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REVIEW

SARS-CoV-2 variants, immune escape, and countermeasures

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Abstract **Coronavirus disease 2019 (COVID-19) has become a global pandemic disease. SARS-CoV-2 variants have aroused great concern and are expected to continue spreading. Although many countries have promoted roll-out vaccination, the immune barrier has not yet been fully established, indicating that populations remain susceptible to infection. In this review, we summarize the literature on variants of concern and focus on the changes in their transmissibility, pathogenicity, and resistance to the immunity constructed by current vaccines. Furthermore, we analyzed relationships between variants and breakthrough infections, as well as the paradigm of new variants in countries with high vaccination rates. Terminating transmission, continuing to strengthen variant surveillance, and combining nonpharmaceutical intervention measures and vaccines are necessary to control these variants.**

Keywords SARS-CoV-2; COVID-19; vaccine; immune escape; breakthrough; prevention

Introduction

As of September 2021, coronavirus disease 2019 (COVID-19) has led to more than 220 million infections, which continue to increase with the spread of new variants. COVID-19 is caused by SARS-CoV-2, a positive single-stranded RNA virus that is a member of the β-coronavirus genus [1]. Coronaviruses are known to exhibit rapid replication and are prone to undergoing errors after entering cells [2,3]. These circulating viruses have been characterized in multiple host species and generate subgenomic RNA during replication, resulting in concerning mutations that cause neutralization, antibody escape, or reduced vaccine efficacy [4]. RNA viruses exhibit error-prone replication with an RNA-dependent RNA polymerase [2]. As a result of its transmission and adaptation in populations worldwide, SARS-CoV-2 has undergone rapid emergence and mutations, especially nonsynonymous mutations or deletions in the S protein, that have resulted in the formation and switches of several dominant lineages in less than 2 years [5].

Given that SARS-CoV-2 variants have aroused great concern and are expected to continue to spread [6,7], the World Health Organization (WHO) has renamed these variants as variants of concern (VOC) and variants of interest (VOI) [8]. VOC are variants with increased transmissibility or detrimental changes in COVID-19 epidemiology; increased virulence or changes in clinical disease presentation; and/or decreased effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics. VOC include B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), and B1.617.2 (Delta), which have become major variants that have overwhelmed more than 90 countries since May 2021. VOI are variants with genetic changes that are predicted or are known to affect viral characteristics. A September 2021 WHO report stated that VOI include C.37 (Lambda) and B.1.621 (Mu).

Although many countries have promoted roll-out vaccination, the immune barrier has not yet been fully established because of the uneven and inequitable distribution of vaccines. Thus, people remain susceptible to COVID-19. In countries with high vaccination coverage rates [9], such as the UK and Israel, new cases, including breakthrough infections after vaccination, caused by novel variants have appeared [10].

We here discuss SARS-CoV-2 VOC, including their characteristics, infectivity, and pathogenicity; vaccine efficacy against variants; and the effect of new variants

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in countries with high vaccination coverage. We then propose several countermeasures in accordance with the current situation and trends of these variants.

Genomic characteristics, transmissibility, and pathogenicity of circulating variants

D614G variants

In D614G variants, aspartic acid is replaced with glycine at position 614 of the spike protein. D614G variants are often detected with SNP sites 241, 3037, and 14408 simultaneously in reference to the SARS-CoV-2 genome (GenBank: MN908947.3). The global dispersal and increasing frequency of the D614G variant are considered to be a selective advantage and a random founder effect [11,12] originating from genetic drift during the early evolution of SARS-CoV-2. D614G has been detected in Europe since January 2020 and has spread to North America, Oceania, South America, and Asia, where it has become an important typing locus. As of September 2021, the D614G strain has accounted for 98% of all sequenced viruses [13].

Accumulating evidence suggests that the D614G strain has spread more rapidly than the original virus [12]. The D614G variant demonstrates increased infectivity *in vivo* and superior transmission as inferred from epidemiological data [12]. It can affect the structure of the spike protein and thus increase binding affinity for human angiotensin-converting enzyme 2 (ACE2), which is needed to gain cell entry [14]. However, this variant does not affect disease severity [12].

