Review Article

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Delta variant: Partially sensitive to vaccination, but still worth global attention

Meng Zhang[1], Yanchao He[1], Zhijun Jie[1,2]

[1]Department of Pulmonary and Critical Care Medicine, Shanghai Fifth People's Hospital, Fudan University, Shanghai 200240, China.

[2]Center of Community-Based Health Research, Fudan University, Shanghai 200240, China

ABSTRACT

The pandemic coronavirus disease 2019 (COVID-19) has rapidly spread to all countries worldwide. The emergence of its variants has exacerbated this problem. To date, many variants have been identified across the viral genome; the variants of concern are the focus of attention due to their higher transmissibility and resistance to vaccines, especially the delta variant. The delta variant has become the dominant severe acute respiratory syndrome novel coronavirus (SARS-CoV-2) variant worldwide, causing severe panic as it is highly infectious. A better understanding of these variants may help in the development of possible treatments and save more lives. In this study, we summarize the characteristics of the variants of concern. More importantly, we summarize the results of previous studies on the delta variant. The delta variant has a high transmissibility rate and increases the risk of hospitalization and death. However, it is partially sensitive to vaccines. In addition, nonpharmaceutical interventions are valuable during epidemics. These interventions can be used against the delta variant, but managing this variant should still be taken seriously.

Key words: severe acute respiratory syndrome novel coronavirus, variants of concern, vaccine, delta variant

INTRODUCTION

Since the pandemic occurred, severe acute respiratory syndrome novel coronavirus (SARS-CoV-2) has rapidly spread in all countries worldwide, with nearly 200 million confirmed cases and over 4 million deaths reported worldwide.[1] SARS-CoV-2 belongs to the cluster of β-coronaviruses with positive-sense, single-stranded RNA (ssRNA).[2] It is much easier for RNA viruses to mutate due to the intrinsically error-prone nature of RNA polymerase during replication.[3] The gene correction mechanism in coronaviruses such as SARS-CoV-2 increases the replication accuracy and viral transcription; this means that the mutation accumulation rate would be slower than that of other RNA viruses.[4] At present, according to the characteristics of the variants, the US government interagency organizations have divided the variants into three classes: (1) variants of interest (VOI); (2) variants of concern (VOC): B.1.1.7 (alpha variant), B.1.351 (beta variant), B.1.617.2 (delta variant), and P.1 (gamma variant); and (3) variants of high consequence: none of the variants have been classified as variants of high consequence.[5]

Among these variants, delta variant, which was first reported in India, has surpassed the alpha variant and has gradually become the major global pandemic variant since June 2021, with 89% of coronavirus disease 2019 (COVID-19) patients infected with this variant on July 26, 2021.[6,7] Similar to other SARS-CoV-2 variants, the delta variant can attack cells by binding between viral spike proteins and host angiotensin-converting enzyme 2 (ACE2),[8-11] during which the receptor-binding domain (RBD) on the spike protein plays a fundamental role.[12-14] RBD is also a dominant immune epitope of the spike protein.[15-17] The mutations in

Address for Correspondence:
Prof. Zhijun Jie, Department of Pulmonary and Critical Care Medicine, Shanghai Fifth People's Hospital, Fudan University, No 128 Ruili Road, Minhang District, Shanghai 200240, China.
E-mail: jiezjlxh@163.com

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the spike protein significantly increase the infectivity and transmissibility of the delta variant.[18-20] Colhoff, staff of the World Health Organization (WHO), stated that the delta variant has now spread to 92 countries worldwide. More than 10,000 new cases per day were confirmed in the UK, 99% of which were caused by the more infectious delta variant; it replaced the alpha variant and became the main British pandemic variant.[21,22] In the USA also, the proportion of COVID-19 cases caused by the delta variant is increasing, which was approximately 31.1% (95% confidence interval [CI], 24.6%–48.3%) on July 20; now, it has exceeded the proportion of COVID-19 cases caused by the alpha variant, with a proportion of 82.2% (95% CI, 78.3%–86.0%).[23] It has become a huge concern in many countries, threatening the control and prevention of the global epidemic, especially in some developing countries with poorly prepared public health systems.[24,25] This study summarizes the characteristics of VOC, especially the results of previous studies on the transmissibility and clinical severity of the delta variant, and the vaccine efficacy. We provide advice on maintaining a positive, but serious attitude in the midst of the COVID-19 pandemic and suggestions on the prevention and control of epidemics.

