Critical Challenges to SARS-CoV-2 Delta variant

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Abstract: The outbreak of COVID-19 has brought varying degrees of challenges globally, including full capacity of the medical system, economic recession and patient casualties. While countries are struggling to cope with the COVID-19 pandemic, reports on its variants have increased gradually, with spreading in the population by more powerful infectiousness, faster transmission or more deadly toxicity. Delta is a variant of SARS-CoV-2 originated in India. Infections have been reported in many countries. In absence of specific drugs and limited vaccine protection, there are still challenges in dealing with the spread of Delta variants. Here we will describe the characteristics of Delta variant and related outbreak cases briefly, as well as putting forward the prevention and countermeasures in relation to Delta variant.

1. Introduction

1.1 SARS-CoV-2

At the end of 2019, the pneumonia epidemic caused by coronavirus gradually spread around the world, becoming another major respiratory infectious disease that affects the normal life of humanity in this century, just after Middle East Respiratory Syndrome (MERS) occurred in 2012. As of August 24, 2021, a total of 21,324,137 people has been diagnosed globally, and 4,419,932 people have died. At present, judging from the new trends in majority of countries, the pandemic has not yet bottomed out, and the prevention as well as treatment is still in emergency.

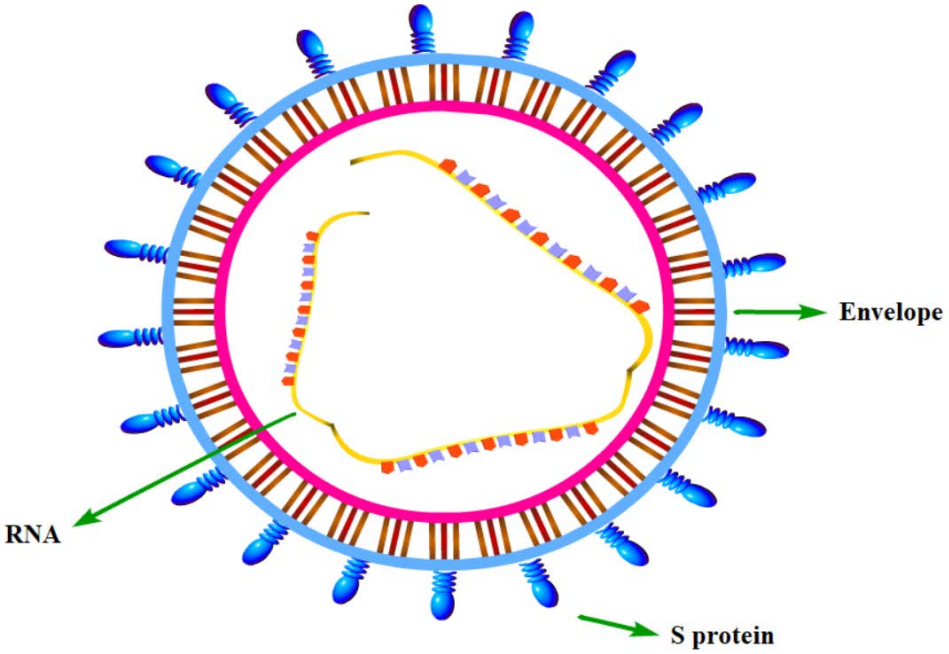

Fig.1 Simple structure diagram of SARS-CoV-2.

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the etiological agent of the Coronavirus disease 2019 (COVID-19). As shown in Fig. 1, It is an enveloped, single-stranded and positive-sense RNA virus, of which concentrated in the size of 60-140 nm [1]. As a kind of beta coronavirus, SARS-CoV-2 can infect mammals, causing respiratory-related syndromes such as

headache, rhinorrhea, fever, cough, fatigue and dyspnea in humans [2, 3]. Since amounts of the early symptoms are similar to the common cold, it is often difficult for the infected to alert that they are infected by SARS-CoV-2. Hence, causing human-to-human transmission via coughing or direct contact [3-5]. Even though SARS-CoV-2 can be inactivated by ultraviolet light (UV), heating or spraying 75% ethanol, there is no clinically specific drug for SARS-CoV-2, but there are dozens of vaccines available to mankind [6, 7]. In addition, the source of SARS-CoV-2 is still uncertain [7]. Genome sequencing studies have shown that the DNA of SARS-CoV-2 and bat coronavirus are at a similarity of 89% [3]. Therefore, it is believed that the virus originated from bats in early stages, which is consistent with the origin of MERS-CoV [3, 8]. But there is no sufficient reason to conclude the realness of it. Nowadays, there even appears the man-made virus and laboratory leaks hypothesis, but none of them has been rigorously confirmed by science.

