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REVIEW

Impact of the Delta variant on vaccine efficacy and response strategies

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ABSTRACT

Introduction: The Delta variant of SARS-CoV-2 has caused a new wave of the COVID-19 epidemic in many countries. It is the most infectious variant of SARS-CoV-2 to date, and its high infectivity means that a higher proportion of the population needs to be vaccinated to reduce the disease burden, which poses a substantial public health challenge.

Areas covered: The evolution of the Delta variant is reviewed, including an overview of the Delta Plus variant with a K417N mutation in the RBD, which may confer an improved immune evasion ability. Decreases in serum neutralizing antibody titers after vaccination against Delta were greater than those against Alpha but less than those against Beta. The protective efficacy of existing vaccines against the Delta variant have declined and is related to the number of doses and the time since vaccination.

Expert opinion: The currently used vaccines are effective against hospitalization/severe disease due to the Delta variant. Accelerating the popularization of vaccination, improving the coverage rate, and the implementation of intervention measures, such as wearing masks, are effective means to control the spread of the Delta variant and other variants. However, vaccination alone against SARS-CoV-2 without intervention measures may lead to continuous spread and the emergence of new variants.

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1. Introduction

While the global pandemic caused by the Alpha variant of SARS-CoV-2 is not yet over, the Delta variant has spread in many countries, causing the epidemic to rebound. The weekly epidemiological update on COVID-19 released by the WHO on 20 July 2021 indicated that 180 countries or regions had reported Alpha variant cases, 130 countries had reported Beta variant cases, 78 countries had reported Gamma variant cases, and 124 countries had reported Delta variant cases, and the Delta variant is expected to become the main epidemic strain in the world in the coming months [1]. On July 14, the WHO announced the beginning of a third wave of the coronavirus pandemic, and the Delta variant was the leading factor [2]. The WHO and the European Center for Disease Prevention and Control jointly released an epidemic report on 23 July 2021. The report indicated that the Delta variant has become the main transmitted SARS-CoV-2 variant in 19 of 28 countries that completed SARS-CoV-2 genome sequencing in the 2-week period from June 28 to 11 July 2021, accounting for as high as 68.3% of isolates, exceeding the Alpha variant (22.3%), the previous dominant type in these countries [3]. The Delta variant has become the main variant of concern (VOC) in the world.

High infectivity is a characteristic of the Delta variant [4,5]. Some studies have reported that the infectivity of this strain is 97% or 100% greater than that of the original epidemic strain [5,6]. In addition, its mutation in the RBD results in improved immune evasion, and there are several reports of breakthrough infection after complete vaccination. Studies have shown that compared with the original strain WT/D614G, the serum neutralizing antibody titers against the Delta variant after inoculation with the Pfizer vaccine are 1.41–11.30 times lower [7–12]. The protection rate of this vaccine in Israel decreased from 94% to 39% as the Delta variant increased [13]. The Delta variant is not only ravaging countries with low vaccine coverage, such as Indonesia, Thailand, Myanmar, Nepal, and other countries in Southeast Asia as well as African countries but is also triggering a new wave of the epidemic in countries with high vaccination coverage, such as the United Kingdom and Israel, which challenges the protective efficacy of vaccines in the real world. At present, research has shown that countries or populations with high vaccination rates have lower rates of severe illness and mortality when this strain is prevalent, suggesting that current vaccines still have a certain protective effect [14,15]. In response to the spread of the Delta variant, the Israeli Ministry of Health announced on 11 July 2021 that the country began to provide a third dose of the COVID-19 vaccine produced by Pfizer to adults with a weak immune system. This made Israel the first country in the world to provide booster doses of the COVID-19 vaccine.

Full-course vaccination can provide protection against serious diseases and deaths from all four VOCs. However, some countries with high vaccination rates, such as Israel, the United Kingdom, and the United States, have experienced new outbreaks, and Southeast Asian countries with low vaccination rates, such as Indonesia, Thailand, and Vietnam, have experienced sharp increases in the number of cases recently. The