REASONS OF MUTATION

Mutation is a common phenomenon in the evolution of viruses, and SARS-CoV-2 is no exception. Mutation provides an opportunity for viruses to adapt to a new host and/or evade the host immune response.[26] Coronavirus has a non-structural protein with exoribonuclease activity, which can perform gene correction.[27,28] It also allows the coronavirus to continuously mutate compared with other RNA viruses,[29] making it easier for a novel coronavirus to invade the host and cause damage.

As the virus spreads, selective pressure drives the retention of certain new mutations.[2] With regard to SARS-CoV-2, the spread of this virus to a huge amount of susceptible population allows virus replication, and thus induces more new mutations. The different strengths of the immune response of patients during host-to-host transmission contribute to selective pressure, which probably promotes the retention of adaptive mutations, facilitating faster spread and longer incubation period and even causing immune evasion.[29] For instance, high population density and inadequate epidemic control in India created opportunities for the emergence of delta variants, which accumulated new mutations such as T19R, T478K, and P681R.[30,31] However, not all mutations have the incredible ability to increase or decrease infectivity. The mutation may be caused by the genetic drift,[32] including the gene hitchhiker or founder effect. A typical example of SARS-CoV-2 mutation is the D614G mutation.[33,34] The D614G mutation may result from replacement of the hitchhiker gene. D614G is accompanied by a mutation in ORF1A/B (P4715L), which may enhance the variant's adaptability and in turn benefit the advantageous mutation – D614G.[35,36]

With the transmission of the virus among the population, American epidemiologist Fauci stated, "You still have a fixed immunogen and a virus that is changing. Sooner or later, you are going to get a mutant that evades that."[37] The SARS-CoV-2 variant, like delta variant, may gain a significant adaptation advantage and greatly influence the efficacy of existing therapeutic regimens.[38] To effectively control the variants, more studies on the specific origin and evolution of SARS-CoV-2 variants are warranted in order to develop new methods, such as blocki ng one step of the evolution of variants.[39]

GLOBAL MAINSTREAM VARIANT – DELTA VARIANT

VOC are more infectious than VOI and can cause severe diseases. In addition, patients infected with VOC have produced significantly less neutralizing antibodies (NAbs) regardless of the status of infection or vaccination, making it difficult for some tests to diagnose the infection and reducing the effectiveness of treatments and vaccines.[5] Herein, we aimed to summarize the characteristics of VOC (Table 1), especially a detailed description of the delta variant in terms of infectivity, severity, and impact on vaccines (Tables 2 and 3), which has become a global concern.

Characteristic mutations in spike protein

Delta variants have a variety of new mutations, including T19R, T478K, and P681R, which were not found in previous variants (Figure 1). The D614G mutation is shared with other VOC and increases the infection titers.[35] In addition to the D614G mutation, the delta variant has some important mutations such as L452R, T478K, and P681R. Like N501Y, the L452R and T478K mutations are also located in the RBD, suggesting that they may also have an effect on the infectivity of the variant.[40] Deng *et al.*[26] infected 293T cells, which stably expressed the ACE2 receptor and the TMPRSS2 cofactor of SARS-CoV-2, with a pseudovirus carrying the L452R mutation. In 293T cells, the reproductive number of pseudoviruses carrying the L452R mutation was 5.8–14.7 times higher than that of pseudoviruses carrying the D614G mutation, suggesting a higher infectivity of the L452R mutation. In addition, researchers have employed the TopNetTree model to predict the binding free energy (BFE) changes of RBD and ACE2 induced by mutations. The infectivity of different variants is directly proportional to the BFE between the

Table 1: The characteristics of VOC

VOC	Alpha variant	Beta variant	Gamma variant	Delta variant
Alternative name	20I/501Y.V1 VOC202012/01 B.1.1.7	20H/501.V2 B.1.351	20C/S:452R CAL.20C P.1	20A/S:478K B.1.617.2
First identification	September 2020 UK	October 2020 South Africa	January 2021 Japan/Brazil	October 2020 India
Affected nations	182	131	81	132
Transmissibility	Increase > 50%	Increase > 50%	Increase 40%–120%	Increase > 100%
Severity	Increased risk of hospitalization Increased fatality	Increased reinfection rate	Increased mortality Increased reinfection rate	Increased risk of hospitalization and deaths
Immunogenicity (neutralization antibody)	Mildly to moderately reduce Significantly reduce with E484K mutation	Significantly reduce	Moderately reduce	Moderately reduce
Reference	[3],[5],[70],[71],[72],[73],[74],[75]	[5],[75],[76],[77],[78]	[3],[5],[26],[75] [79],[80]	[5],[18],[22],[49],[63],[75], [81]

VOC: variants of concern.

