the neutralizing ability of natural infection or vaccine immune sera against Alpha, Beta, and Gamma decreased by 1.5, 8.7, and 5.0 times, respectively, compared to that of lineage B. In a phase III clinical trial of the Sinovac inactivated vaccine (CoronaVac) conducted in Turkey, the efficacy against symptomatic COVID-19 was 84%.[67] In a Phase III clinical trial conducted in Brazil, the overall VE was only 50%, which may be associated with the local Gamma variant. After the first epidemic peak, Iquitos, Peru had one of the highest rates of seroprevalence of anti-SARS-CoV-2 antibodies worldwide. Nevertheless, the city experienced a second wave starting in January 2021, probably due to the emergence of Gamma, which has shown higher transmissibility and reinfection rates.[68]

Delta variant

The Delta variant was first discovered in India in October 2020, began to spread rapidly in early April 2021, resulting in a third wave of outbreaks around the world.[69,70] As of July 2022, Delta has spread to at least 132 countries and regions.[11] On 11 May 2021, Delta was designated by the WHO as the fourth global novel coronavirus VOC after Alpha, Beta, and Gamma.[10] The mutation sites in Delta that have attracted the most attention are L452 R and E484Q in the RBD region. In particular, L452 R in the RBD of the Epsilon variant may improve the ability of the virus to invade cells and escape the immune system.[71] E484Q is similar to E484K in the South African and Brazilian variants and may enhance immune escape. Delta does not have a mutation at the E484 position in the RBD; however, it contains the T478K mutation, which may be associated with its strong infectivity. The Delta Plus (AY.1) variant has an additional K417N mutation, which lowers the affinity to hACE2 while conferring escape from neutralizing antibodies.[25,26] Delta exhibits stronger infectivity compared to those of Alpha, Beta, and Gamma. Allen et al.[72] conducted a matched case–control study and estimated that the odds ratio for household transmission was 1.64 among Delta variant cases (95% CI; 1.26–2.13, $p < .001$) compared to those of Alpha cases. Campbell et al.[73] indicated that the estimated increase in the transmissibility of Delta is 97% (95% CI; 76–117) relative to that of non-VOC/VOI, which is significantly higher than estimates of 29% (95% CI; 24–33%), 25% (95% CI; 20–30%), and 38% (95% CI; 29–48%) for Alpha, Beta, and Gamma, respectively. By combining models for the first and second pandemic waves in India, Yang et al.[74] predicted that Delta is 60% more infectious than the WT strain (95% CI; 46–81%) and immune escape occurred in 46% (95% CI: 0–68%) of individuals who were infected with the WT strain and developed specific immunity.

Many vaccine breakthrough infections have also been reported during the Delta pandemic. Sharma et al.[75] conducted a study of 325 healthcare workers in Delhi, India and found 37 cases of breakthrough infections (11%), most of which (94%) were mild. The estimated protective efficacies of the BNT162b2, mRNA-1273, and ChAdOx1 vaccines against infection with Delta are 56–88%, 72%, and 60–67%, respectively, which are slightly lower than the protective efficacies against Alpha (66–95%, 83%, and 66–64%, respectively).[12,17,76] However, the prevention of severe illness and death is a major parameter for evaluating VE. With the spread of the epidemic and the emergence of variants, the evaluation of COVID-19 VE may require more emphasis on critical illness and mortality. The case fatality rate for Delta is only 0.3% in the UK and is lower than the global average in other countries with high vaccination rates.[77] Public Health England has reported that the efficacy of the BNT162b2 and the ChAdOx1 vaccines after two doses against Delta-related hospitalization are 96% and 92%, respectively, which are very similar to the VE against Alpha-related hospitalization.[78]

Omicron variant

On 24 November 2021, South Africa reported the SARS-Cov-2 B.1.1.529 lineage to the WHO for the first time, and the mutant strain was assigned the name Omicron by the WHO 2 days later.[79] As of January, 2022, Omicron has spread to 171 countries and regions, causing the ongoing fourth wave of the COVID-19 epidemic.[1,80] Omicron carries more than 30 amino acid substitutions in the S protein, including 15 amino acid changes (G339D, S371 L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493K, G496S, Q498 R, N501Y, and Y505 H) in the RBD, covering almost all of the key mutations in the previous VOCs (Alpha, Beta, Gamma, and Delta).[37,40] These mutations enhance humoral immune evasion and have a huge impact on the effectiveness of vaccines and monoclonal antibody drugs.[81,82] The first epidemiological study of Omicron cases in Denmark provided insights into the early indications of severity. Of the first 785 Omicron cases in Denmark, 73% were symptomatic, 27% were asymptomatic, and 1% were hospitalized, including one case requiring intensive care and no deaths.[83] In the UK, based on the rate of S gene target failure (SGTF), the Omicron infection growth rate was estimated to be 0.35 per day, consistent with a doubling time of approximately 2 days.[84] Similarly, Omicron had an apparent growth advantage of 0.24 per day (95% CI: 0.16–0.33) over Delta, which is equivalent to a 5.4-fold (95% CI: 3.1–10.1) weekly increase in South Africa.[85] Consequently, Omicron has been the dominant variant in South Africa, UK, USA, and other countries. In terms of disease severity, Omicron-infected individuals showed lower rates of hospitalization or emergency care than those of patients infected with Delta (adjusted odds ratio of 30–52%) in South Africa, UK, USA, and Canada.[86–89] The upper and lower human respiratory tract are mostly protected by IgG and secretory IgA1 respectively. Current intramuscular COVID-19 vaccination mainly produced serum IgG but not mucosal IgA1.[90] Recently, compared with previous VOCs, the replication of Omicron in the upper respiratory tract is rapid but attenuated in the lung, which may explain, in part, why Omicron evades immunity better and causes milder disease symptoms.[69,91,92]

The threat posed by Omicron is closely related to its effect on current vaccine effectiveness.[19,79] A total of 87% of these Omicron-infected individuals were fully vaccinated, boosted, or previously infected with SARS-CoV-2.[83] Andrews et al. reported that there is limited protection against Omicron after 15 weeks of vaccination with 2 doses of the ChAdOx1 vaccine. After 2 doses of the BNT162b2 vaccine, the protection rate gradually decreased over time, from 88% at 2–9 weeks to 49% at 10–14 weeks and 34–37% at 15 weeks.[82] In South Africa, the effectiveness of BNT162B2 against infection with Omicron was 70%, with a 20% reduction compared to that against non-Omicron variants.[19] Two doses of the mRNA-1273 vaccine showed an efficacy against infection with Omicron of only 30% (95% CI, 5–49%) at 14–90 days and declined quickly thereafter.[93]

Protective ability of COVID-19 vaccines against VOCs

In vitro cross-neutralization

Vaccine-induced clinical sera and SARS-CoV-2 convalescent sera can be used for cross-neutralization assays to determine the protective efficacy of existing vaccines against variants. Cross-neutralization results for vaccine-induced immune and convalescent sera against Alpha, Beta, Gamma, Delta, and Omicron have been published (Table 1.).[7,9,13,47,53,94–131] Compared to those for the WT strain or the D614 variant, VOCs showed decreased antibody titers to different degrees.

When convalescent sera were tested using Alpha, Beta, Gamma, Delta, and Omicron pseudoviruses, neutralizing antibody titers decreased by 1.6–4.5, 4.6–21.8, 3.4–6.5, 1.9–5.0, and 15–47.1 times, respectively. When mRNA/adenovirus vaccine-induced immune sera were tested using Alpha, Beta, Gamma, Delta, and Omicron pseudoviruses, neutralizing antibody titers decreased by 0.6–3.9, 1.5–42.4, 2.2–6.7, 1.6–11.3, and 8.6–44 times, respectively. When convalescent sera were tested using live viruses of Alpha, Beta, Gamma, Delta, and Omicron variants, neutralizing antibody titers decreased by 1.0–2.9, 2.1–13.3, 1.8–3.1, 2.7–6.8, and 20.7 times, respectively. When mRNA/adenovirus vaccine-induced immune sera were tested using live viruses of Alpha, Beta, Gamma, Delta, and Omicron variants, neutralizing antibody titers decreased by 0.3–8.9, 3.0–16.0, 2.6–8.8, 1.4–9.0, and 17.9–39.9 times, respectively (Table 1.).