Alpha (B.1.1.7)

The alpha variant, also known as VOC-202012/01, 20B/501Y.V1, or the B.1.1.7 lineage, was first detected in the UK in September 2020. It contains 14 nonsynonymous point mutations and three deletions, among which eight are located in the spike protein: N501Y, △H69/△V70, △Y144, A570D, P681H, T716I, S982A, and D1118H. In mice, N501Y increases the affinity between the receptor binding domain (RBD) and ACE2 and thus enhances the replication capability of the mutant. △H69/△V70 was first found in patients with long-term infection and has possibly arisen as a result of viral evolution under immune selection pressure in infected individuals [15]. P681H, which is located in the furin cleavage site, may be associated with increased viral infectivity [7]. At present, the evolutionary path of the Alpha variant has not been elucidated.

As of September 2021, Alpha variant strains account for 33% of all of the viral strains detected in countries or regions worldwide, such as Europe [13]. From April 2021 to early June 2021, the proportion of the Alpha variant showed a significant reduction likely because Delta variant strains have significantly increased since April. Compared with pre-existing viruses, the Alpha variant is transmitted more efficiently by 43% to 90% [16] and has a higher viral load [17]. Furthermore, it is associated with a 61%–64% increased risk of death in cases of COVID-19 infections [18,19].

Beta (B.1.351)

The Beta variant, also known as 20H/501Y.V2 or the B.1.351 lineage, was first detected in South Africa in October 2020 and has expanded since December 2020. The Beta variant possesses three mutations in its RBD region: K417N, E484K, and N501Y. Other mutations in its spike proteins include L18F, D80A, D215G, R264I, and A701V. The coexistence of K417N, E484K, and N501Y has resulted in the reduced antibody response of several neutralization antibodies and vaccines [7].

As of September 2021, the Beta variant accounts for 1% of all the uploaded viral genomes found worldwide; this variant has been mainly found in South Africa and other African countries or regions [13]. The Beta variant had spread significantly from October 2020 to April 2021. Similar to the Alpha variant, the Beta variant has shown a decreasing trend since April 2021 [13]. B.1.351 adapted in the population through global spread, and B.1.351.1, B.1.351.2, and B.1.351.3 subsequently appeared with accumulated mutations. The transmissibility of the Beta variant may increase by approximately 50% [20,21]. The pathogenicity of the Beta variant has neither significantly increased in cell experiments nor in real-world data from South Africa [22].

Gamma (P.1)

The Gamma variant, also known as 501Y.V3 or the P.1 lineage, was first detected on January 6, 2021, from four Japanese individuals arriving in Tokyo who had traveled to the Brazilian Amazon a few days earlier [23]. In addition to E484K, K417T, and N501Y, the Gamma variant has a signature set of unique amino acid changes in its spike protein. These mutations include L18F, T20N, P26S, D138Y, R190S, H655Y, and T1027I. The Alpha and Beta variants share the N501Y mutation, whereas the Beta and Gamma variants share the E484K mutation. The Gamma variant evolved during human transmission and produced new variants during its subsequent spread. These new variants include the P.2 (Zeta) and P.3 (Theta) variants. The Zeta variant carries only the E484K mutation without the other two related mutations, namely, N501Y and K417T.

Evolutionary analyses [24] have revealed that the Gamma variant did not accumulate in a single chronically infected patient but was acquired successively in multiple infections, that is, due to selection pressure from the

population. Since August 2020, the progenitor virus of the P.1 lineage has spread rapidly throughout the Brazilian state of Amazonas. This evolutionary pattern suggests that natural selection under host–virus interaction is the driving force of the emergence and worldwide spread of the Gamma variant [25]. The successive lineage replacements in the Amazonas were driven by a complex combination of poor nonpharmaceutical intervention (NPI) and the emergence of a Gamma variant with increased transmissibility.

This variant has been reported to increase the transmissibility of the virus (1.4–2.2 times) and has even caused a widespread second round of the COVID-19 epidemic in the capital of the Amazonas in early 2021; however, its pathogenicity remains unclear, and it may be associated with a possible increase in transmissibility [23]. As of September 2021, the cumulative percentage of Gamma variant strains is approximately 3% [13].