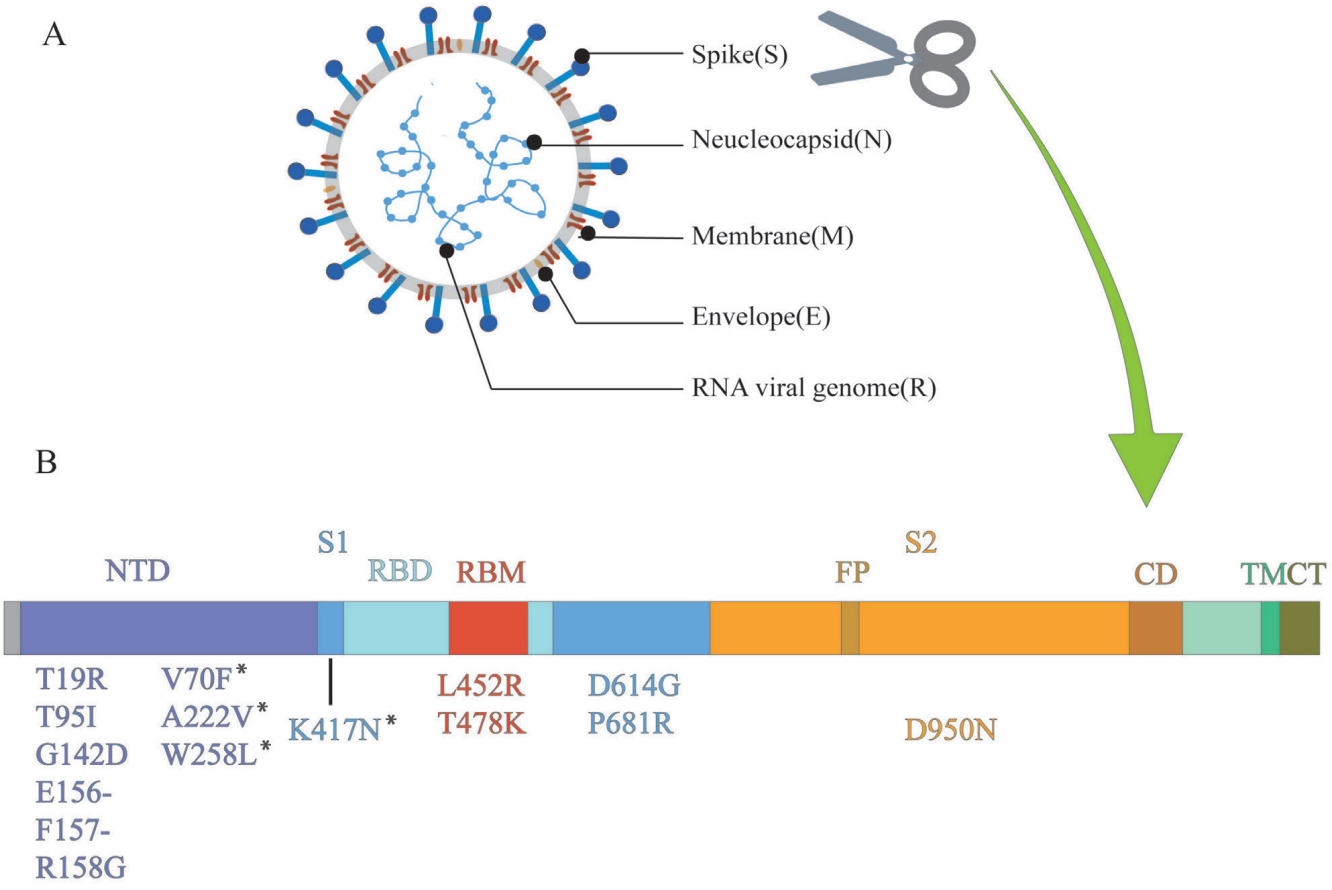

Figure 1: Structure of SARS-CoV-2 and mutations of delta variant. (A) SARS-CoV-2 forms coated spherical particles with diameters of 100–160 nm. It contains a 27–32 kb positive ssRNA genome. Envelope glycoproteins spike protein (S), envelope (E), membrane (M), and nucleocapsid (N) are encoded by 3' terminal genome. (B) Spike protein is critical for the virus to invade the host, which is also a key focus in the research on SARS-CoV-2. S1 and S2 subunits and a transmembrane domain constitute a spike protein. Scissor cuts at the boundary of S1 and S2. RBD containing the core-RBD and RBM, and NTD are on S1, which undertakes the role of binding to the host cell receptor, especially RBD, while S2 consists of FP, CD, and CT, contributing to membrane fusion. Mutations of delta variant are marked in the figure. ssRNA: single-stranded RNA; NTD: amino-terminal domain; RBD: receptor-binding domain; RBM: receptor-binding motif; FP: fusion peptide; CD: connecting domain; TM: transmembrane domain; CT: cytoplasmic tail; SARS-CoV-2: severe acute respiratory syndrome novel coronavirus. *Detected in some sequences of delta variant, but not all.

Table 2: The effects of Delta variant on neutralizing antibody

Vaccine	Serological assay	Samples	Reference objects	Serum specimen	Median age	Country	Result	Reference
BNT162B2	Pseudovirus	20	Wild type	Two doses	NA	USA	GMT: wild type was 502 B.1.617.2-spike was 355 B.1.617.2-v2-spike was 343	[22]
	Live virus	250	Wild type	Two doses One dose	42	UK	Two doses: NAbTs: 5.8-fold reduced (95% CI 5.0–6.9) One dose: 68% had low NAbTs (IC_{50}* < 40)	[63]
	Pseudovirus	36	Wild type	Two doses	48	Israel	Delta-S1#: NAbTs: 2.6-fold reduced (95% CI, 1.8–3.5) Delta-S2: NAbTs: 2.1-fold reduced (95% CI, 1.7–2.5)	[82]