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Article highlights

- Following the Alpha variant, the Delta variant is a newly emerging variant which is causing another wave of SARS-CoV-2 epidemics worldwide, no matter whether the vaccination coverage in these countries is high or low;
- The Delta variant is by far the most infectious SARS-CoV-2 variant, and its high infectivity indicates the need to increase the vaccination rate to control the epidemic, which poses a greater challenge for humans to overcome SARS-CoV-2.
- The Delta variant keeps evolving, and the immune escape ability of the Delta+ strain might be enhanced because of an extra mutation at position 417 in the RBD region. It is necessary to further strengthen the monitoring the evolution and immune escape of the Delta variant;
- The Delta variant has a certain immune escape ability. The neutralization titer reduction of the vaccine immune serum against the Delta variant is higher than that of Alpha and lower than that of Beta;
- The vaccine efficacy in the large-scale vaccination against the Delta variant showed a certain degree of decline. In addition, the vaccine efficacy is related to the doses of vaccination and the time post-inoculated;
- Increasing the vaccination coverage, and taking intervention measures such as wearing masks, maintain social distance are important to control the spread of the Delta variants. Failure to take intervention measures in high epidemic areas might lead to the continued circulation of SARS-CoV-2 and the emergence of new immune escape variants.

Delta variant is gradually becoming the dominant epidemic strain globally; accordingly, it is necessary to continuously assess the risks and adjust countermeasures. In this paper, the etiological and epidemiological characteristics of the Delta variant are reviewed, the protective effects of vaccines currently in use are summarized, and corresponding countermeasures are proposed.

2. Etiological characteristics

The Delta variant contains L452R, T478K, D614G, and P681R (Delta-AY.1 with additional K417N mutation) mutations in the S protein domain; these mutations have been detected in other VOCs/VOIs and may affect the infectivity of viruses or resistance to specific antibodies.

The L452 residue does not directly contact the ACE2 receptor. However, because it is located in the hydrophobic plaques of the RBD in the spike protein, mutations lead to structural changes that promote the interaction between the spike protein and ACE2 receptor [16,17]. In addition, it promotes virus replication by increasing spike stability, virus infectivity, and virus fusion [18]. L452R is also the main mutation in the "Epsilon variant" B.1.429 and is related to an increase in the viral load and an approximately 20% increase in transmissibility [19]. A pseudovirus assay confirmed that this mutation is related to an increase in ACE2 binding and infectivity [20]. Compared with the D614G mutation alone, the ability of a pseudovirus carrying the L452R mutation to infect 293T cells increases by 6.7–22.5 times and the ability to infect HAO-ACE2 cells increases by 5.8–14.7 times [19]. In addition, this mutation can cause the vaccine-induced serum neutralizing antibody titer against the pseudovirus to decrease by 3–6 times [20,21], and the pseudovirus can escape many authorized monoclonal antibodies [21,22]. Furthermore, K452R is the only mutation in CAL.20A (B.1.232). Several independent lineages carrying L452R have been reported in the global GISAID database, suggesting that the L452R mutation alone is of significant adaptive value to SARS-CoV-2 [23].

T478K is located at the interface of Spike/ACE2 interactions. The amino acid change from the polar but uncharged threonine (T) to a basic, charged lysine (K) is predicted to increase the electrostatic potential of surface Spike to a more positive value in a region directly contacting ACE2. Additionally, the larger side chain of lysine is predicted to increase the steric hindrance of the variant, possibly further affecting the Spike/ACE2 interaction [24]. The location of T478K in the interaction complex with human ACE2 may affect the affinity with human cells, thus affecting the infectivity of the virus. This mutation may increase the infectivity of the Mexican variant B.1.1.222 [25]. By analyzing the global GISAID database up to 27 April 2021, it was found that the rapid increase in the T478K mutation frequency in North America and some European countries may indicate that the adaptability of SARS-CoV-2 variants carrying the mutation increased [24]. When Muecksch treated SARS-CoV-2 virus culture with weakly active neutralizing antibody *in vitro*, the T478K/R variant was enriched, suggesting that the mutation at this site may be related to immune evasion [26].

The P681R mutation is located in close proximity to the furin cleavage site (FCS; residues RRAR positioned between 682 and 685) of the SARS-CoV-2 S protein [27]; it increases the number of basic residues in the sub-optimal SARS-CoV-2 spike protein furin cleavage site [28]. It is highly conserved in the Delta variant. An *in vitro* study has shown that the P681R mutation does not increase infectivity; however, the mutant virus shows higher pathogenicity than that of the parent SARS-CoV-2 virus in infected hamsters [29]. The P681R mutation can cause a partial decrease in neutralizing antibodies. A pseudovirus neutralization test showed that the D614G/P681R virus has partial (1.2–1.5 times) resistance to three monoclonal antibodies against the RBD of SARS-CoV-2 S protein. The neutralizing antibody titer of immune serum induced by the BNT162b2 vaccine against the D614G/P681R virus decreased significantly ($p < 0.0001$). In addition, the P681R mutation promoted the cleavage of the spike protein (S protein) mediated by furin and accelerated cell–cell fusion [29]. P681R/P681H also exists in several variants under investigation in the United Kingdom, including A.23.1/E484K, B.1.1.7, and B1.318. However, this mutation needs to occur on the background of other spike protein changes to exert a function on viral infection and transmissibility [28].