The cross-neutralization assays based on the pseudovirus and live virus both suggested that among the five variants, the largest decrease in neutralizing antibody titers was obtained for Omicron, followed by Beta/Delta, and the decrease with Alpha

Table 1. Cross-Neutralizing antibody titers of vaccine-induced immune sera and convalescent sera against VOCs in published studies.

		Variant of concern (live virus)					Variant of concern (pseudoviruses)				
		B.1.1.7	B.1.351	P.1	B.1.617.2	B.1.1.529	B.1.1.7	B.1.351	P.1	B.1.617.2	B.1.1.529
Sample		Alpha	Beta	Gamma	Delta	Omicron	Alpha	Beta	Gamma	Delta	Omicron
Convalescent		1.0–2.9	2.1–13.3	1.8–3.1	2.7–6.8	20.7	1.6–4.5	4.6–21.8	3.4–6.5	1.9–5.0	15–47.1
mRNA vaccine	mRNA-1273	1.8	3.5–3.8	/	~6.8		1.2–2.3	2.2–27.7	2.8–4.8	2.1–3.8	8.6–33
	BNT162b2	0.3–5.8	3.0–16.0	2.6–8.8	1.4–8.4	17.9–39.9	1.3–3.9	4.9–42.4	2.2–6.7	2.8–11.3	21.4–44
Adenovirus vector vaccine	ChAdOx1	1.2–8.9	9.0–11.0	2.9	2.5–9.0	17.9–26.6	/	1.5–4.0	/	4.0–6.2	36
	Ad26.COV2.S	/	/	/	/	/	0.9	3.6	3.4	1.6–3.4	/
	Sputnik V	/	/	/	/	/	0.6	6.3	/	/	/
Inactivated vaccine	BBIBP	0.7	1.6–2.5	/	/	/	/	7.62	/	1.92	11.6
	CoronaVac	2.0	3.3–4.4	/	2.1	4.3	1.6	3.9	3.1	2.5	/
	BBV152	/	3.0	/	2.0–2.7	/	/	/	/	/	/
Recombinant protein vaccine	ZF2001	/	1.6	/	/	/	1.0–1.8	2.8	/	1.4–3.1	/
	NVX-CoV2373	/	/	/	/	/	/	14.5	/	/	/

Neutralizing antibody fold reductions are based on comparisons with the WT or D614 G variant.

was relatively small. Consistent with these conclusions, the protection afforded by vaccination or prior infection against Alpha, Beta, or Delta is robust, while that against Omicron is reduced.[19,132,133]

VE in clinical trials and real-world settings

The emerging SARS-CoV-2 VOCs have raised concerns around potential immune evasion following vaccination. Vaccines have different protective efficacies against VOCs. Approved vaccines against Alpha provide relatively good protection. The effectiveness of ChAdOx1, NVX-CoV2373, BNT162b2, and mRNA-1273 vaccines against infection with Alpha are 64–70%, 86%, 85%, and 83%, respectively.[53,76,138,139] However, the corresponding rates against Beta are significantly decreased, i.e., 10% for the ChAdOx1 vaccine, 49% for the NVX-CoV2373 vaccine, and 57% for the Ad26.COV2.S vaccine.[59,134,135] The protective efficacy of the CoronaVac vaccine in Brazil is only 50%, which is far lower than its protective efficacy in Turkey (92%) and the UAE (79%). The effectiveness of the ChAdOx1 vaccine in Brazil is also lower than those in other countries, and this may also be associated the high frequency of the Gamma variant in the region.[136] The VEs of the ChAdOx1, BNT162b2, and mRNA-1273 vaccines against Delta declined to 60–67%, 56–88%, and 72%, respectively.[12,76] The VEs of the BNT162b2 and mRNA-1273 vaccines against Omicron declined to 55–70% and 30–37%, respectively.[19,93,132] Clinical trial and real-world results for protective efficacy (Table 2) suggest that existing vaccines confer better protection against Alpha and Delta than against Beta and Omicron. However, due to the strong infectivity of VOCs, specifically Delta and Omicron variants, countries and populations in which these variants are more widespread are expected to show higher rates of breakthrough infections. This suggests that epidemic prevention and control cannot rely solely on vaccination, and public health measures, including mass testing, active case finding, community management, travel restrictions, and affected area lockdown, should also be taken during the epidemic.

Methods for evaluating the protective efficacy of vaccines

Neutralizing antibody assays

Currently, the main indicator for evaluating the effect of serum neutralizing antibodies on variants is the fold decrease of neutralizing antibodies against variants compared to that against the WT virus. The principal test method uses the actual virus and pseudoviruses constructed from variants. However, test results for live viruses and pseudoviruses are not comparable, and there are issues associated with standardization.

The main methods that use the actual virus to test for neutralizing antibodies are plaque reduction neutralization tests (PRNT) and cytopathogenic effect assays (CPE). For both methods, there are differences among laboratories in the testing of actual virus variants, making horizontal comparisons of results difficult. For different laboratories using the CPE method and actual viruses to test four candidate neutralizing antibody standards (Samples 22, 44, 77, and 99), interlaboratory geometric coefficient of variations (GCVs) of 63%, 56%, 172%, and 88% have been reported. Setting Sample 22 as the standard with a titer of 1000 U/mL reduced the overall interlaboratory GCVs of Samples 44, 77, and 99 to 23%, 106%, and 48%, respectively. There were also substantial differences in geometric mean titers obtained by CPE and PRNT.[140]

Quantitative results from different laboratories using different pseudovirus vectors are not comparable. Balazs et al.[141] used the pTwist-CMV-BetaGlobin-WPRE-Neo vector to construct a B.1.351-v1-v3 pseudovirus for testing immune sera induced by the BNT162b2 and mRNA-1273 vaccines and found that neutralizing antibodies decreased by 34.5- to 42.4-fold and 19.2- to 27.7-fold relative to the WT virus. A series of pseudoviruses constructed using this platform can be used to evaluate the ability of sera to cross-neutralize different variants and RBD mutation sites. However, Yu et al.[66] reported that the neutralizing antibody titer of immune sera against the Beta variant decreased by an average of 8.7-fold. This differs greatly from the results of Balazs et al., emphasizing the potential problems with the horizontal comparison of results between laboratories. The recently established First WHO International Standard of anti-SARS-CoV-2 immunoglobulin (human) can be used for the calibration and harmonization of serological testing of anti-SARS-CoV-2 neutralizing antibodies. This is expected to improve the standardization of neutralizing antibody titer assays and comparative analyses.[142]

Additional determinants of vaccine efficacy

Variants differ substantially in resistance to immune sera induced by vaccines produced through different technical routes. Inactivated and recombinant vaccines have smaller fold differences in geometric mean titers of neutralizing antibodies against variants than those of mRNA and adenovirus vaccines.[143] Other important factors beyond the testing method may include differences in the antigen epitope (whole virus/S or RBD).

In addition, neutralizing antibody titers in vaccine immune sera may affect the fold reduction in the sera. When variants are used in neutralizing antibody tests, the fold reduction of neutralizing antibodies was higher in high-titer than in low-titer samples (unpublished results from our laboratory).

Recent research suggests that mutation sites in VOCs, such as the Delta and Gamma variants, have little impact on cellular immune responses.[144] In hamsters immunized with the ChAdOx1 vaccine and challenged with the Alpha and Beta variants, although the *in vitro* neutralizing potency of the immune sera against Beta was 9.5-fold lower than that against Alpha, the hamsters challenged with Alpha and Beta were still fully protected; this may be the result of cellular immunity.[145] Barouch et al.[146] analyzed the humoral and cellular immunity of 20 individuals vaccinated with Ad26.COV2.S from the COV1001 Phase I-IIa clinical trial (NCT04436276) and found that Ad26.COV2. S-induced pseudovirus neutralizing antibody titers against Beta and Gamma are 5.0-fold and 3.3-fold lower, respectively, compared to that against WA1/2020 (a WT strain). However, the functional non-neutralizing antibody response and *T*-cell response against SARS-CoV-2 variants remain to a large extent.[146]

Table 2. Clinical trial and real-world efficacy rates of available vaccines against VOCs.