	Pseudovirus	9	D614G	Two doses	31	USA	NAbTs: 3.6-fold reduced	[83]
ChAdOx1	Live virus	106	BNT162B2 Wild type	Two doses One dose	34	UK	Two doses: NAbTs: 2.5-fold reduced (95% CI, 1.4–2.7) relative to BNT162B2 One dose: 85% (95% CI, 68%–94%) had quantifiable NAbTs; 91% (95% CI, 75%–98%) wild type had quantifiable NAbTs	[63][64]
mRNA-1273	Pseudovirus	8	D614G	Two doses	41	USA	NAbTs: fourfold reduced	[83]

NA: not available; GMT: geometric mean neutralizing titers; NAbT: neutralizing antibody titers. IC_{50}*: 50% inhibitory concentration; #delta sample 1 (S1, hCoV-19/Israel/CVL-12804/2021) and sample 2 (S2, hCoV-19/Israel/CVL-12806/2021).

Table 3: The efficacy of vaccine

Vaccine	Samples	Country	Any vaccine	One dose	Two doses	Reference
BNT162B2	4,272	UK	30.7% (95% CI, 25.2%–35.7%)	35.6% (95% CI, 22.7%–46.4%)	88.0% (95% CI, 85.3%–90.1%)	[62]
ChAdOx1	4,272	UK	30.7% (95% CI, 25.2%–35.7%)	30.0% (95% CI, 24.3%–35.3%)	67.0% (95% CI, 61.3%–71.8%)	[62]
mRNA-1273	NA	NA	NA	NA	NA	NA

NA: not available.

RBD of the variants and ACE2. Results revealed that T478K mutation had the largest BFE change, which meant that T478K might be vital to the high infectivity of the delta variant.[41] Double mutation, like L452R and T478K, is more likely to be dominant in enhancing the binding affinity of the spike protein to ACE2.[42] A review of SARS-CoV-2 mutation sites, identified by CoV-GLUES, suggested that P681R, like D614G, was also adjacent to the RBD in the S1 subunit and could switch the RBD to an "open" conformation, promoting the binding between RBD and ACE2.[32,40] Cherian *et al.*[43] analyzed the P681R structure at the furoin cleavage site and revealed its role in enhancing the alkalinity of polybasic stretching. This may contribute to the increased infectivity by increasing the rate of membrane fusion internalization.