Delta (B.1.617.2)

The Delta variant, also known as VUI-21APR-02 or the B.1.617.2 lineage, was first detected in India in late 2020. Several mutations have been found in the spike protein of the Delta variant: T19R, L452R, T478K, D614G, P681R, and D950N. In addition to the RBD in the spike protein, the N-terminal domain (NTD) region of the Delta variant contains multiple amino acid mutations, a characteristic that distinguishes this variant from other VOC. The Delta variant originated from the B.1.617 lineage, which gradually formed B.1.617.1, B.1.617.2, and B.1.617.3 through evolution in the population. The Delta variant was listed as a VOC by the WHO on May 11, 2021 due to its rapid global spread [8]. As of September 2021, the Delta variant accounts for 29% of all the uploaded viral genomes all over the world [26]. India and Turkey reported the highest number of Delta variant cases. The Delta variant has also been detected in Vietnam, the UK, and Russia. As of June 20, 2021, variants from the UK account for 76.7% (49 407/64 449) of all the Delta variants detected globally [13]. During the epidemic period of the Delta variant, the New Delta plus variant (B.1.617.2.1 Delata-AY.1) with K417N mutation appeared and caused infection rates in Louisiana, US, to soar.

The UK government's monitoring report stated that the Delta variant, which accounted for more than 90% of the detected strains in the UK in June 2021 [13], has been responsible for a small rebound since it was first detected in the country in March 2021. The Delta variant can exhibit significantly greater transmission than the Alpha or Kappa variant and has higher replication and spike-mediated entry rates than B.1.617.1 [27,28]. L452R and Y453F can escape the human HLA-A24-presented T-cell response [29]. Moreover, viruses with these two mutations have increased infectivity, enhanced cell fusion, and accelerated viral replication [29]. In terms of pathogenicity, Delta variant infections have higher hospital admission rates or emergency care attendance risks than Alpha variant infections in England [30]. Public Health England (PHE) showed that as of September 2021, the case fatality of the Delta variant is 0.4%, which is approximately one third that of the Alpha variant [31].

VOI and other variants

Lambda (C.37) was first documented in August 2020 and designated as a VOI on June 14, 2021. Its spike mutations include D614G, T859N, L452Q, F490S, T76I, G75V, R246N, and del247/253. The number of Lambda variants increased significantly from April to June 2021 and has shown a decreasing trend since middle of June, 2021. As of September 2021, the Lambda variant accounts for less than 0.5% of total viruses and is mainly distributed in South America [26]. The higher infectiousness of the Lambda variant than that of other variants may be attributed to T76I and L452Q mutations [32].

Mu (B.1.621) was considered as a VOI on August 30, 2021 and has been detected in more than 20 countries.

Iota (B.1.526) was first detected in New York, the US, in November 2020 [33]. Mutations in its S proteins include E484K/S477N, D614G, A701V, T95I, D253G, and L5F, among which S477N has been reported to be associated with the immune escape of multiple vaccines and neutralizing antibodies [34]. The lineages B.1.526.1, B.1.526.2, and B.1.526.3 gradually formed after adaptation in populations. As of September 2021, the Iota variant has accounted for approximately 1% of total viruses [13].

Kappa (B.1.617.1), also known as VUI-21APR-01, was first discovered in India in late 2020. Its spike mutations include L452R, E484Q, D614G, and P681R. The appearance of linkage mutations at the L452R, E484Q/K, and P681R sites in multiple lineages at the same time suggests that the Kappa variant may have originated via convergent evolution [35]. As of September 2021, the Kappa variant accounts for less than 0.5% of reported strains and is distributed mainly in India [13].

Epsilon (B.1.427/429) was first discovered in the US at the end of 2020. Its S protein mutations mainly include D614G, L452R, and W152C. Until September 2021, the Epsilon variant accounted for 2% of total viral sequences and was mainly found in the US [13]. The Epsilon variant is approximately 20% more infectious than other strains [36]. However, its pathogenicity remains unclear.

The mutation sites located in the spike protein may affect immune escape, affinity with receptors, and RBD structure. Furthermore, SARS-CoV-2 is highly glycosylated especially in its spike and N proteins [7]. The acquisition of a new glycosylation motif may lead to immune escape by shielding epitopes from antibody binding [37]. The mutations L18F, P26S, D138Y,

DEL145, and R246I in the NTD may be the targets of antibody recognition due to their proximity to glycosylation sites [38].