Vaccine	No. of clinical trial	Clinical phases	Country	No. of participants	Age (years)	Efficacy (%)		Reference
						Total	VOC	
ChAdOx1	NCT04444674	I/II	South Africa	2,026	18–65	22	10 (Beta)[c]	Madhi, et al.[13]
ChAdOx1	NCT04400838	II/III	UK	8,534	≥18	/	70 (Alpha); 82 (non-Alpha)[c]	Emary, et al.[53]
NVX-CoV2373	/	/	/	/	/	/	>85 (Alpha); <50 (Beta)[c]	Callaway, et al.[137]
NVX-CoV2373	NCT04533399	2a–b	South Africa	6,324	18–84(HIV-)	60 (HIV-)	51 (Beta, HIV–)[b]	Shinde, et al.[15]
NVX-CoV2373	EudraCT number: 2020–004123-16	III	UK	15,187	/	/	86 (Alpha); 96 (non-Alpha)[c]	Heath, et al.[139]
BNT162b2	ISRCTN11041050	prospective cohort study	UK	23,324	≥18	/	85 (Alpha, two doses)[b]	Hall, et al.[140]
BNT162b2	real world	/	Israel	6,538,911	≥16	95	95 (Alpha)[c]	Haas, et al.[17]
BNT162b2	real world	/	Qatar	/	/	/	90 (Alpha); 75 (Beta)[c]	Abu-Raddad, et al.[16]
BNT162b2	real world	/	Canada	421,073	/	/	66 (Alpha); 56 (Delta)[b]	Nasreen, et al.[76]
mRNA-1273							83 (Alpha); 72 (Delta)	
ChAdOx1							64 (Alpha); 67 (Delta)	
BNT162b2	real world	/	UK	/	/	/	93 (Alpha); 88 (Delta)[c]	Bernal, et al.[12]
ChAdOx1							66 (Alpha); 60 (Delta)	
BNT162b2	real world	/	South Africa	133,437	/	/	70 (Omicron); 93 (non-Omicron)[c]	Collie, et al.[19]
mRNA-1273	real world	/	USA	6, 657	≥18	/	44 (Omicron); 80 (Delta)[c]	Tseng, et al.[93]
BNT162b2	real world		Denmark	5,767	/	/	55 (Omicron); 87 (Delta)[c]	Hansen, et al.[132]
mRNA-1273							37 (Omicron); 88 (Delta)	

[a]Against mild to moderate illness.
[b]Against symptomatic COVID-19.
[c]Against infection.

In large-scale vaccination campaigns conducted in various countries, accurate evaluations of the real-world cross-protective efficacy of available vaccines against variants as well as the immunogenicity of vaccines in clinical trials require the standardization of neutralizing antibody assay methods. In addition to these assays, studies focused on the standardization of methods for cellular immunity assays for novel coronavirus vaccines are necessary.

Strategies and measures for responding to variants

Rapid large-scale inoculation with available COVID-19 vaccines

Current widely distributed COVID-19 vaccines show some protective efficacy against variants. The primary goal of epidemic prevention and control is to accelerate the vaccination of susceptible individuals and establish an immune barrier as soon as possible. Recently, the WHO has expressed that "we are in a very dangerous period of this pandemic and [urge] leaders across the world to work together to ensure that ... people in every country are vaccinated". Currently, all countries have accelerated COVID-19 vaccination. As of January, 2022, >10 billion doses of the COVID-19 vaccine have been administered worldwide; China, India, and the United States rank in the top three with >3 billion, >2 billion, and >0.6 million doses administered, respectively.[3] The most important issue limiting the global vaccination rate is the availability of vaccines in underdeveloped countries, especially in Africa and other regions.

Improving the immunogenicity of available vaccines

It is currently believed that the immunogenicity of existing vaccines can be improved primarily through booster doses and sequential immunization. Johnson & Johnson has launched a Phase III clinical trial to test the protective efficacy of two doses of the Ad26.COV2.S vaccine. Moderna has considered adding a third dose of its vaccine to increase neutralizing antibody titers. On July, 2021, Pfizer issued a statement indicating that it is considering adding a third dose of the COVID-19 vaccine to be administered 6 months after the second dose and plans to apply for emergency use authorization by the U. S. Food and Drug Administration (FDA) in August. However, the FDA and CDC immediately issued an emergency joint statement in response confirming that current evidence shows that individuals who have been fully vaccinated with the COVID-19 vaccine and those who are in the process of being vaccinated can avoid severe illness and death, even with the currently circulating Delta variant.[147] On July 12 in Geneva, WHO Director-General Tedros Adhanom Ghebreyesus stated that wealthy countries should not administer a third booster dose to citizens before other countries are able to begin COVID-19 vaccination programs. Owing to the severe resurgence of the epidemic, the Ministry of Health of Israel announced on July that it would provide a third dose of BNT162b2 to immunocompromised adults starting immediately, and Israel became the first country to administer COVID-19 third booster shots.[148]

Our laboratory reported for the first time that prime-boost immunization in mice with different vaccines can effectively improve immunogenicity.[149] Müller et al.[150] evaluated ChAdOx1 nCoV-19 for the initial immunization and then a BNT162b2 booster shot administered eight weeks later. The serum neutralizing activity of the sequentially immunized volunteers, as evaluated using Alpha pseudoviruses, increased by 3.9-fold, whereas the neutralizing effect against Beta and Delta variants decreased by about 2-fold compared to those of volunteers vaccinated with two doses of BNT162b2. The University of Oxford launched a preliminary clinical trial to investigate the alternate use of different COVID-19 vaccines. More than 800 volunteers in England were recruited to evaluate the efficacy of four different combinations of Oxford-AstraZeneca and Pfizer vaccines for initial vaccination and booster doses. Data released on June 25 showed that the mixed BNT162b2 and ChAdOx1 vaccination protocol produced a strong immune response against the SARS-CoV2 spike protein of the WT strain. The vaccination order influenced the immune response, e.g., ChAdOx1/BNT162b2 induced a higher antibody titer and a stronger *T*-cell response compared to those for BNT162b2/ChAdOx1.[151] Notably, in a prior report, the frequency of mild-moderate adverse reactions in these two mixed groups was also relatively high.[152] In mainland China, the Jiangsu Provincial Center for Disease Control and Prevention launched the "Study on Sequential Immunization of Recombinant COVID-19 Vaccine (Ad5 Vector) and RBD-based Protein Subunit Vaccine" trial (NCT04833101) in May 2021.

The UK Public Health Service has updated their guidelines for the use of COVID-19 vaccines, announcing that if the first dose of a vaccine received by an individual is not effective, then an alternative vaccine can be used. The US FDA has also considered vaccine combinations. However, the implementation of sequential vaccination requires more safety-related research.

Development of vaccines targeting variants

VOCs may escape vaccine-induced immunity and increase morbidity and mortality. Furthermore, additional SARS-CoV-2 variants are highly likely to arise. Accordingly, current vaccines based on the original SARS-CoV-2 genomic sequence (NC_045512) cannot provide adequate protection against variant outbreaks and must be modified to address this problem. The WHO, FDA, EMA, and UK have successively issued guidelines for the development and clinical trials of vaccines against variants.[153–156] As defined in the WHO guidelines, a "modified COVID-19 vaccine" refers to a vaccine against a SARS-CoV-2 VOC for which the only alteration is in the virus variant, without changes in the manufacturing process, controls, and facilities for vaccine production. Non-clinical studies are encouraged for the evaluation of emergent SARS-CoV-2 variants, and clinical trials should be conducted as noninferiority trials in which the immune response induced by the modified vaccine is compared to the immune response induced by the original COVID-19 vaccine. The primary analysis should compare the neutralizing antibodies against the VOC induced by the modified COVID-19 vaccine and the original vaccine. In addition to the

evaluation of neutralizing antibodies, the UK guidelines clearly state that "in all subjects, the immune response should include determination of binding antibodies, neutralizing antibodies and *T*-cell response (at least an Elispot assay)."[154] In addition, both the FDA and EMA indicate that the data requirements to support the authorization of variant vaccines may differ due to differences in vaccine platform technologies;[153,155] this should be considered in preclinical and clinical studies.