The critical mutations of the delta variant mainly occur in the spike protein. Among them, mutations in and adjacent to the RBD, such as L452R, T478K, D614G, and P681R, are due to their ability to invade the host. In addition, the accumulation of these mutations modifies the characteristics of the delta variant, offering a new way to understand its traits.

Transmissibility of the delta variant

Campbell *et al.*[44] analyzed 1,722,652 sequences of SARS-

CoV-2 uploaded to the hCOV-19 database of the Global Initiative of Sharing All Influenza Data. They applied a competitive growth multinomial logistic model to estimate the effective reproduction rate of each variant. Compared with VOI, the effective reproduction rate of the delta variant was 97% (95% CI, 76%–117%). In this study, the delta variant was the VOC with the highest effective reproduction number, implying that this variant has extremely high transmissibility and might also be the variant with the highest transmissibility to date. Allen *et al*.[45] assessed the probability of familial transmission (≥ 2 cases within 14 days) of the delta variant in a case–control study conducted in the UK. A total of 3,765 clustered families were sequenced to match 7,530 sporadic cases (a single case in each family). After adjusting for age, sex, ethnicity, index of multiple deprivation, and inoculation status of indicative cases, the odds ratio of household transmission of the delta variant compared with that of the alpha variant was 1.64 (95% CI, 1.26–2.13). In a study published in the Chinese Center for Disease Control and Prevention, Zhang *et al*.[46] reported the clear chain of transmission of the initial 68 infections in Guangdong and found that the mean incubation period was 4.4 days (95% CI, 3.9–5.0), with a mean interval of transmission of 2.9 days (95% CI, 2.4–3.3), which was shorter than the initial mean incubation period of 5.2 days (95% CI, 4.1–7.2) and the mean interval of transmission of 7.5 days (95% CI, 5.3–19) for SARS-CoV-2 virus.[47]

The delta variant is the most prevalent variant worldwide, with remarkably high transmissibility. Regardless of the parameter indicating transmissibility, the delta variant shows incredible superiority compared with the alpha variant, which was once preponderant. To control the damage caused by the delta variant, effective measures to control the transmission are warranted.

Impacts of the delta variant on clinical severity

A highly transmissible variant, such as the delta variant, may rapidly increase the number of confirmed cases within a short period of time as well as the number of hospital admissions. Inadequate medical personnel and facilities may contribute to the increased mortality rates.

Considering the abovementioned factors, whether the delta variant can cause serious clinical consequences remains a concern. Sheikh *et al*.[48] evaluated the risk of hospitalization associated with the delta variant. In their study, inpatients with COVID-19 were defined as those who tested positive for SARS-CoV-2 within 14 days of admission. Patients with hospital-acquired COVID-19 were excluded from the study. In the EAVE II platform, a Scotland-wide COVID-19 surveillance platform, they found that delta variant-related cases were associated with an increased risk of COVID-19 hospitalization, compared with the alpha variant-related cases (hazard ratio, 1.85; 95% CI, 1.39–2.47), as reported in a cohort analysis after adjustment of cofounders. A study from the UK showed that the number of COVID-19 cases in the UK increased, as was the number of hospital admissions. On June 9, more than 1,000 people were admitted to the hospital daily due to COVID-19. With regard to the previous outbreak, the number had dropped to a few hundreds by mid-May. Figures from Public Health England showed that 90% of cases in the UK were caused by this variant, with more than 42,000 cases reported, suggesting that this variant might be associated with a higher risk of hospitalization.[9] Ong *et al*.[49] conducted a retrospective cohort study comparing the outcomes of patients infected with the delta variant in early 2021 with those of patients infected with the wild-type virus in Singapore. From January 1, 2021 to May 22, 2021, data of 838 cases of VOC infection were collected. After adjusting for age and sex, the delta variant-related infections were associated with higher oxygen consumption, intensive care unit (ICU) admission, or death (adjusted odds ratio [aOR]: 4.90; 95% CI, 1.43–30.78). For the 157 patients with VOC admitted to their center, the aOR of pneumonia related to the delta variant was 1.88 (95% CI, 0.95–3.76). In addition, the delta variant was incredibly associated with a longer estimated median duration (18 *vs*. 13 days) after adjusting for age, sex, comorbidities, and vaccination. This variant seems to have the potential to increase the severity of disease. Another retrospective cohort study in Ontario constructed a mixed-effects logistic regression model using ICU admission and death as outcome variables.[50] After adjustment, in contrast to non-VOC strains, the risk rates of poor clinical outcome due to infection with the delta variant were 120% (95% CI, 93%–153%) for hospitalization, 287% (95% CI, 198%–399%) for ICU admission, and 137% (95% CI, 50%–230%) for deaths. The trial lacked data on vaccination status at the individual level, and the confounding factors were difficult to exclude due to the ongoing vaccination programs. In addition, some Indian doctors have suggested that the delta variant may cause gangrene, hearing loss, loss of appetite, and other atypical symptoms in infected patients.[51]