Most of the monoclonal antibodies against the NTD of the spike protein have lost their neutralizing activity against the Alpha and Beta variants, whereas several RBD-directed antibodies have retained their neutralization capability [39,40]. K417N specifically escapes LY-CoV016, and E484K specifically escapes LY-CoV555 [40]. Moreover, the risk of resistance may be reduced with the use of the cocktails of more than two monoclonal antibodies targeting distinct epitopes [41]. These cocktails include REGN-COV [42] and the combination of bamlanivimab (LY-CoV555) and etesevimab (LY-CoV016) [40]. REGN-COV (casirivimab and imdevimab) retains satisfactory neutralization activity against the Alpha, Beta, Gamma, Delta, L452R, and E484K variants [42].

Vaccine effectiveness against variants

People need vaccination to build immunity for protection against SARS-CoV-2 infections. The resistance of emerging and circulating variants to various vaccines has aroused great concern. Numerous experiments and trials have been performed to evaluate these effects, and clinical data will continue to be accumulated to determine whether existing vaccines are losing effectiveness against new emerging variants.

Several studies have evaluated the resistance of different variants to various vaccines. In general, no significant change has been found in the neutralization activity of D164G strains and the Alpha variant, which was approximately 1–4 times lower than that of the wild strain [20,39,43–49]. The neutralization activity of inactivated BBIBP-CorV and ConoraVac vaccine-elicited sera against the Beta variant is 30%–50% of that against wild-type strains [47]. Similarly, the neutralization activity of the BNT162B2 and mRNA-1273 vaccine against the Beta variant had decreased [39,46,48,49]. The neutralization activity of the recombinant vaccine RBD ZF2001 against the Beta variant had decreased by approximately 1.6 times [50]. The neutralization activity of BNT162B2, mRNA-1273, and the ConoraVac vaccine against the Gamma variant had decreased by approximately 4–7 times [48,49]. Compared with that against the Alpha variant, the neutralization activity against the Delta variant was 3 to 8 times lower in the serum of recovered patients and BNT162B2-vaccinated patients [28,51]. Serum from AZD1222 vaccine-elicited patients after only one dose barely inhibited the Delta variant [51]. The transmission of the Delta variant was associated with escape from antibodies targeting the S protein epitope. Additionally, the Delta variant can escape neutralizing antibodies specific to the NTD region [7].

The effectiveness of vaccines against VOC has been evaluated in several settings (Fig. 1A). Novavax reported that in a phase III trial involving 29 960 participants in the US and Mexico, NVX-COV2373 provided 90% protection (95%CI 82.9%–94.6%) against SARS-CoV-2 infections and 100% protection against moderate to severe COVID-19. Comprehensive protection against VOC and VOI variants was 93% and 100% for non-VOC/VOI strains [52]. The protection rate of the Chadox1 nCoV-19 (AZD1222) vaccine against the Alpha variant was 70% to 74.5% [43,53]. The BNT162b2 vaccine trail in Israel, which is dominated by the Alpha variant ($> 90\%$), reported a protection rate of 94% [54]. In studies conducted in Qatar, the BNT162b2 vaccine was found to be approximately 87% effective against the Alpha variant [55]. Two doses of BNT162b2 were 93.7% effective against the Alpha variant in the UK. The effectiveness of the mRNA vaccine NVX-COV2373 against the Alpha variant was 85.6% [56]. In South Africa, the adenovirus vector vaccine AstraZeneca AZD1222 had a low-level protection rate of 21.9% among more than 2000 HIV-negative people and a protection rate of only 10.4% against the Beta variant [57]. NVX-COV2373 was reported to present only 49.4% effectiveness in South Africa [44]. A study carried out in Qatar showed that the BNT162b2 vaccine had a protection rate of 72.1% against the Beta variant [55]. In Brazil, wherein the Gamma variant is prevalent, the ConoraVac vaccine showed a vaccine protection rate of 50.7% [58]. The ConoraVac vaccine exhibited 65.9% and 90.3% effectiveness for SARS-CoV-2 infection and COVID-19-related deaths, respectively, in Chile [59], wherein mostly P.1 (Gamma variant), B.1.1.348, and C.37(Lambda) lineages are circulating. Two doses of the BNT162b2 vaccine provided 79% to 88% protection against the Delta variant [53,60]. The effectiveness of two doses of AZD1222 vaccine was 60%–67% against the Delta variant [53,61]. Full vaccination with inactivated vaccines was 59.0% effective against the Delta variant in China [62].