In the process of SARS-CoV-2 invading host cells, Spike (S protein) and RdRp may play important roles. S protein is a trimeric transmembrane protein that mediates cell fushion during virus infection [9]. By recognizing and fusing with ACE2 on the host cell, S protein could promote SARS-CoV-2 to enter normal cells [10]. Subsequently, the nuclear genes of virus begin to replicate, synthesize and transcribe. Studies have shown that SARS-CoV-2 has two modes of RNA synthesis: The de novo synthesis and primer-dependent synthesis [3]. Different from the de novo synthesis strategy which uses nucleotides for RNA synthesis, primer-dependent synthesis tends to use RdRp to synthesize RNA by means of primers and short oligonucleotides. Both methods of RNA synthesis need to be completed with the assistance of RdRp. The combination of RdRp and replication-related factors can mediate the genome replication of SARS-CoV-2, and the extension of the RNA is done by RdRp through the addition of nucleotides or triggered by its analogues [3]. In view of the special role of S protein and RdRp in the process of SARS-CoV-2 infecting humans, they may be potential targets for drug discovery. Thus, the development of drugs and vaccines may be carried out successfully to fight against the COVID-19 pandemic.

1.2 SARS-CoV-2 Delta variant

SARS-CoV-2 is a kind of RNA virus with high tendency to mutate. Since the outbreak of the COVID-19 in late 2019, more than ten related variants have evolved, including α, β, γ, δ, ε, ζ, η, θ, ι, κ and λ,part of variant of concern(VOC)and variant of interest(VOI)are shown in Table. 1[11-13]. The emergence of SARS-CoV-2 variants may change its original transmission ability and environmental adaptability to a certain extent, as well as traditional treatment methods or vaccine protection effectiveness as a result, adding more obstacles to disease control, drug and vaccine research and development.

Table.1 Summary of SARS-CoV-2 VOC & VOI.

Variant	Characterization	Pango lineage	Origin	Date
α	VOC	B.1.1.7	United Kingdom	Sep 2020
β	VOC	B.1.351	South Africa	May 2020
γ	VOC	P.1	Brazil	Nov 2020
δ	VOC	B.1.617.2	India	Oct 2020
η	VOI	B.1.525	United Kingdom	Dec 2020
ι	VOI	B.1.526	United States of America	Nov 2020
κ	VOI	B.1.617.1	India	Oct 2020
λ	VOI	C.37	Peru	Dec 2020

In October 2020, the Delta variant (B.1.617.2) was discovered for the first time in India. Subsequently, the Delta variant gradually spread around the world and evolved into one of the dominant strains. Compared with the first identified Alpha variant, although the Delta variant has little difference in viral load (VL), it has a higher virus transmission ability. Studies have shown that the transmissibility of Delta variant is nearly 40% higher than that of Alpha variant [14]. To date, according to reports, Delta variants have appeared in more than 100 countries and regions, contributing

to the recent rapid increase in the number of infections worldwide [14]. Hence, it was identified as VOC by WHO on May 11, 2021[15]. It is clear that the transmissibility of Delta variant should not be underestimated, and prevention for invasion of Delta variant is urgent and inevitable in most countries.

So far, it is reported that S protein mutation is common in different types of SARS-CoV-2 variants [11]. The sequence analysis of the Delta variant showed that there were 656 mutation sites at all [14]. With a view to S protein, mutations in key sites such as L452R, T478K and P681R were found to be associated with the enhancement of the infectivity and antibody resistance of Delta variants [16, 17]. Although the S protein is changeable in SARS-CoV-2, there is still a tight interaction between the RBD (Receptor-Binding Domain) of S protein and ACE2 (Angiotensin Converting Enzyme 2) [18]. Studies have shown that L452R and T478K mutations may further improve the binding ability of S protein and human ACE2 and increase the stability of the binding complex [14, 19]. The P681R mutation is related to the enhancement of the virus transmission ability [19]. These mutations in S protein may disturb the binding ability of the monoclonal antibody and the RBD, promoting SARS-CoV-2 a higher antibody resistance, and results in unfavorable phenomenon as the immune escape [18].