Overall, delta variants with high transmissibility augment the risks of hospitalization and death. However, a comprehensive evaluation tool for assessing disease severity is warranted; moreover, close attention should be paid to the different symptoms of patients infected with the delta variant and those infected with the wild-type variant, especially individuals with more severe symptoms.

Efficacy of vaccines on the delta variant

Given that the delta variant is more transmissible than the

alpha variant, is the vaccine still protective? To date, many vaccines have been introduced, such as BNT162B2[52,53] and Chadox1,[54,55] and many biotechnology companies are manufacturing these vaccines.[56-60]

A prospective cohort study was conducted in Scotland to investigate the effects of vaccines before the emergence of the delta variant. It is estimated the hospitalization rate of patients infected with SARS-CoV-2 after the first dose of vaccine by fitting a time-dependent Cox model and a Poisson regression model with adverse propensity weights. Among 1,331,993 people with a mean age of 65 years (standard deviation: 16.2) who received the vaccine (from December 8, 2020 to February 22, 2021), the first dose of BNT162B2 reduced the hospitalization rates by 91% (95% CI, 85%–94%) on days 28–34 after vaccination, while Chadox1 reduced the risk by 88% (95% CI, 75%–94%); these results suggest that vaccination can greatly reduce the risk of hospitalization.[61] After the global spread of the delta strain, Bernal *et al.*[62] explored the efficacy of two vaccines, BNT162B2 and Chadox1, on symptomatic delta variant-infected patients in a test-negative, case–control design. On the contrary, regardless of the type of vaccine, the efficacy of one vaccine dose was 30.7% (95% CI, 25.2%–35.7%) in delta variant-infected patients, which was considerably lower than that in alpha variant-infected patients (48.7%; 95% CI, 45.5%–51.7%). By contrast, the efficacy of two doses of BNT162B2 against the delta variant was 88.0% (95% CI, 85.3%–90.1%), while the efficacy of two doses of Chadox1 against the delta variant was 67.0% (95% CI, 61.3%–71.8%).

The neutralization effect of the vaccines on the delta variant was also explored. Liu *et al.*[22] assessed antibody neutralization by introducing different mutations in spike protein genes into the wild-type SARS-CoV-2 variant. Although the neutralization effect of BNT162B2 on B.1.617.1 was weak, it had an effective neutralization effect on other B.1.617 lineage variants, including the delta variant. Wall *et al.*[63] found that for the delta variant, two doses of BNT162B2 induced a 5.8-fold reduction in serum antibody neutralization titer (95% CI, 5.0–6.9) in a high-throughput SARS-CoV-2 virus assay, which was significantly higher than that of the alpha variant (2.6-fold; 95% CI, 2.2–3.1). Additionally, increase in age was markedly correlated with a decrease in the production of NAbs in all variants. In addition, a high-throughput live-virus SARS-CoV-2 neutralization assay showed that the delta variant reduced the expression of Chadox1-induced NAbs, in contrast to BNT162B2. Data from 106 participants after they received one dose (median time: after the first dose of 41 days) or two doses of Chadox1 (median time: after the second dose, 31 days) were included, and the median interval between doses was 63 days. Two doses of Chadox1 vaccine generated a 2.5-fold (1.4–2.7) reduction in NAb activity against the delta variant, compared with two doses of the BNT162b2 vaccine. Two doses of the BNT162B2 vaccine seemed to be more effective against the delta variant.[64]

Although the BNT162B2 and Chadox1 vaccines are less effective against the delta variant than against the wild-type SARS-CoV-2 variant, the vaccines are still protective, based on the findings of NAb titer experiments and large clinical trials. Despite the high transmissibility and high risk of hospitalization and death caused by infection with the delta variant, the BNT162B2 and Chadox1 vaccines remain effective and protective.