However, COVID-19 vaccines remain effective against SARS-CoV-2 infection requiring hospitalization, ICU admission, and emergency care visits. In patients who were admitted to hospitals with different mutant variants, the effectiveness of mRNA vaccination ($\geqslant$14 days after the second dose) was 89% against infection leading to hospitalization, 90% against infection leading to ICU admission, and 91% against infection leading to an emergency care visit [63]. Another retrospective study found that in 126 of the 12 383 patients infected with the Delta variant, of whom 83 were unvaccinated and only 3 were vaccinated with 2 doses, the protection rate was approximately 95% [31]. A cohort study in England reported that the hospital admission or emergency care attendance rates for a subgroup of vaccinated patients

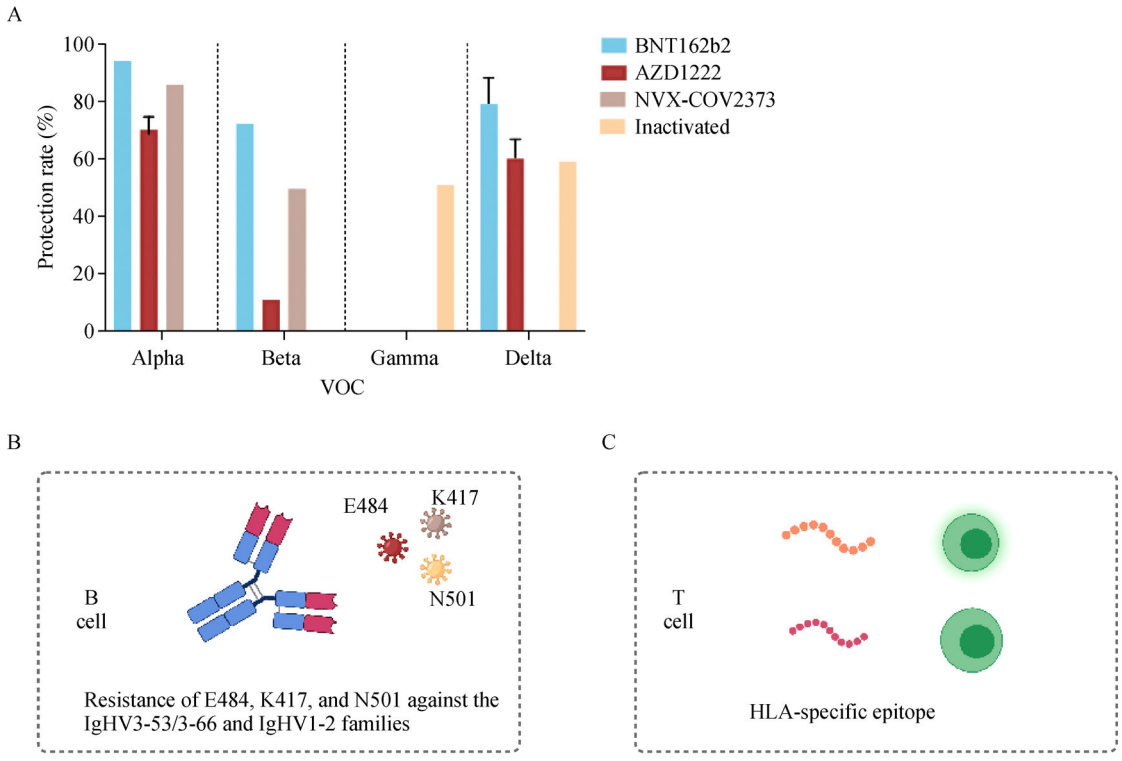

Fig. 1 Effectiveness of different vaccines against VOC and examples of the potential immune escape mechanism of variants. (A) Protection rate of different vaccines (BNT162b2, AZDq222, NVX-COV2373, and inactivated vaccine) against VOC (Alpha, Beta, Gamma, and Delta variants). Bars show the protection rate ranges of AZD1222 against the Alpha variant and of BNT162b2 and AZD1222 against the Delta variant. (B and C) Examples of the potential immune escape mechanism of SARS-CoV-2 variants. The B panel shows that resistance against the IgHV3-53/3-66 and IgHV1-2 family may be the mechanism of the E484, K417, and N501 variants. The C panel illustrates that specific HLA types possess a distinct epitope that could lead to different T cell responses.