There is substantial evidence that the VE of current vaccines against Omicron is substantially reduced. Moderna, Johnson & Johnson, Pfizer, and other pharmaceutical companies have begun vaccine research and development for Omicron variants. On November 26, Moderna announced that it will adjust the direction of vaccine development for Omicron, including the rapid development of a candidate (mRNA-1273.529) vaccine.[157] On November 30, Johnson & Johnson announced that it will carefully test the effectiveness of existing vaccines against the Omicron strain and, if necessary, will develop a vaccine against this strain.[158] On December 2, Novavax announced that it initiated the development of an Omicron-specific vaccine construct.[159] On December 8, Pfizer announced that a new vaccine developed specifically for Omicron is expected to be available within 100 days.[160] On December 22, AstraZeneca and Oxford University claimed to be collaborating on a new version of a vaccine against Omicron.[161]

Summary

Currently, a variety of variants are prevalent and cause outbreaks around the world. Since the Alpha and Delta epidemics in many countries or regions, Omicron has caused another large-scale resurgence of the pandemic and has gradually became the dominant strain worldwide. VOCs have some ability to escape specific immunity induced by vaccines, infections, and some monoclonal antibody treatments, which can lead to breakthrough infections after vaccination. The high transmissibility of Delta and Omicron has recently forced many countries and regions to reimplement lockdown measures. Accordingly, SARS-CoV-2 variants have become a major public health issue worldwide. Emergency response measures include accelerating COVID-19 vaccination campaigns worldwide and adopting lockdown measures, depending on local conditions, while closely monitoring the evolution of the SARS-CoV-2 virus. Vaccine developers must respond rapidly to produce a new generation of variant-specific or universal vaccines for epidemic prevention and control. Standardized *in vitro* variant neutralizing antibody titer assays and well-designed phase III clinical trials will provide reliable data on the efficacy of these vaccines against variants and contribute to the development and application of variant-specific vaccines.

Disclosure statement

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled.

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References

1. World Health Organization(WHO). COVID-19 vaccine tracker and landscape; 2022 [accessed 2022 Jan 18]. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines.
2. World Health Organization(WHO). Status of COVID-19 vaccines within WHO EUL/PQ evaluation process; 2021 [accessed 2021 Nov 11]. https://www.who.int/teams/regulation-prequalification/eul/covid-19.
3. World Health Organization(WHO). WHO Coronavirus (COVID-19) Dashboard; 2022 [accessed 2022 Jan 18]. https://covid19.who.int/.
4. Canton R, De Lucas Ramos P, Garcia-Botella A, Garcia-Lledo A, Gomez-Pavon J, Gonzalez Del Castillo J, et al. New variants of SARS-CoV-2 Rev Esp Quimioter. 2021;34(5):419-428.
5. Harvey WT, Carabelli AM, Jackson B, Gupta RK, Thomson EC, Harrison EM, et al. SARS-CoV-2 variants, spike mutations and immune escape. Nat Rev Microbiol. 2021;19:409–24.
6. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (Delta) variant. N Engl J Med. 2021;385:585–94.
7. Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. Nature. 2021;596:276–80.
8. Rössler A, Riepler L, Bante D, von Laer D, Kimpel J. SARS-CoV-2 Omicron variant neutralization in serum from vaccinated and convalescent persons. N Engl J Med. 2022;386:698-700.
9. Zhou D, Dejnirattisai W, Supasa P, Liu C, Mentzer AJ, Ginn HM, et al. Evidence of escape of SARS-CoV-2 variant B.1.351 from natural and vaccine-induced sera. Cell. 2021;184:2348–61.e6.
10. World Health Organization(WHO). Tracking SARS-CoV-2 variants; 2022 [accessed 2022 Jan 18]. https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/.
11. World Health Organization(WHO). COVID-19 Weekly Epidemiological Update; 2021 [accessed 2021 July 27]. https://www.who.int/docs/default-source/coronaviruse/20210722_weekly_epi_update_50_updated.pdf.
12. Bernal JL, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of COVID-19 vaccines against the B.1.617.2 variant. N Engl J Med . 2024;385:585-594.
13. Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al. Efficacy of the ChAdox1 nCov-19 Covid-19 vaccine against the B.1.351 variant. N Engl J Med. 2021;384:1885–98.
14. Sadoff J, Gray G, Vandebosch A, Cárdenas V, Shukarev G, Grinsztejn B, et al. Safety and efficacy of Single-Dose Ad26.COV2.S vaccine against Covid-19. N Engl J Med. 2021;384:2187–201.
15. Shinde V, Bhikha S, Hoosain Z, Archary M, Bhorat Q, Fairlie L, et al. Efficacy of NVX-CoV2373 Covid-19 vaccine against the B.1.351 variant. N Engl J Med. 2021;384:1899–909.
16. Abu-Raddad LJ, Chemaitelly H, Butt AA. Effectiveness of the BNT162b2 Covid-19 vaccine against the B.1.1.7 and B.1.351 variants. N Engl J Med. 2021;385:187–89.
17. Haas EJ, Angulo FJ, McLaughlin JM, Anis E, Singer SR, Khan F, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. Lancet. 2021;397:1819–29.
18. CNCB . Israel says Pfizer Covid vaccine is just 39% effective as delta spreads, but still prevents severe illness [accesed 23 July 2021]. https://www.cnbc.com/2021/07/23/delta-variant-pfizer-covid-vaccine-39percent-effective-in-israel-prevents-severe-illness.html.
19. Collie S, Champion J, Moultrie H, Bekker L-G, Gray G. Effectiveness of BNT162b2 vaccine against Omicron variant in South Africa. N Engl J Med . 2022;386:494–96.

20. Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature. 2020;581:215–20.
21. McCallum M, Marco A, Lempp F, Tortorici MA, Pinto D, Walls AC, et al. N-Terminal domain antigenic mapping reveals a site of vulnerability for SARS-CoV-2. Cell. 2021;184(9):2332-2347.e16.
22. Cerutti G, Guo Y, Zhou T, Gorman J, Lee M, Rapp M, et al. Potent SARS-CoV-2 neutralizing antibodies directed against spike N-terminal domain target a single supersite. Cell Host & Microbe. 2021;29:819–33 e7.
23. Martínez-Flores D, Zepeda-Cervantes J, Cruz-Reséndiz A, Aguirre-Sampieri S, Sampieri A, Vaca L. SARS-CoV-2 vaccines based on the Spike Glycoprotein and implications of new viral variants. Front Immunol. 2021;12. doi:10.3389/fimmu.2021.701501.
24. Wang R, Zhang Q, Ge J, Ren W, Zhang R, Lan J, et al. Analysis of SARS-CoV-2 variant mutations reveals neutralization escape mechanisms and the ability to use ACE2 receptors from additional species. Immunity. 2021;54:1611–21 e5.
25. Chen C, Boorla VS, Banerjee D, Chowdhury R, Cavener VS, Nissly RH, et al. Computational prediction of the effect of amino acid changes on the binding affinity between SARS-CoV-2 spike protein and the human ACE2 receptor. Proceedings of the National Academy of Sciences .2021;118:(42) e2106480118.
26. Gan HH, Twaddle A, Marchand B, Gunsalus KC. Structural modeling of the SARS-CoV-2 Spike/Human ACE2 complex interface can identify high-affinity variants associated with increased transmissibility. J Mol Biol. 2021;433:167051.
27. Barton MI, MacGowan SA, Kutuzov MA, Dushek O, Barton GJ, van der Merwe PA. Effects of common mutations in the SARS-CoV-2 Spike RBD and its ligand, the human ACE2 receptor on binding affinity and kinetics. Elife. 2021;10:e70658.
28. Davies NG, Abbott S, Barnard RC, Jarvis CI, Kucharski AJ, Munday JD, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. Science. 2021;372:eabg3055.
29. Baum A, Fulton BO, Wloga E, Copin R, Pascal KE, Russo V, et al. Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. Science. 2020;369:1014–18.
30. Diamond M, Chen R, Xie X, Case J, Zhang X, VanBlargan L, et al. SARS-CoV-2 variants show resistance to neutralization by many monoclonal and serum-derived polyclonal antibodies. Research Square. 2021;rs.3.rs-228079.
31. Wang P, Nair MS, Liu L, Iketani S, Luo Y, Guo Y, et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. Nature. 2021;593:130–35.
32. Weisblum Y, Schmidt F, Zhang F, DaSilva J, Poston D, Lorenzi JCC , et al. Escape from neutralizing antibodies by SARS-CoV-2 spike protein variants. Elife. 2020;9:e61312.
33. Collier DA, De Marco A, Ferreira I, Meng B, Datir RP, Walls AC, et al. Sensitivity of SARS-CoV-2 B.1.1.7 to mRNA vaccine-elicited antibodies. Nature. 2021;593:136–41.
34. Greaney AJ, Loes AN, Crawford KHD, Starr TN, Malone KD, Chu HY, et al. Comprehensive mapping of mutations in the SARS-CoV-2 receptor-binding domain that affect recognition by polyclonal human plasma antibodies. Cell Host & Microbe. 2021;29:463–76 e6.
35. Andreano E, Piccini G, Licastro D, Casalino L, Johnson NV, Paciello I, et al. SARS-CoV-2 escape in vitro from a highly neutralizing COVID-19 convalescent plasma doi: . bioRxiv. 2020.12.28.424451.
36. McCallum M, Bassi J, De Marco A, Chen A, Walls AC, Di Iulio J, et al. SARS-CoV-2 immune evasion by the B.1.427/B.1.429 variant of concern. Science. 2021;373(6555):648-654.
37. Mannar D, Saville JW, Zhu X, Srivastava SS, Berezuk AM, Tuttle KS, et al. SARS-CoV-2 Omicron variant: antibody evasion and cryo-EM structure of spike protein–ace2 complex. Science. 2022;375(6582):760-764.
38. Teruel N, Crown M, Bashton M, Najmanovich R. Computational analysis of the effect of SARS-CoV-2 variant Omicron Spike protein mutations on dynamics, ACE2 binding and propensity for immune escape. bioRxiv; 2021. https://doi.org/10.1101/2021.12.14.472622.
39. Fratev F. The high transmission of SARS-CoV-2 Omicron (B.1.1.529) variant is not only due to its hACE2 binding: a free energy of perturbation study. bioRxiv; 2021. https://doi.org/10.1101/2021.12.04.471246.
40. Lan J, He X, Ren Y, Wang Z, Zhou H, Fan S, et al. Structural and computational insights into the SARS-CoV-2 Omicron RBD-ACE2 interaction. bioRxiv; 2022. https://doi.org/10.1101/2022.01.03.474855.
41. cov-lineages.org. PANGO. B.1.1.7; 2021. https://cov-lineages.org/global_report_B.1.1.7.html.
42. Rambaut, A, Nick Loman, N, Pybus, O, Barclay, W, Barrett, J, Carabelli, A, et al. Preliminary genomic characterisation of an emergent SARS-CoV-2 lineage in the UK defined by a novel set of spike mutations 2021. https://virological.org/t/preliminary-genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-the-uk-defined-by-a-novel-set-of-spike-mutations/563.
43. Starr TN, Greaney AJ, Hilton SK, Ellis D, Crawford KHD, Dingens AS, et al. Deep mutational scanning of SARS-CoV-2 receptor binding domain reveals constraints on folding and ACE2 binding. Cell. 2020;182:1295–310. e20.
44. Kemp SA, Collier DA, Datir RP, Ferreira I, Gayed S, Jahun A, et al. SARS-CoV-2 evolution during treatment of chronic infection. Nature. 2021;592:277–82.
45. Volz E, Mishra S, Chand M, Barrett JC, Johnson R, Geidelberg L, et al. Transmission of SARS-CoV-2 Lineage B.1.1.7 in England: insights from linking epidemiological and genetic data. medExiv 2020. https://doi.org/10.1101/2020.12.30.20249034.
46. Tanaka H, Hirayama A, Nagai H, Shirai C, Takahashi Y, Shinomiya H, et al. Increased transmissibility of the SARS-CoV-2 Alpha variant in a Japanese population International journal of environmental research and public health. 2021;18 (15): 7752.
47. Barouch DH, Stephenson KE, Sadoff J, Yu J, Chang A, Gebre M, et al. Durable humoral and cellular immune responses 8 months after Ad26.COV2.S vaccination. N Engl J Med. 2021;385:951–53.
48. A-Ry C, Yu J, McMahan K, Liu J, Chandrashekar A, Maron JS, et al. Differential kinetics of immune responses elicited by Covid-19 vaccines. N Engl J Med. 2021;385:2010–12.
49. Cohen KW, Linderman SL, Moodie Z, Czartoski J, Lai L, Mantus G, et al. Longitudinal analysis shows durable and broad immune memory after SARS-CoV-2 infection with persisting antibody responses and memory B and T cells. Cell Rep Med. 2021;2:100354.
50. Azkur AK, Akdis M, Azkur D, Sokolowska M, van de Veen W, Brüggen M-C, et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. Allergy. 2020;75:1564–81.
51. Novazzi F, Baj A, Genoni A, Spezia PG, Colombo A, Cassani G, et al. SARS-CoV-2 B.1.1.7 reinfection after previous COVID-19 in two immunocompetent Italian patients. J Med Virol. 2021;93:5648–49.
52. Loconsole D, Sallustio A, Accogli M, Leaci A, Sanguedolce A, Parisi A, et al. Investigation of an outbreak of symptomatic SARS-CoV-2 VOC 202012/01-lineage B.1.1.7 infection in healthcare workers, Italy. Clin Microbiol Infect 2021;27(8):1174.e1-1174.e4.
53. Emary KRW, Golubchik T, Aley PK, Ariani CV, Angus B, Bibi S, et al. Efficacy of ChAdox1 nCov-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. Lancet. 2021;397:1351–62.
54. Heath PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, et al. Safety and efficacy of NVX-CoV2373 Covid-19 vaccine. N Engl J Med 2021. 385(13):1172-1183.
55. cov-lineages.org. PANGO. B.1.351; 2021. https://cov-lineages.org/global_report_B.1.351.html.
56. Staub T, Arendt V, Lasso de la Vega EC, Braquet P, Michaux C, Kohnen M, et al. Case series of four re-infections with a SARS-CoV-2 B.1.351 variant, Luxembourg, February 2021. Euro Surv. 2021;26(18):2100423.
57. Saha S, Tanmoy AM, Hooda Y, Tanni AA, Goswami S, Sium SMA, et al. COVID-19 rise in Bangladesh correlates with increasing detection of B.1.351 variant. BMJ Global Health. 2021;6(5):e006012.