REACTING OPTIMISTICALLY, BUT CAUTIOUSLY

As mentioned above, despite the fact that the delta variant is highly transmissible and increases the risk of hospitalization, the vaccines remain effective and protective. Vaccination popularization must be accelerated to achieve herd immunity. In addition, a brief report by Krammer *et al.*[65] mentioned that in patients who had been immunized against SARS-CoV-2, especially those who were infected with SARS-CoV-2, the immune response to a single dose of vaccine exceeded that of uninfected individuals who received two doses of vaccine; the frequency of systemic side effects was higher than that in uninfected individuals. This means that people who were infected in the past probably only need a single dose of vaccine, which, given the limited supply of vaccine, could increase the number of people who can be vaccinated and amplify coverage. This is good news and raises realistic hope for countries with vaccination plans to encourage universal vaccination. We should not be overly alarmed and excessively anxious about the emergence of the delta variant and should be more optimistic.

Notably, the delta variant can be transmitted through the respiratory tract, hands, contaminants, and aerosols.[1] Therefore, wearing of face masks, maintaining social distance, and avoiding high-traffic areas are essential NPIs. More attention should be paid to the functions of NPIs. Currently, there are no effective drugs for the treatment of delta variants. A previous WHO trial pointed out that currently used antiviral drugs, such as remdesivir, hydroxychloroquine, lopinavir, and interferon regimens, had little effect on COVID-19–hospitalized patients, with no significant improvement in the overall mortality or length of hospitalization.[66] At present, vaccination and NPIs are the two powerful tools. Moreover, vaccination alone cannot sufficiently control the epidemic. Moore *et al.*[67] developed a mathematical model to study the vaccination status and NPIs according to age and

region of the UK, which was consistent with a series of epidemiological data from the UK. In terms of vaccination, relaxation of prevention and control measures would still trigger a peak in the number of COVID-19 cases. Even if the protection rate of vaccination was assumed as 85%, the complete relaxation of prevention and control would likely increase the mortality rate. The model incorporated a planned two-dose vaccination schedule (12 weeks apart, with protection beginning 14 days after vaccination). For some countries that were considered as the center of the pandemic outbreak, it is of referential significance to implement strict NPIs.

Furthermore, with the transmission among large numbers of people, new mutations and variants might better adapt to the host. Although current vaccines are effective, a small percentage of fully vaccinated people can still be infected when exposed to the virus. These cases are referred to as vaccine breakthroughs.[68] Delta variant has been proved to be capable of causing vaccine breakthrough and dominates vaccine breakthrough infections with higher respiratory viral loads in India.[69] While facing an unknown future, all these demonstrate that NPIs are now essential in controlling the epidemic. However, precautionary measures should still be implemented during this epidemic, prevention and control policies should not be easily loosened, and vaccination should be continued.

It is not a war in one country or region. Several national organizations are implementing measures to win the invincible war, such as the Centers for Disease Control and Prevention in the USA (CDC), Public Health England (PHE), and the Chinese CDC. More countries are invited to join them, not only in aggregating regional confirmed cases but also in understanding the different traits of the variants and keeping track of the latest developments in the mutation of the variants, so that more reasonable and valid public health decisions and vaccine recommendations can be determined and applied globally. Furthermore, a brighter future is expected with the arrival of more effective drugs.

CONCLUSION

The delta variant is the most prevalent SARS-CoV-2 variant worldwide. This variant has high transmissibility and increases the risk of hospitalization and death, probably causing more severe diseases, which needs to be confirmed by conducting additional studies. The delta variant partially reduces the effectiveness of vaccines, but it does not mean that these vaccines are invalid. Vaccines and NPIs have the potential to control the pandemic, which greatly relieves our concerns. The future of the delta variant is unknown; we should stay optimistic, but remain cautious.

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Conflict of Interest

None declared.

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