(⩾21 days after the first vaccination dose and with and without a second dose) showed no significant difference between patients with the Delta variant (6.4%) and patients with the Alpha variant (5.3%) [64]. The effectiveness of two-dose vaccination was 70.2% against moderate COVID-19 and 100% against severe COVID-19 in patients infected with the Delta variants in China.

The potential mechanisms of immune escape include T and B cell response (Fig. 1B) and human susceptibility. Although the $CD4^+$ T cell response to the variants remained stable, SARS-CoV-2 variants escaped humoral immunity in convalescent patients with COVID-19 and vaccine recipients; this phenomenon may be one of the reasons for immune escape [65]. In addition, the resistance of E484, K417, and N501 against the IGHV3-53/3-66 and IGHV1-2 families decreased the activities of the vaccine and the neutralizing antibody [66]. The SARS-CoV-2 mutations in MHC-I-restricted epitopes could evade $CD8^+$ T cell response [67]. Specific HLA types could lead to different human T cell responses, including enhancement or weakening and changes in neutralization activity [68].

The similarity in antigens among distinct variants may help the development of vaccines with universal protection. The convalescent plasma from recovered patients infected with the Alpha variant had high neutralization activity against the Delta variant. The opposite trend was found in recovered patients with the Beta variant; the two variants lacked cross-neutralization activity due to the significantly different amino acid mutations in their RBDs, whereas the Alpha and Delta variants had similar antigenic properties [45]. The development of vaccines with universal effectiveness against different variants is therefore worthwhile.

Relationships between variants and breakthrough infections

Given that vaccines do not provide full protection, breakthrough infections can occur, and their protection rate has gradually declined [69]. Although the incidence of breakthrough infections in vaccinated individuals is extremely low, variants mediate the majority of cases of breakthrough infections (Fig. 2) [70]. The breakthrough

rate among 3000 health workers who received AZD1222 vaccinations in India was 1.6% [10] with a median occurrence time of 29.5 days after vaccination. As of the end of April 2021, 10 262 breakthrough infections have been detected in 10 262 out of 101 million people (0.01%) in the US, of which 64% were caused by SARS-CoV-2 variants [71]. The breakthrough infections in Israeli healthcare workers had a detection rate of 2.6%, and 85% was caused by the Alpha variant [72]. In health workers who completed vaccination in the US, the attack rate was < 0.3 per 1000 persons from March to June 2021 and 5.7 per 1000 persons in July 2021; these infections were mainly caused by the Delta variant [69].

Effectiveness against VOC after vaccination may decrease within a particular time window [73]. Vaccinees who tested positive for SARS-CoV-2 at least 7 days after their second dose were more likely to be infected by the Beta variant than by other variants. The Alpha variant caused most of the breakthrough infections in patients who tested positive for SARS-CoV-2 between 2 weeks after their first dose and 6 days after their second dose. In addition to VOC strains, the B.1.429 lineage and mutations △H69/△V70, △Y144, and L18F [10] in the spike protein cause breakthrough infection. These mutations cause immune escape. Therefore, breakthrough infection should be monitored closely.

Most of the viral strains that have been found to cause breakthrough infections are VOC strains, which have become the dominant variants worldwide. The typing of these VOC is consistent with that of the local prevalent variants. Clinical analysis showed that most of breakthrough infections were mild or asymptomatic, and old age and anemia may be their risk factors [74]. Compared with uninfected controls, patients with breakthrough infections had relatively lower neutralizing antibody titers that were associated with increased infectivity [72]. The serial testing of asymptomatic patients may be helpful for identifying variations in neutralizing antibody and T and B cell responses [10]. The viral mechanism and host immune response in breakthrough infection needs to be further explored.

Paradigm of new variants in countries with high vaccination rates

The proportions of individuals who had received at least one vaccine dose in Israel, the UK, and the US have all surpassed 50%. As of September 2021, Israel and the UK have current vaccination dose rates of 167 and 135 doses per 100 people, respectively, and full vaccination rates of 63% and 65%, respectively. In the US, the vaccine dose rate is 114 doses per 100 people, and the complete vaccination rate is 54% [9].