2. Case analyses of Delta variant emerging

Since SARS-CoV-2 Delta variant has infected over 100 countries and regions, the number of reported cases is getting higher than ever before. Recently, in weekly report on COVID-19 pandemic, WHO stated that the Delta variant has appeared in 163 countries and regions around the world, with an increase of 15 compared with two weeks ago[20]. At the same time, according to GISAID, the Delta variant accounted for more than 87% of the global variant sequences. Thus, the Delta variant has gradually become the main pandemic strain in the world.

As per the data, a study has shown that nearly 90% of the confirmed cases in France at this stage are caused by the Delta variant [14]. In Asia, the Korea Center for Disease Control and Prevention (KCDC) reported that there were 1202 new confirmed cases of COVID-19 on August 3, with 64% were infected with the Delta variant, which turns out to be the main strain spreading in South Korea [21]. As for China, a new round of COVID-19 caused by the Delta variant erupted in July. At least 19 provinces have reported infections, and the cumulative number of infections has exceeded 1,300. However, under the strict control and isolation measures of the Chinese government, there have been few reports of new cases these days, and the epidemic has been successfully eliminated [22].

3. Medical measures for Delta variant

3.1 Diagnosis

Diagnosis is crucial to the discovery of diseases, early and accurate diagnosis may prevent the spread of infectious diseases. In view of the clinical symptoms of most patients infected with SARS-CoV-2 are similar to those of the common cold, people are often hard to aware. Studies have shown that patients are still infectious before they show obvious clinical symptoms, and the proportion of asymptomatic one continues to rise [23, 24]. Therefore, accurate diagnosis is indispensable for controlling the spread of diseases. Nowadays, with the rapid development of medical technology, diagnosis technology for infectious disease has gradually improved. In terms of SARS-CoV-2 as well as its variants, diagnosis methods can be classified into molecular, serological, radiological and virus culture ones [25, 26]. Apparently, various diagnostic methods possess diverse characteristics, along with different applicable environments. The pros and cons of the above diagnosis methods are summarized in Table 2.

Table.2 Different methods in SARS-Cov-2 Clinical Diagnosis [25, 26].

Method	Approach	Mechanism	Advantage	Disadvantage
Molecular Diagnostic	Polymerase chain reaction (PCR), Reverse transcription loop-mediated scription loop-mediated isothermal amplification (RT-LAMP), Next-generation sequencing (NGS)	Identification and amplification of viral genetic material from collected cases	No need to cultivate viruses in vitro, identify the key genes of the virus, can determine whether the virus has changed	Expensive, requires differences in the positive genes identified by professionals, different countries or regions, may levy the mutated virus
Radiological Diagnostic	Chest X-ray (CXR) Chest computed tomography (CT)	Judge inflammation by examining the changes of lung imaging in patient	Observe the inflammation of the lungs to determine the severity of the infection, suitable for early diagnosis	Professionals who are familiar with lung inflammation are required, there are differences in imaging among patients, hard to determine whether lung inflammation is caused by SARS-Cov-2
Serological Diagnostic	Neutralization assay, Enzyme-linked immunosorbent assay (ELISA), Chemiluminescent immunoassay (CLIA), Rapid diagnostic tests (RDT)	Identify the presence of antibodies in the sample to be tested	An auxiliary method of molecular diagnosis with strong specificity and can detect early infection	Viral antibodies are also present in people vaccinated or cured, hard to accurately determine whether the subject is currently infected
Virus-cell Culture	Using specific cell lines such as Vero E6 and LLC-MK2 cells to culture viruses under suitable conditions	After virus replicates, the infected cells will undergo apoptosis and cause cell death, and the uninfected cells will maintain normal cell morphology	A gold standard for diagnosis of most pathogens, with good sensitivity and specificity	Due to the long period of virus culture (about 14 days) and high requirements for biosafety conditions, it is not recommended to be used in clinical diagnosis

Besides, the investigation of the contact history of patients is necessary, which will help to screen potential infected persons in time. As SARS-CoV-2 and its variants are more contagious, especially Delta variant. Thus, the investigation should include the patient's whereabouts and contacts. In this way, on one hand, it is convenient to delineate the dangerous areas of people who may be infected. On the other hand, it helps to identify close contacts and control the spreading in time. On top of that, the disease control department may determine the source of the patient's infection from investigation. Pointing a clear way for virus control.