In addition to the three important mutation sites mentioned above, the Delta-AY.1 variant has the K417N mutation, which has potentially serious consequences. K417N was first reported in the RBD region of the Beta variant and can bind to N501Y, thus increasing the binding between spike proteins and ACE2 receptors in the variant [30–33] and possibly reducing the susceptibility of the virus to neutralizing antibodies by more than 10 times [31–33]. The K417N mutation, together with the conserved L452R mutation in the Delta variant (also found in the CAL.20C/B.1.427/B.1.429 epsilon variant detected in California), may increase vaccine escape by Delta-AY.1. At

present, very few Delta-AY.1 strains have been reported; accordingly, the infectivity, immune evasion, and pathogenicity of delta+ strains are still unclear.

3. Infectivity and pathogenicity

3.1. Infectivity

High infectivity is the most important characteristic of the Delta variant, which is up to 60% more transmissible than the Alpha variant [4,34]. An analysis of VOCs revealed that the mean effective reproduction number relative to non-VOC /VOI of B.1.1.7 is 29%, B.1.351 is 25%, and P.1 is 38%, while that of B.1.617.2 is 97% [5].

From May 21 to 23 June 2021, a case-related epidemic occurred in four cities in Guangdong Province, China, with 167 Delta cases reported. The R0 (basic reproductive number) was 3.2 [6], higher than 2.2 reported previously [35]. Further analysis demonstrated that the high infectivity of the Delta variant is related to its high viral load and short incubation period. By tracking the close contacts of 62 isolated patients with COVID-19, the viral load of the study subjects was determined. The average time from initial contact with the Delta variant to positive PCR detection was 4 days, while the time to infection with the original strain in 2020 (based on 63 patients) was 6 days, indicating that the replication speed of the Delta variant was accelerated and the viral load in patients infected with the Delta variant was 1260 times that in the controls [36]. The increased infectivity of the Delta variant may mean that the vaccination rate needed to control the epidemic will be higher than that needed for earlier variants.

To control the epidemic, Guangdong Province has adopted a series of rigorous intervention measures, including large-scale testing, active detection of cases, and lockdown of epidemic areas, with effective results in controlling the epidemic. It is estimated that the effective reproduction number (Rt) increased from 3.0 on May 27 to 3.5 on May 29, decreased after May 30, reached 1.0 on June 6, and remained near 1.0 from June 7 to June 15. After June 16, Rt was lower than 1.0, and no new cases were reported from June 19 to June 23 [6].

3.2. Pathogenicity

It is estimated that the fatality rate for Delta is close to 0.3%, compared with 1.9% for Alpha [37]. This does not mean that the pathogenicity of the Delta variant has decreased but indicates that vaccination has played a key role in reducing the fatality rate of the Delta variant.

The pathogenicity of the Delta variant is greater than that of the previous epidemic strains of SARS-CoV-2. Based on sequence-confirmed records of Delta and Alpha variant cases in the United Kingdom from 29 March 2021 to 20 May 2021, a stratified Cox proportional hazard regression of 38,805 cases with confirmed variant types showed that compared with Alpha variant cases, after adjusting for confounders (e.g. age, sex, ethnicity area of residence, index of multiple deprivation, week of diagnosis, and vaccination status), the risks of hospitalization within 14 days of sampling (HR 2.6195% CI 1.56–4.36, $p < 0.001$) and emergency care visits or hospitalization in the same period (HR 1.67, 1.25–2.23, $p < 0.001$) increased significantly in Delta variant cases [38].

Cox proportional hazard regression was used to estimate risk factors for the time from testing to hospitalization among individuals who tested positive in Scotland. The analysis included personal data for patients who tested positive from 1 April 2021 to 30 May 2021. Compared with S gene-negative cases (Alpha, 2.39), the risk ratio of hospitalization was higher in S gene-positive cases (Delta) (HR 2.39, 95% 1.72–3.31) [38]

A study in Ontario, Canada found that compared with non-VOC SARS-CoV-2 strains, the adjusted risk associated with Delta variant increases 120% (93–153%) for hospitalization, 287% (198–399%) for ICU admission, and 137% (50–230%) for death, compared with 59% (49–69%) for hospitalization, 105% (82–134%) for ICU admission, and 61% (40–87%) for death for N501Y-positive variants [39].