The Delta variant accounts for more than 98% of the confirmed cases in Israel and the UK in August 2021 [26]. The number of new cases in the UK increased to an average of 9016 cases per day in June 2021. The Delta variant may be responsible for some of the rebound since it was first detected in the UK in March 2021 (Fig. 2A). In the US, the Delta variant accounted for 80% of the cases, especially in Utah, Kansas, and Missouri, in August 2021 [75]. Given that the Delta variant accounted for a high proportion of all cases, the 7-day case-fatality rate has continued to increase and has even surpassed 1% since the end of October 2021 [26] (Fig. 2B). In Israel, the number of new cases has also increased since the end of July 2021, and the 7-day case-fatality rate has reached 0.3%–0.4% [26] (Fig. 2C).

In Israel, more than 50% of new cases are patients under 20 years old who have not yet received vaccines. The PHE of the UK reported that the increase across the UK is being driven by younger age groups, many of whom have now been invited for vaccination as the jab rollout is extended to anyone aged 18 years and over [76]. From July 30 through August 31, 2021,1 137 804 people who were 60 years of age or older received a third dose, namely, booster vaccination, in Israel. The governments of countries have attempted to control the resurgence of cases caused by Delta variant by deploying new vaccination strategies and proper NPI. Although the vaccination rates in Israel, the UK, and the US are at the forefront of the world, breakthrough cases were confirmed (Fig. 2D), accounting for approximately 0.01%–5.7% of vaccinated patients [10,69,70,73,74]. As a result, promoting vaccination widely and strengthening prevention measures despite high population coverage rates are still needed. However, whether a booster dose should be received now or deferred and the specific booster strategy until the primary vaccination is made available to additional people remains controversial.

Future directions and countermeasures

Animal experiments and real-world studies have shown that adaptive mutations can occur *in vivo*, especially under the selection pressure of viral transmission, antiviral therapy, and public health interventions. In essence, stopping the spread of SARS-CoV-2 is the way to stop the continued emergence of variants.

Host–pathogen interaction promotes B cell evolution for protection against existing variants. The immune response of patients who had recovered from COVID-19 showed that neutralization capability and RBD-specific memory B cell numbers remained relatively stable over 6–12 months, and vaccination could significantly enhance humoral immunity [77]. Broad responses to vaccines may involve somatic mutation; memory B cell clonal turnover; and the development of antibodies, including those against