3.2 Current clinical treatment

Because of the highly contagiousness, patients need to be treated in isolation, with measures include supportive programs such as oxygen inhalation or ventilator-assisted breathing, as well as treatment with a variety of antiviral drugs [27]. However, there is still no specific medicine for the treatment of SARS-CoV-2 and its variants [6, 7]. The most commonly used clinical antiviral drugs include Remdesivir, Umifenovir, Hydroxychloroquine, and part of HIV treatment drugs like Lopinavir and Ritonavir. Their combinations are currently used in the treatment [27].

Remdesivir is one of the most effective drugs for clinical treatment of SARS-CoV-2. A final report based on a double-blind, randomized, placebo-controlled experiment over Remdesivir suggests a faster recovery time, more effective prevention of the progression of respiratory diseases and more likely to reduce the proportion of patients with respiratory support. Thus, reducing the burden on the medical system [28].

Hydroxychloroquine, a commonly used drug for the prevention and treatment of malaria, is also involved in the treatment of SARS-CoV-2. Hydroxychloroquine can not only inhibit the fusion of virus and cells, but also has immunomodulatory ability, which can prevent inflammation and organ damage [29, 30]. Therefore, it is hypothesized that by virtue of the above-mentioned characteristics of hydroxychloroquine, it may be possible to prevent viruses from entering cells and regulate the body's immune system to prevent cytokine storms from occurring, thereby slowing the course of the disease. However, actual clinical studies have shown that hydroxychloroquine has a limited effect in the treatment of SARS-CoV-2 and cannot effectively prevent SARS-CoV-2 infection [31]. And because its application and the safety of COVID-19 are still unclear, there are still controversies, and its clinical application needs to be further explored [32].

Umifenovir is a broad-spectrum antiviral drug commonly used in influenza treatment [33]. It can inhibit the fusion of virus and host cells and prevent viral nucleic acid replication [34, 35]. According to reports, Umifenovir can inhibit SARS-CoV-2 activity in vitro [36]. Studies have shown that the combined use of Umifenovir, Lopinavir and Ritonavir will significantly improve the patient's condition [37]. Lopinavir and Ritonavir are most commonly used drugs for the treatment of AIDS. Studies have shown that Lopinavir and Ritonavir have inhibitory activities against MERS-Cov both in vitro and animal experiments [38, 39]. At the same time, in vitro inhibitory effects on SARS-CoV [40]. However, the curative effect of Lopinavir and Ritonavir does not seem to be ideal, and no significant clinical symptom relief or reduction in mortality has been observed [41]. Perhaps more restrictive conditions are needed to observe objective mitigation.

In addition, many therapeutic drugs are still undergoing clinical trials, including a combination of multiple drugs [27]. These programs may find the best direction for the treatment of SARS-CoV-2 as well as its variants.

4. Countermeasures in prevention

Vaccines are one of the most important barriers to prevent infections or diseases. After the outbreak of COVID-19, countries around the world have contributed to vaccine research and development. There are now a variety of vaccines under development or been approved, the vaccination is on continuing. According to data, as of September 3, 2021, 22 vaccines have been approved worldwide, 45 vaccines have entered phase III, and 427 clinical trials are in progress [42]. A summary for approved vaccines is listed in Table 3.

Table 3. The summary of approved vaccines [42].

Vaccine	R & D	Type	Clinical trials
ZyCoV-D	Zydus Cadila	DNA based	Phase I: CTRI/2021/03/032051, CTRI/2020/07/026352 Phase II: CTRI/2021/03/032051, CTRI/2020/07/026352