4. Neutralizing ability of vaccine immune serum against the Delta variant

The neutralizing ability of vaccine immune serum against the Delta variant in the published researches were summarized in Table 1. Compared with WT/Alpha, the neutralizing titer against Delta live virus induced by ChAdOx1, an adenovirus vector vaccine developed by Oxford-AstraZeneca decreased by 2.5–9.0 times, greater than the decrease for the Alpha variant (2.33–3.40 times) and smaller than that for the Beta variant (2.50–9.05 times), which were VOCs used in the same study [7–9,40]. Covishield, a similar vaccine produced by AstraZeneca in India, had a 3.28-fold decrease in immune serum neutralizing ability after two shots against the Delta variant as compared with D614G, consistent with the trend for ChAdOx1. The geometric mean titer of immune serum after one shot was lower than that after two shots and the degree of decrease was greater than that after two shots, suggesting the importance of the second dose [41]. Using a pseudovirus to test the immune serum after two shots of ChAdOx1, the neutralizing antibody titer against the Delta variant decreased by 4.01–6.20 times compared with that against WT, which was similar to the results obtained using live virus [9,10]. In addition, cross-neutralization data for the Johnson & Johnson adenovirus vector vaccine Ad26.COV2.S have been reported [42,43]. Compared with WT/D614G, the immune serum neutralizing antibody titer against the Delta variant after one shot decreased by 1.72–3.40 times, which was greater than the decreases for the Alpha variant (0.90–1.25 times) and Gamma variant (1.45–1.60 times) and lower than that for the Beta variant (2.97–3.60 times).

The mRNA vaccine BNT162b2 developed by Pfizer is one of the most widely used vaccines in the world. Compared with WT/Alpha, the immune serum neutralizing antibody titer against Delta live virus decreased by 1.41–8.40 times after two shots, greater than the decrease for the Alpha variant (2.60–5.80 times) and smaller than that for the Beta variant (4.20–16.00 times), which were VOCs used in the same study [7–9,46,47]. In a series of studies [7–9], the immune serum after two shots of BNT162b2 and ChAdOx1 was compared, and the neutralization ability of BNT162b2 serum against the Delta variant decreased slightly less than

Table 1. The vaccine neutralizing ability of vaccine immune serum against the Delta variant.