58. Bian L, Gao F, Zhang J, He Q, Mao Q, Xu M, et al. Effects of SARS-CoV-2 variants on vaccine efficacy and response strategies. Expert Rev Vaccines. 2021;20(4):365–73. doi:10.1080/14760584.2021.1903879.
59. Novavax. Novavax COVID-19 vaccine demonstrates 89.3% efficacy in UK Phase 3 trial; 2021 [accessed 2021 Jan 28]. https://ir.novavax.com/2021-01-28-Novavax-COVID-19-Vaccine-Demonstrates-89-3-Efficacy-in-UK-Phase-3-Trial.
60. U.S. Food and Drug Administration (FDA). Vaccines and related biological Products Advisory Committee February 26, 2021 meeting announcement; 2021[accessed February 26, 2021]. https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-february-26-2021-meeting-announcement.
61. Callaway E. Pfizer COVID vaccine protects against worrying coronavirus variants. Nature. 2021;593:325–26.
62. cov-lineages.org. PANGO. P.1; 2021. https://cov-lineages.org/global_report_P.1.html.
63. Faria NR, Mellan TA, Whittaker C, Claro IM, Candido DDS, Mishra S, et al. Genomics and epidemiology of a novel SARS-CoV-2 lineage in Manaus, Brazil. medRxiv. 2021. doi:10.1101/2021.02.26.21252554.
64. Faria NR, Mellan TA, Whittaker C, Claro IM, Candido DDS, Mishra S, et al. Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil. Science. 2021;372:815–21.
65. Supasa P, Zhou D, Dejnirattisai W, Liu C, Mentzer AJ, Ginn HM, et al. Reduced neutralization of SARS-CoV-2 B.1.1.7 variant by convalescent and vaccine sera. Cell. 2021;184:2201–11. e7.
66. Chen X, Chen Z, Azman AS, Sun R, Lu W, Zheng N, et al. Comprehensive mapping of neutralizing antibodies against SARS-CoV-2 variants induced by natural infection or vaccination. medRxiv 2021;2021.05.03.21256506. doi:10.1101/2021.05.03.21256506.
67. Tanriover MD, Doğanay HL, Akova M, Güner HR, Azap A, Akhan S, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. Lancet. 2021;398:213–22.
68. Álvarez-Antonio C, Meza-Sánchez G, Calampa C, Casanova W, Carey C, Alava F, et al. Seroprevalence of anti-SARS-CoV -2 antibodies in Iquitos, Peru in July and August, 2020: a population-based study. Lancet Global Health. 2021;9: e925–e31.
69. Peacock TP, Brown JC, Zhou J, Thakur N, Newman J, Kugathasan R, et al. The SARS-CoV-2 variant, Omicron, shows rapid replication in human primary nasal epithelial cultures and efficiently uses the endosomal route of entry. bioRxiv 2022; 2021.12.31.474653.
70. Callaway E. Delta coronavirus variant: scientists brace for impact. Nature. 2021;595:17–18.
71. Tchesnokova V, Kulasekara H, Larson L, Bowers V, Rechkina E, Kisiela D, et al. Acquisition of the L452R mutation in the ACE2-Binding interface of spike protein triggers recent massive expansion of SARS-CoV-2 variants. J Clin Microbiol. 2021;59:e0092121.
72. Allen H, Vusirikala, A, Flannagan, J, Twohig, KA, Zaidi, A, Chudasama, D *et al*. Increased household transmission of COVID-19 cases associated with SARS-CoV-2 variant of concern B.1.617.2: a national case control study. The Lancet Regional Health- Europe. 2022;12:100252.
73. Campbell F, Archer B, Laurenson-Schafer H, Jinnai Y, Konings F, Batra N, et al. Increased transmissibility and global spread of SARS-CoV-2 variants of concern as at June 2021. Euro surveillance : bulletin Europeen sur les maladies transmissibles. European Communicable Disease Bulletin. ;2021;26(24):2100509.
74. Yang W, Shaman J. COVID-19 pandemic dynamics in India and impact of the SARS-CoV-2 Delta (B.1.617.2) variant. medExiv; 2021 https://doi.org/10.1101/2021.06.21.21259268.
75. Sharma P, Mishra S, Basu S, Tanwar N, Kumar R. Breakthrough infection with SARS-CoV-2 and its predictors among healthcare workers in a medical college and hospital complex in Delhi, India. Cureus. 2021;13(10):e19070. doi:10.7759/cureus.19070.
76. Nasreen S, Chung H, He S, Brown KA, Gubbay JB, Buchan SA, et al. Effectiveness of COVID-19 vaccines against variants of concern in Ontario, Canada. medRxiv; 2021. https://doi.org/10.1101/2021.06.28.21259420.
77. CNN. Why Covid-19 outbreaks in countries using Chinese vaccines don't necessarily mean the shots have failed [accessed July 03, 2021] https://edition.cnn.com/2021/07/02/china/vaccines-sinovac-sinopharm-intl-hnk-dst/index.html.
78. Public Health England. Vaccines highly effective against hospitalisation from Delta variant; 2021 [Accessed 2021 June 14]. https://www.gov.uk/government/news/vaccines-highly-effective-against-hospitalisation-from-delta-variant.
79. World Health Organization(WHO). Enhancing response to Omicron SARS-CoV-2 variant 2022 [accessed January 21, 2022]. https://www.who.int/publications/m/item/enhancing-readiness-for-omicron-(b.1.1.529)-technical-brief-and-priority-actions-for-member-states.
80. Qin S, Cui M, Sun S, Zhou J, Du Z, Cui Y, et al. Genome characterization and potential risk assessment of the novel SARS-CoV-2 variant Omicron (B.1.1.529). Zoonoses. 2021;1(1) doi:10.15212/ZOONOSES-2021-0024
81. Cao Y, Wang J, Jian F, Xiao T, Song W, Yisimayi A, et al. Omicron escapes the majority of existing SARS-CoV-2 neutralizing antibodies. Nature 2022;602(7898):657-663.
82. Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. Effectiveness of COVID-19 vaccines against the Omicron (B.1.1.529) variant of concern. medRxiv; 2021. https://doi.org/10.1101/2021.12.14.21267615.
83. Espenhain L, Funk T, Overvad M, Edslev SM, Fonager J, Ingham AC, et al. Epidemiological characterisation of the first 785 SARS-CoV-2 Omicron variant cases in Denmark, December 2021. Euro Surveillance. 2021;26(50):2101146.
84. UK Health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England Technical briefing 31; 2021 [accessed 2021 Dec 10]. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1042367/technical_briefing-31-10-december-2021.pdf.
85. Viana R, Moyo S, Amoako DG, Tegally H, Scheepers C, Althaus CL, et al. Rapid epidemic expansion of the SARS-CoV-2 Omicron variant in southern Africa. Nature. 2022;603(7902):679-686.
86. Wolter N, Jassat W, Walaza S, Welch R, Moultrie H, Groome M, et al. Early assessment of the clinical severity of the SARS-CoV-2 omicron variant in South Africa: a data linkage study. Lancet. 2022;399(10323):437-446.
87. UK Health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England technical briefing: update on hospitalisation and vaccine effectiveness for Omicron VOC-21NOV-01 (B.1.1.529); 2021 [accessed 2021 Dec 31]. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1045619/Technical-Briefing-31-Dec-2021-Omicron_severity_update.pdf.
88. Ulloa AC, Buchan SA, Daneman N, Brown KA. Early estimates of SARS-CoV-2 Omicron variant severity based on a matched cohort study. Ontario, Canada: medRxiv 2022:2021.12.24.21268382.
89. Lewnard JA, Hong PM VX, Kahn R, Lipsitch M, Tartof SY. Clinical outcomes among patients infected with Omicron (B.1.1.529) SARS-CoV-2 variant in Southern California. medRxiv 2022. https://doi.org/10.1101/2022.01.11.22269045.
90. Krammer F. SARS-CoV-2 vaccines in development. Nature. 2020;586:516–27.
91. Shuai H, Chan J-W, Hu B, Chai Y, Yuen T-T, Yin F, et al. Attenuated replication and pathogenicity of SARS-CoV-2 B.1.1.529 Omicron. Nature 2022;603(7902):693-699.
92. Halfmann PJ, Iida S, Iwatsuki-Horimoto K, Maemura T, Kiso M, Scheaffer SM, et al. SARS-CoV-2 Omicron virus causes attenuated disease in mice and hamsters. Nature 2022;603(7902):687-692.
93. Tseng HF, Ackerson BK, Luo Y, Sy LS, Talarico CA, Tian Y, et al. Effectiveness of mRNA-1273 against SARS-CoV-2 omicron and delta variants. Nat Med. 2022;10.1038/s41591-022-01753-y.