			Phase III: CTRI/2021/01/030416
TAK-919 (mRNA-1273)	Takeda (Moderna)	RNA based	Phase I: NCT04677660 Phase II: NCT04677660
CoronaVac	Sinovac	Inactivated	Phase I: NCT04352608, NCT04383574, NCT04551547 Phase II: NCT04979949, NCT04352608, NCT04383574, NCT04551547, NCT04884685, NCT04992182, PHRR210210-003308 Phase III: NCT04942405, NCT04800133, NCT04456595, NCT04582344, NCT04617483, NCT04651790, NCT04992260, PHRR210210-003308, NCT04508075, 669/UN6.KEP/EC/2020
Vero Cell	Sinopharm (Wuhan)	Inactivated	Phase I: ChiCTR2000031809 Phase II: NCT04885764, ChiCTR2000031809 Phase III: NCT04885764, NCT04612972, NCT04510207, ChiCTR2000034780, ChiCTR2000039000
BBIBP-CorV (Vero Cells)	Sinopharm (Beijing)	Inactivated	Phase I: ChiCTR2000032459 Phase II: NCT04988048, NCT04962906, NCT04983537, NCT04998240, ChiCTR2000032459 Phase III: NCT04612972, NCT04510207, NCT04917523, NCT04984408, ChiCTR2000034780, NCT04560881, BIBP2020003AR
COVIran Barekat	Shifa Pharmed Industrial Co	Inactivated	Phase I: IRCT20201202049567N1, IRCT20201202049567N2 Phase II: IRCT20201202049567N3 Phase III: IRCT20201202049567N3
Covishield	Serum Institute of India (Oxford/AstraZeneca)	Non-Replicated Viral Vector	Phase II: CTRI/2020/08/027170 Phase III: CTRI/2020/08/027170
BNT162b2	Pfizer /BioNTech	RNA based	Phase I: NCT04889209, NCT04839315, NCT04969601, NCT04588480, NCT04936997, NCT04816643, EUCTR2020-005442-42, EUCTR2020-001038-36, NCT04380701 Phase II: NCT04949490, NCT04368728, NCT04889209, NCT04894435, NCT04761822, NCT04969263, NCT04969601, NCT04907331, NCT04588480, NCT04649021, NCT04824638, NCT04895982, NCT04754594,

			ISRCTN73765130, ISRCTN69254139, EUCTR2020-005442-42, EUCTR2020-001038-36, NCT04380701, NCT04860739, EUCTR2021-001978-37 Phase III: NCT04368728, NCT04805125, NCT04951323, NCT04754594, NCT04713553, NCT04816669, EUCTR2020-005442-42
AZD1222	Oxford /AstraZeneca	Non-Replicated Viral Vector	Phase I: NCT04684446, NCT04760730, NCT04568031, NCT04816019, PACTR202005681895696, PACTR202006922165132, NCT04444674, EUCTR2020-001072-15, NCT04324606 Phase II: NCT04973449, NCT04894435, NCT04988048, NCT04885764, NCT04684446, NCT04686773, NCT04962906, NCT04983537, NCT04760730, NCT04992182, NCT04907331, NCT04998240, NCT04568031, ISRCTN73765130, ISRCTN69254139, ISRCTN15638344, CTRI/2020/08/027170, PACTR202005681895696, NCT04860739, EUCTR2021-001978-37, PACTR202006922165132, NCT04444674, EUCTR2020-001228-32, NCT04400838, EUCTR2020-001072-15, NCT04324606 Phase III, NCT04973449, NCT05007951, NCT04864561, NCT04885764, NCT04800133, NCT04516746, NCT04540393, CTRI/2020/08/027170, EUCTR2020-001228-32, NCT04400838, ISRCTN89951424, NCT04536051
mRNA-1273	Moderna	RNA based	Phase I: NL9275, NCT04785144, NCT04813796, NCT04889209, NCT04839315, NCT04283461 Phase II: NL9275, NCT04889209, NCT04894435, NCT04761822, NCT04405076, NCT04748471, NCT04847050, NCT04649151, NCT04796896, NCT04930770, NCT04969263, NCT04988048, ISRCTN73765130

			Phase III: NCT04805125, NCT04649151, NCT04796896, NCT04470427, NCT04811664, NCT04806113, NCT04860297
SARS-CoV-2 Vaccine (Vero Cells)	Minhai Bio technology Co	Inactivated	Phase I: NCT05003479, ChiCTR2000038804, NCT04758273 Phase II: NCT05003466, ChiCTR2000039462, NCT04756323 Phase III: NCT04852705
MVC-COV1901	Medigen	Protein Subunit	Phase I: NCT04487210 Phase II: NCT04695652, NCT04822025, NCT04951388
QazVac	Kazakhstan RIBSP	Inactivated	Phase I: NCT04530357 Phase II: NCT04530357 Phase III: NCT04691908
Ad26.COV2.S	Janssen (Johnson & Johnson)	Non-Replicated Viral Vector	Phase I: NCT04889209, NCT04509947, NCT04894305, NCT04436276, EUCTR2020-001483-28 Phase II: NCT04765384, NCT04889209, NCT04436276, EUCTR2020-001483-28, NCT04535453, EUCTR2020-002584-63-DE Phase III: NCT04838795, NCT04505722, NCT04614948, ISRCTN14722499
Sputnik V	Gamaleya	Non-Replicated Viral Vector	Phase I: NCT04437875, NCT04684446, NCT04760730, NCT04436471, 241 Phase II: NCT04437875, NCT04988048, NCT04684446, NCT04686773, NCT04587219, NCT04640233, NCT04954092, NCT04962906, NCT04983537, NCT04760730, NCT04436471, 241 Phase III: NCT04640233, NCT04564716, NCT04530396, NCT04642339, NCT04656613, NCT04954092
Sputnik Light	Gamaleya	Non-Replicated Viral Vector	Phase I: NCT04713488 Phase II: NCT04713488 Phase III: NCT04741061
EpiVacCorona	FBRI	Protein Subunit	Phase I: NCT04527575 Phase II: NCT04527575 Phase III: NCT04780035
KoviVac	Chumakov Center	Inactivated	Phase I: 502 Phase II: 502