No.	Vaccine	Method	No. of samples	Sample information	Ref strain	Delta (fold reduction)	Other VOC (fold reduction)			Reference
							Alpha	Beta	Gamma	
1	ChAdOx1	live virus (IC50)	63	2 doses	WT	2.5	2.4	2.5	/	[40]
2	BNT162b2	live virus (PRNT50)	20	2 doses, phase 2/3 clinical trial (NCT04368728)	WT	1.41	/	/	/	[46]
3	BNT162b2	live virus (IC50)	159	2 doses	WT	5.8	2.6	4.9	/	[47]
4	convalescent	live virus	20	/	D614G	4.6	/	3.3	/	[49]
	BBV152	(PRNT50)	17	28 days after 2 doses		2.7	/	3	/	
5	Covishield	live virus	31	1 dose	D614G	4.54	/	/	/	[41]
		(PRNT50)	31	2 doses		3.28	/	/	/	
			15	SARS-COV-2 recovered + 1 dose		2.91	/	/	/	
			19	SARS-COV-2 recovered + 2 doses		2.62	/	/	/	
			20	breakthrough after 2-dose immunization		1.9	/	/	/	
6	convalescent	live virus	/	early pandemic UK	WT	2.67	2.94	13.32	3.13	[7]
		(FRNT50)	18	infected with Alpha		2.78	1.84	4.78	3.1	
			17	infected with Beta		6.07	1.73	0.52	1.05	
			14	infected with Gamma		2.9	1.05	0.57	0.26	
	BNT162b2		25	2 doses		2.5	3.28	7.56	2.63	
	ChAdOx1		25	2 doses		4.29	2.33	9.05	2.86	
7	convalescent	live virus	26	/	Alpha	4	/	/	/	[8]
	BNT162b2	(ED50)	16	2 doses		3	/	16	/	
	ChAdOx1		20	2 doses		5	/	9	/	
8	convalescent	live virus (ED50)	78	/	WT	2.6 ~ 3.5	1.2 ~ 2.2	3.6 ~ 6.6	/	[44]
9	BNT162b2/ mRNA-1273	live virus (ID50)	30	2 doses	WT	3	/	4.2	/	[45]
10	convalescent	live virus	30	Natural Infection 2020(D614G)	WT	33.69	13.07	9.91		[50]
			30	Natural Infection 2021(Alpha)		10.57	2.15	3.25		
	CoronaVac		60	2 doses		31.64	17.35	22.11		
11	convalescent	live virus (NT50)	12	/	WT	5.7	2.3	8.2	/	[9]
	ChAdOx1	live virus	10	2 doses	WT	9	3.4	/	/	
	BNT162b2	(ID50)	10	2 doses		8.4	5.8	/	/	
	ChAdOx1	pseudoviruses	33	2 doses	D614G	6.2	/	/	/	
	BNT162b2		32	2 doses		2.9	/	/	/	
12	Ad26.COV2.S	pseudovirus	8	1 dose, phase 3 ENSEMBLE trial participants (VAC31518COV3001)	D614G	3.4	0.9	3.6	1.6	[42]
13	Ad26.COV2.S	pseudovirus	10	8 mouths after 1 dose	WT	1.72	1.25	2.97	1.45	[43]
14	BNT162b2	pseudoviruses	37	1 dose	WT	1.41	/	12.74	/	[10]
			50	2 doses		11.3	/	9.56	/	
	ChAdOx1		50	1 dose		3.99	/	4.58	/	
			18	2 doses		4.01	/	1.48	/	
15	convalescent	pseudoviruses	20	/	D614G	2.34	1.34	/	/	[51]
	CoronaVac		20	7–14 days after 2 doses		2.47	1.62	/	/	
	ZF2001		10	26–30 days after 2 doses (n = 8) and 14 days after 3 doses (n = 2)		3.08	1.8	/	/	
16	mRNA-1273	pseudoviruses	8	2 doses, phase 1 clinical trial (NCT04283461)	D614G	2.1	1.2	6.9 ~ 8.4	3.2	[48]
17	ZF2001	pseudoviruses	28	3 doses	D614G	1.37	1.03	2.14	1.72	[52]
18	convalescent	pseudoviruses	/	/	WT	1.96	/	5.75	/	[11]
	BNT162b2		15	2 doses		2.83	/	11.13	/	
19	convalescent	pseudoviruses	8	/	D614G	2.3	/	3	/	[12]
	BNT162b2		6	2 doses		4	/	3.4	/	
	mRNA-1273		3	2 doses		3.8	/	2.2	/	

Annotation: Ref strain = the reference strain; fold reduction = $^{\text{theGMTofRefstrain}}/_{\text{theGMTofvariant}}$.

that of ChAdOx1 serum. Using the pseudovirus to test the immune serum after two shots of BNT162b2, its neutralizing antibody titer against the Delta variant decreased by 2.83–11.30 times compared with that against WT/D614G, consistent with the results obtained using live virus [9–12]. In addition, Choi et al. and Tada et al. [12,48] reported cross-neutralization data for mRNA-1273, another widely used mRNA vaccine. Compared with D614G, the immune serum neutralizing antibody titer against the Delta variant after two shots decreased by 2.10–3.80 times, greater than the decrease for the Alpha variant (1.20 times) and smaller than that for the Beta variant (2.20–8.40 times).

Few studies have evaluated cross-neutralization of inactivated and recombinant protein vaccines against the Delta variant. Compared with D614G, the immune serum neutralizing antibody titer of inactivated vaccine BBV152 developed in India against Delta live virus decreased by 2.7 times, which was less than the decrease in neutralizing antibody titers against the Beta variant (3.0 times) used in the same study [49]. Compared with the WT, the neutralizing antibody titer of

the inactivated vaccine CoronaVac developed by Sinovac in China decreased by 31.64 times, which was higher than the decrease in the Alpha and Beta variants used in the same study (17.35 and 22.11 times). It should be noted that the detection method used in this study was quite different from those in other studies, and the convalescent serum of D614G-infected patients detected using the Delta variant decreased by 33.69 times, which exceeded that of CoronaVac vaccine immune serum [50]. Hu et al. [51] used the Delta pseudovirus to detect the immune serum neutralizing antibody levels after two shots of CoronaVac and found that compared with D614G, the neutralizing titer decreased by 2.47 times, which was greater than the decrease for the Alpha variant (1.62 times). The immune serum neutralizing antibody after two or three shots of another vaccine, ZF2001, developed in China decreased by 1.37–3.08 times compared with D614G, which was greater than the decrease for the Alpha variant (1.03–1.80 times) used in the same study [51,52].