94. Stamatatos L, Czartoski J, Wan Y-H, Homad LJ, Rubin V, Glantz H, et al. mRNA vaccination boosts cross-variant neutralizing antibodies elicited by SARS-CoV-2 infection. Science. 2021;372:1413–18.
95. Collier DA, De Marco A, Ferreira IATM, Meng B, Datir RP, Walls AC, et al. Sensitivity of SARS-CoV-2 B.1.1.7 to mRNA vaccine-elicited antibodies. Nature. 2021;593:136–41.
96. Wang P, Nair MS, Liu L, Iketani S, Luo Y, Guo Y, et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. bioRxiv; 2021. doi:10.1101/2021.01.25.428137.
97. Garcia-Beltran WF, Lam EC, St Denis K, Nitido AD, Garcia ZH, Hauser BM, et al. Multiple SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity. Cell. 2021;184:2523.
98. Muik A, Wallisch A-K, Sänger B, Swanson KA, Mühl J, Chen W, et al. Neutralization of SARS-CoV-2 lineage B.1.1.7 pseudovirus by BNT162b2 vaccine–elicited human sera. Science. 2021;371:1152–53.
99. Shen X, Tang H, Pajon R, Smith G, Glenn GM, Shi W, et al. Neutralization of SARS-CoV-2 Variants B.1.429 and B.1.351. N Engl J Med. 2021;384:2352–54.
100. Ikegame S, Siddiquey MNA, Hung C-T, Haas G, Brambilla L, Oguntuyo KY, et al. Neutralizing activity of Sputnik V vaccine sera against SARS-CoV-2 variants. Nat Commun. 2021;12:4598.
101. Kuzmina A, Khalaila Y, Voloshin O, Keren-Naus A, Bohehm L, Raviv Y, et al. SARS CoV-2 escape variants exhibit differential infectivity and neutralization sensitivity to convalescent or post-vaccination sera. Available at SSRN: https://ssrn.com/abstract=3789258.2021.
102. Shen X, Tang H, McDanal C, Wagh K, Fischer W, Theiler J, et al. SARS-CoV-2 variant B.1.1.7 is susceptible to neutralizing antibodies elicited by ancestral spike vaccines. Cell Host & Microbe. 2021;29:529–39.e3.
103. Hoffmann M, Arora P, Groß R, Seidel A, Hörnich BF, Hahn AS, et al. SARS-CoV-2 variants B.1.351 and P.1 escape from neutralizing antibodies. Cell. 2021;184:2384–93.e12.
104. Deng X, Garcia-Knight MA, Khalid MM, Servellita V, Wang C, Morris MK, et al. Transmission, infectivity, and antibody neutralization of an emerging SARS-CoV-2 variant in California carrying a L452R spike protein mutation. medRxiv 2021. doi:10.1101/2021.03.07.21252647.
105. Dejnirattisai W, Zhou D, Supasa P, Liu C, Mentzer AJ, Ginn HM, et al. Antibody evasion by the P.1 strain of SARS-CoV-2. Cell. 2021;184:2939–54.e9.
106. Bates TA, Leier HC, Lyski ZL, McBride SK, Coulter FJ, Weinstein JB, et al. Neutralization of SARS-CoV-2 variants by convalescent and BNT162b2 vaccinated serum. Nat Commun. 2021;12:5135.
107. Vv E, Norwood C, Floyd K, Lai L, Me D-G, Wh H, et al. Infection- and vaccine-induced antibody binding and neutralization of the B.1.351 SARS-CoV-2 variant. Cell Host Microbe. 2021;29:516–21.e3.
108. Tada T, Dcosta BM, Samanovic MI, Herati RS, Cornelius A, Zhou H, et al. Convalescent-Phase sera and vaccine-elicited antibodies largely maintain neutralizing titer against global SARS-CoV-2 variant spikes. mBio. 2021;12:e00696-21.
109. Vv E, Wh H, Xie X, Ahmed R, Ms S. Neutralizing antibodies against SARS-CoV-2 variants after infection and vaccination. Jama. 2021;325:1896–98.
110. Lustig Y, Nemet I, Kliker L, Zuckerman N, Yishai R, Alroy-Preis S, et al. Neutralizing response against variants after SARS-CoV-2 infection and One Dose of BNT162b2. N Engl J Med. 2021;384:2453–54.
111. Vv E, Norwood C, Floyd K, Lai L, Me D-G, Wh H, et al. Reduced binding and neutralization of infection- and vaccine-induced antibodies to the B.1.351 (South African) SARS-CoV-2 variant. bioRxiv. 2021;2021.02.20.432046.
112. Chen RE, Zhang X, Case JB, Winkler ES, Liu Y, VanBlargan LA, et al. Resistance of SARS-CoV-2 variants to neutralization by monoclonal and serum-derived polyclonal antibodies. Nat Med. 2021;27:717–26.
113. Planas D, Bruel T, Grzelak L, Guivel-Benhassine F, Staropoli I, Porrot F, et al. Sensitivity of infectious SARS-CoV-2 B.1.1.7 and B.1.351 variants to neutralizing antibodies. Nat Med. 2021;27:917–24.
114. Betton M, Livrozet M, Planas D, Fayol A, Monel B, Védie B, et al. Sera neutralizing activities against severe acute respiratory syndrome Coronavirus 2 and multiple variants 6 Months after hospitalization for Coronavirus disease 2019. Clin Infect Dis. 2021;73:e1337–e44.
115. Wall EC, Wu M, Harvey R, Kelly G, Warchal S, Sawyer C, et al. AZD1222-Induced neutralising antibody activity against SARS-CoV-2 Delta VOC. Lancet. 2021;398:207–09.
116. Liu J, Liu Y, Xia H, Zou J, Weaver SC, Swanson KA, et al. Bnt162b2-Elicited neutralization of B.1.617 and other SARS-CoV-2 variants. Nature. 2021;596:273–75.
117. Wall EC, Wu M, Harvey R, Kelly G, Warchal S, Sawyer C, et al. Neutralising antibody activity against SARS-CoV-2 VOCs B.1.617.2 and B.1.351 by BNT162b2 vaccination. Lancet. 2021;397:2331–33.
118. Sapkal GN, Yadav PD, Sahay RR, Deshpande G, Gupta N, Nyayanit DA, et al. Neutralization of Delta variant with sera of Covishield™ vaccines and COVID-19-recovered vaccinated individuals. J Travel Med. 2021;28(7):taab119.
119. Yadav PD, Sapkal GN, Ella R, Sahay RR, Nyayanit DA, Patil DY, et al. Neutralization of Beta and Delta variant with sera of COVID-19 recovered cases and vaccinees of inactivated COVID-19 vaccine BBV152/Covaxin. J Travel Med. 2021;28(7):taab104.
120. Liu C, Ginn HM, Dejnirattisai W, Supasa P, Wang B, Tuekprakhon A, et al. Reduced neutralization of SARS-CoV-2 B.1.617 by vaccine and convalescent serum. Cell. 2021;184:4220–36.e13.
121. Haveri A, Ekström N, Solastie A, Virta C, Österlund P, Isosaari E, et al. Persistence of neutralizing antibodies a year after SARS-CoV-2 infection in humans. Eur J Immunol. 2021;51:3202–13.
122. Carreño JM, Alshammary H, Singh G, Raskin A, Amanat F, Amoako A, et al. Reduced neutralizing activity of post-SARS-CoV-2 vaccination serum against variants B.1.617.2, B.1.351, B.1.1.7+E484K and a sub-variant of C.37. medRxiv; 2021. https://doi.org/10.1101/2021.07.21.21260961.
123. Mlcochova P, Kemp SA, Dhar MS, Papa G, Meng B, Ferreira IATM, et al. SARS-CoV-2 B.1.617.2 Delta variant replication and immune evasion. Nature. 2021;599:114–19.
124. Vacharathit V, Aiewsakun P, Manopwisedjaroen S, Srisaowakarn C, Laopanupong T, Ludowyke N, et al. CoronaVac induces lower neutralising activity against variants of concern than natural infection. Lancet Infect Dis. 2021;21:1352–54.
125. Davis C, Logan N, Tyson G, Orton R, Harvey WT, Perkins JS, et al. Reduced neutralisation of the Delta (B.1.617.2) SARS-CoV-2 variant of concern following vaccination. PLoS Pathog. 2021;17:e1010022.
126. Jongeneelen M, Kaszas K, Veldman D, Huizingh J, Rvd V, Schouten T, et al. Ad26.Cov2. S elicited neutralizing activity against Delta and other SARS-CoV-2 variants of concern bioRxiv; 2021. https://doi.org/10.1101/2021.07.01.450707.
127. Choi A, Koch M, Wu K, Dixon G, Oestreicher J, Legault H, et al. Serum neutralizing activity of mRNA-1273 against SARS-CoV-2 variants. J Virol. 2021;95:e01313–21.
128. Hu J, X-Y W, Xiang J, Peng P, F-L X, Wu K, et al. Reduced neutralization of SARS-CoV-2 B.1.617 variant by convalescent and vaccinated sera. Genes & Diseases;2021. doi:10.1016/j.gendis.2021.11.007.
129. Zhao X, Zheng A, Li D, Zhang R, Sun H, Wang Q, et al. Neutralisation of ZF2001-elicited antisera to SARS-CoV-2 variants. Lancet Microbe. 2021;2(10):e494.
130. Hoffmann M, Hofmann-Winkler H, Krüger N, Kempf A, Nehlmeier I, Graichen L, et al. SARS-CoV-2 variant B.1.617 is resistant to bamlanivimab and evades antibodies induced by infection and vaccination. Cell Rep. 2021;36(3):109415.
131. Tada T, Zhou H, Dcosta BM, Samanovic MI, Mulligan MJ, Landau NR. Partial resistance of SARS-CoV-2 Delta variants to vaccine-elicited antibodies and convalescent sera. iScience. 2021;24(11):103341.