CIGB-66	Center for Genetic Engineering and Biotechnology (CIGB)	Protein Subunit	Phase I: RPCEC00000345, RPCEC00000346 Phase II: RPCEC00000345, RPCEC00000346 Phase III: RPCEC00000359
Ad5-nCoV	CanSino	Non-Replicated Viral Vector	Phase I: NCT04568811, NCT04840992, ChiCTR2000030906, NCT04313127 Phase II: NCT04840992, NCT04566770, NCT05005156, ChiCTR2000031781, NCT04341389 Phase III: NCT04526990, NCT04540419
Covaxin	Bharat Biotech	Inactivated	Phase I: CTRI/2020/09/027674, CTRI/2020/07/026300, NCT04471519 Phase II: NCT04918797, CTRI/2020/09/027674, CTRI/2020/07/026300, NCT04471519 Phase III: NCT04918797, CTRI/2020/11/028976, NCT04641481
ZF2001	Anhui Zhifei Longcom	Protein Subunit	Phase I: NCT04961359, NCT04445194, NCT04636333, NCT04550351, ChiCTR2000035691 Phase II: NCT04466085, NCT04813562 Phase III: ChiCTR2000040153, NCT04646590

However, these vaccines do not seem to be effective in inhibiting Delta variant, of whom may escape from immunological recognition [43]. At present, there have been clinical reports of vaccine breakthrough cases correlation to BNT162b2, Covaxin, Covishield and other vaccines [43-45]. Studies have shown that the sensitivity of Delta variants to vaccines like BNT162b2 may be reduced by about 8-20 times [43]. At the same time, it has been discovered that the antibodies in cured patients may not be enough to neutralize the Delta variant while the existing breakthrough cases rarely have severe cases, and generally present asymptomatic or mild infections [45]. In other words, vaccination is an effective strategy to prevent the deterioration of the disease. Although a variety of vaccines lack the ability to prevent Delta variant, the immune antibodies produced by the vaccine in the human body will be one of the most significant ways to protect us from infection.

In addition, being careful about personal hygiene, washing hands frequently, ventilating frequently, not eating raw food, and maintaining a good attitude will all help us protect us from the virus. In crowded places, wear a mask and keep a distance of more than 1 meter from others if necessary. Finally, everyone should follow the advice of doctors and experts, protect ourselves from the extremely contagious SARS-CoV-2 Delta variant, and work together for an early back to pre-COVID 19 life.

5. Conclusion

So far, SARS-CoV-2 is still raging around the world, not only causing infections and deaths of a large number, but also posing challenges to the world economy. SARS-CoV-2 has changed the way we used to live as it were, and we are trying to adapt to the post-COVID 19 world. The Delta variant is one of the most contagious variants of the SARS-CoV-2. Its emergence has caused a surge in the number of confirmed cases in globally, adding more obstacles to the prevention instantly. There is no clinically effective drug for SARS-CoV-2 as well as its variants, and the combination strategies of antiviral drugs are mostly adopted. Nowadays, a variety of vaccines have been approved. However,

with the emergence of Delta variant, the potency of the vaccine declined, and vaccine breakthrough cases have gradually increased. Luckily, most patients are asymptomatic or mildly ill, indicating antibodies produced by the vaccine can still provide adequate protection. In addition to timely vaccination, frequent hand washing, frequent ventilation, wearing masks, and maintaining personal hygiene are beneficial to prevention. With the continuous development of advanced medical technology, I hold the view that we will defeat SARS-CoV-2 and come back to pre-COVID 19 life in the future.

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