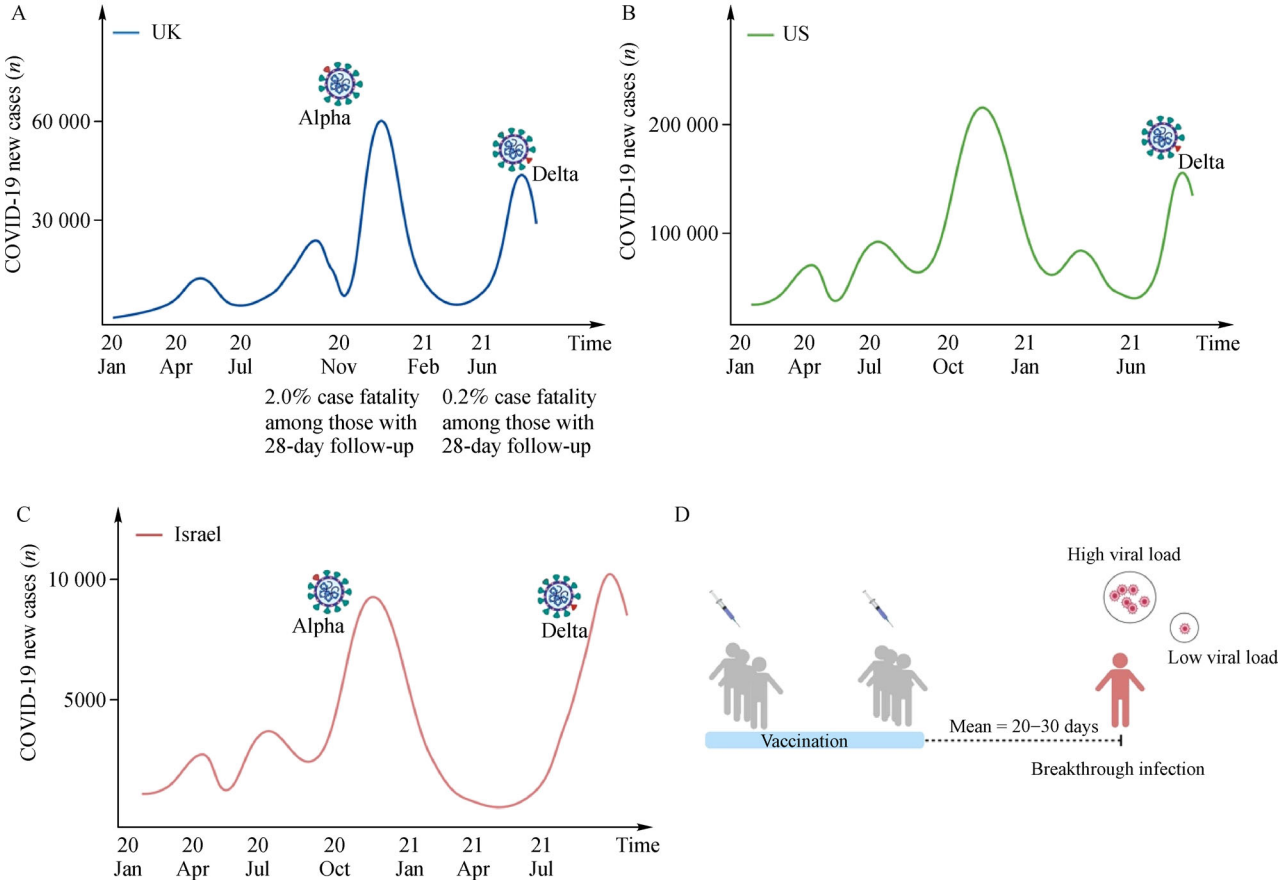

Fig. 2 Paradigm of new variants in countries with high vaccination rates. (A) Trend of cases in the UK since January 2020. (B) Trend of cases in the US since January 2020. (C) Trend of cases in Israel since January 2020. (D) Characteristics of postvaccination breakthrough infections.

variants, thus suggesting that the evolution of B cells against variants [78] affects host–virus interaction and coevolution.

Although the relationship between antibody titers and effectiveness has not been fully defined, the relationship between serum neutralization titers and protective power has been preliminarily solved through models. The neutralization level needed for 50% protection against detectable SARS-CoV-2 infection has been estimated to be 20.2% of the mean convalescent level [79].

COVID-19 vaccination could protect unvaccinated populations as well. Studies on unvaccinated adolescents under 16 years of age in Israel showed that for every 20% of the vaccinated population, the rate of infections in the unvaccinated population dropped by two times [80]. Additionally, vaccination with BNT162b2 and mRNA-1273 could provide unvaccinated family members with 8.7% protection against viruses 2 weeks after the first dose of the vaccine and 42.9% protection after 10 weeks [81]. This situation indicates the possibility of building an immune barrier and that vaccination could reduce viral transmission.

The mRNA-1273.351 vaccine against the Beta variant is in phase I clinical trials in the US [82]. At the same time, the recombinant subunit protein vaccine RS-B.1.351 against the Beta variant have induced high titers of neutralizing antibodies against B.1.351 in mice and clinical trial subjects. Pfizer/BioNtech is seeking FDA approval for booster vaccination against the Delta variant [83]. A framework for evaluating vaccines against variants has been suggested [84]. Given the evidence for the effectiveness of existing vaccines against VOC, we might expand the coverage of variants, change to a new variant S antigen, or use a polyvalent S-antigen formulation in the future.

As of September 2021, approximately 40% of the world population has received at least one vaccine dose [9]. However, a large amount of people around the world remains susceptible to infection and are particularly susceptible to severe COVID-19 and even death because they are not yet vaccinated or have not yet received the full vaccination course. The WHO recommends continuing to take a comprehensive approach using all of the tools at our

disposal to prevent infection; these tools include recognizing different levels of risks, vaccinations, and NPI [85]. Several models have confirmed the effectiveness of NPI, which includes social distancing, self-isolation, school closure, and travel restrictions [86]. The R0 cannot be reduced below 1 through vaccination alone [87]. As a result, the combination of NPI measures and vaccination should remain in place.

Conclusions

Although we have learned how to respond to emerging infectious diseases from our experiences with influenza and SARS-CoV, many challenges remain. Vaccines remain effective in preventing SARS-CoV-2 variants. Terminating virus transmission, continuing to strengthen variant surveillance and NPI measures, and promoting vaccines are necessary to prevent the spread of these variants.

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Compliance with ethics guidelines

Yi Zhang, Haocheng Zhang, and Wenhong Zhang declare that they have no competing interests. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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