132. Hansen CH, Schelde AB, Moustsen-Helm IR, Emborg H-D, Krause TG, Mølbak K, et al. Vaccine effectiveness against SARS-CoV-2 infection with the Omicron or Delta variants following a two-dose or booster BNT162b2 or mRNA-1273 vaccination series: a Danish cohort study. medRxiv 2021. https://doi.org/10.1101/2021.12.20.21267966.
133. Altarawneh H, Chemaitelly H, Tang P, Hasan MR, Qassim S, Ayoub HH, et al. Protection afforded by prior infection against SARS-CoV-2 reinfection with the Omicron variant. medRxiv 2022; 2022.01.05.22268782. https://doi.org/10.1101/2022.01.05.22268782.
134. Johnson & Johnson. Johnson & Johnson COVID-19 vaccine authorized by U.S. FDA for emergency use - first single-shot vaccine in fight against global pandemic https://www.jnj.com/johnson-johnson-covid-19-vaccine-authorized-by-u-s-fda-for-emergency-usefirst-single-shot-vaccine-in-fight-against-global-pandemic.
135. Oxford. Oxford Covid-19 vaccine trial results; 2021 [accessed 2021 Feb 7]. https://www.wits.ac.za/covid19/covid19-news/latest/oxford-covid-19-vaccine-trial-results.html.
136. Voysey M, Ann Costa Clemens S, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Single-Dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdox1 nCov-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. Lancet. 2021;397:881–91.
137. Callaway E, Mallapaty S. Novavax offers first evidence that COVID vaccines protect people against variants. Nature. 2021;590:17.
138. Heath PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, et al. Safety and efficacy of NVX-CoV2373 Covid-19 vaccine. N Engl J Med. 2021;385:1172–83.
139. Hall VJ, Foulkes S, Saei A, Andrews N, Oguti B, Charlett A, et al. COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study. Lancet. 2021;397:1725–35.
140. Guan L, Yu Y, Wu X, Nie J, Zhang J, Wang Z, et al. The first Chinese national standards for SARS-CoV-2 neutralizing antibody. Vaccine. 2021;39:3724–30.
141. Garcia-Beltran WF, Lam EC, St Denis K, Nitido AD, Garcia ZH, Hauser BM, et al. Multiple SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity. Cell. 2021;184:2372–83 e9.
142. National Institute for Biological Standards and Control (NIBSC). First WHO international standard anti-SARS-CoV-2 immunoglobulin (Human); 2021. https://www.nibsc.org/documents/ifu/20-136.pdf.
143. Huang B, Dai L, Wang H, Hu Z, Yang X, Tan W, et al. Serum sample neutralisation of BBIBP-CorV and ZF2001 vaccines to SARS-CoV-2 501Y.V2. Lancet Microbe. 2021;2:e285.
144. Nathan A, Rossin EJ, Kaseke C, Park RJ, Khatri A, Koundakjian D, et al. Structure-Guided T cell vaccine design for SARS-CoV-2 variants and sarbecoviruses. Cell. 2021;184(17):4401-4413.e10.
145. Fischer RJ, van Doremalen N, Adney DR, Yinda CK, Port JR, Holbrook MG, et al. ChAdox1 nCov-19 (AZD1222) protects hamsters against SARS-CoV-2 B.1.351 and B.1.1.7 disease. Nat Commun. 2021;12(1):5868.
146. Alter G, Yu J, Liu J, Chandrashekar A, Borducchi EN, Tostanoski LH, et al. Immunogenicity of Ad26.COV2.S vaccine against SARS-CoV-2 variants in humans. Nature. 2021;596(7871):268-272.
147. U.S. Food and Drug Administration (FDA). Joint CDC and FDA statement on vaccine boosters; 2021 [accessed 2021 July 08]. https://www.fda.gov/news-events/press-announcements/joint-cdc-and-fda-statement-vaccine-boosters.
148. Ministry of Health. The Vaccination Advisory Committee Presented Data and Recommended the Administration of a Third Dose to Older Adults; 2021. https://www.gov.il/en/departments/news/29072021-04
149. He Q, Mao Q, An C, Zhang J, Gao F, Bian L, et al. Heterologous prime-boost: breaking the protective immune response bottleneck of COVID-19 vaccine candidates. Emerging Microbes & Infections. 2021;10:629–37.
150. Groß R, Zanoni M, Seidel A, Conzelmann C, Gilg A, Krnavek D, et al. Heterologous ChAdox1 nCov-19 and BNT162b2 prime-boost vaccination elicits potent neutralizing antibody responses and T cell reactivity. EBioMedicine. 2022;75:103761.
151. Liu X, Shaw RH, Stuart ASV, Greenland M, Dinesh T, Provstgaard -Morys S, et al. Safety and immunogenicity of heterologous versus homologous prime-boost schedules with an adenoviral vectored and mRNA COVID-19 vaccine (Com-COV): a single-blind, randomised, non-inferiority trial. Lancet. 2021;398(10303):856-869.
152. Oxford. Preliminary data suggests mixing Covid-19 vaccine increases reactogenicity; 2021. [accessed 2021 May 13]. https://www.ox.ac.uk/news/2021-05-13-preliminary-data-suggests-mixing-covid-19-vaccine-increases-reactogenicity.
153. U.S. Food and Drug Administration (FDA). Emergency use authorization for vaccines to prevent COVID-19-guidance for industry; 2021 [accessed 2021 May 25]. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19.
154. Medicines & Healthcare products Regulatory Agency. Guidance on strain changes in authorised COVID-19 vaccines; 2021. [accessed 2021 March 04]. https://www.gov.uk/government/publications/access-consortium-guidance-on-strain-changes-in-authorised-covid-19-vaccines/guidance-on-strain-changes-in-authorised-covid-19-vaccines.
155. European Medicines Agency (EMA). Reflection paper on the regulatory requirements for vaccines intended to provide protection against variant strain(s) of SARS-CoV-2; 2021 [accessed 2021 Feb 25]. https://www.ema.europa.eu/en/regulatory-requirements-vaccines-intended-provide-protection-against-variant-strains-sars-cov-2.
156. World Health Organization(WHO). Considerations for evaluation of modified COVID-19 vaccines. In: (RPQ) RaP, ed; 2021 [Accessed 2021 Mar 12]. https://extranet.who.int/pqweb/sites/default/files/documents/Addendum_Evaluation_Modified_Covid-19%20Vaccine.pdf
157. Omicron COVID same old, scariant or game changer? 2021. https://member.procurementleaders.com/wp-content/uploads/The%20State%20of%20the%20Pandemic%20-%20with%20Juan%20Enriquez.pdf.
158. Johnson & Johnson. Johnson & Johnson to evaluate its COVID-19 vaccine against New Omicron COVID-19 variant; 2021 [accessed 2021 Nov 29]. https://www.jnj.com/johnson-johnson-to-evaluate-its-covid-19-vaccine-against-new-omicron-covid-19-variant.
159. Novavax. Novavax statement on Omicron variant response; 2021. [accessed 2021 Dec 02]. https://ir.novavax.com/Novavax-Statement-on-Omicron-Variant-Response
160. Pfizer. Pfizer and BioNtech Provide Update on Omicron Variant; 2021. [accessed 2021 Dec 08]. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-provide-update-omicron-variant.
161. AstraZeneca, Oxford Announce Work on New Version of COVID-19 Vaccine Against Omicron; 2021 [accessed 2021 Dec 22]. https://www.republicworld.com/world-news/uk-news/astrazeneca-oxford-announce-work-on-new-version-of-covid-19-vaccine-against-omicron.html.