The above results suggest that for many widely used vaccines at present (including adenovirus vector vaccines, mRNA vaccines, inactivated vaccines, and recombinant protein vaccines), the immune serum neutralizing ability against the Delta variant *in vitro* is weaker than that against the Alpha variant but stronger than that against the Beta and Gamma variants. However, as a more infectious VOC, the Delta variant poses a substantial threat to the real-world protective efficacy of these vaccines.

The results of a multi-center retrospective cohort study in Singapore showed that the fully vaccinated individuals who occurred breakthrough infections of the Delta variant presented with milder symptoms than those unvaccinated patients [53]. Real-world data from health care workers in Israeli also showed that breakthrough infection symptoms were mild or asymptomatic in the fully vaccinated workers. Moreover, the author pointed out that the vaccine efficacy is closely correlated with the peak neutralizing antibody titer [54]. However, further researches are urgent needed to investigate the correlation between antibody level and breakthrough infection of Delta and other VOCs.

5. Impact of the Delta variant on the vaccine efficacy

For the vast majority of vaccines approved and distributed in many countries, Phase II/III clinical studies were completed before the Delta variant outbreak, and their efficacies were mainly based on populations exposed to the D614G, Alpha, Beta, and Gamma variants. The spread of the Delta variant challenges their real-world protection efficacy (Table 2). In the mass vaccination campaign in the United Kingdom, ChAdOx1 and BNT162b2 vaccines were administered to the adult population in two shots. Real-world data obtained from October 2020 to May 2021 showed that the two vaccines have similar efficacies after one shot, with protection rates against the Alpha and Delta variants of 51.1% and 33.5%, respectively. However, protective efficacies of BNT162b2 after two shots against the Alpha and Delta variants (93.4% and 87.9%) were significantly higher than those after two shots of ChAdOx1 (66.1% and 59.8%) [55]. These results are basically consistent with data from Scotland [56][57]. On the whole, BNT162b2 is superior to ChAdOx1 in protecting against the Alpha and Delta variants.

However, due to the early completion of population immunization, the protective effect of BNT162b2 against the Delta variant in Israel has declined. During the epidemic caused by the Alpha variant, the overall protection rates of BNT162b2 against SARS-CoV-2 infection and against the Alpha variant were 95.3% and 94.5%, respectively [58]. According to data released by the Israeli Ministry of Health on July 22, the protection rates against SARS-COV-2 infection of the COVID-19 vaccine developed by Pfizer in the United States was reduced to 39% in Israeli due to the impact of the Delta variant. However, it is worth noting that the rate of protection against infection progressing to hospitalization was 88% and against severe illness was 91.4% [13].

Real-world data from Canada can better reflect the protective efficacy of different vaccines and numbers of doses in mild and severe cases. Nasreen et al. evaluated the efficacies of the BNT162b2, mRNA-1273 and ChAdOx1 vaccines against VOCs, including the Delta variant, from December 2020 to May/June 2021 in Canada and found that, in individuals with moderate symptoms, the protection rates after full vaccination with BNT162b2 (2 doses) and ChAdOx1 (1 dose) against the Delta variant were 87% and 67%, similar to those against the Alpha variant (89% and 64%) and higher than those against the Beta/Gamma variant (84% and 48%). There is a lack of data on the protective efficacy of mRNA-1273 vaccines after two shots, and the protection rates against the Alpha, Beta/Gamma, and Delta variants after one shot were 83%, 77%, and 72%, respectively, exceeding estimates for the other two vaccines. Full vaccination with two shots of BNT162b2/mRNA-1273 had significantly higher protection rates against VOCs and non-VOCs compared with those for one shot. In the hospitalized/deceased population, the protection rates of the three vaccines after one shot and two shots were higher than those for individuals with moderate symptoms. Full vaccination with BNT162b2/mRNA-1273 can protect against 94–96% of severe cases and deaths. Although the protection rate of ChAdOx1 for severe cases and death is only 83–88%, it is 21–35% higher than that for individuals with moderate symptoms [15].

In addition, during the Delta variant outbreak in mainland China, the protection rate of domestic inactivated vaccine against infection from close contact was 69%, the protection rate against progression to pneumonia was 73%, and protection against severe illness was over 95% [59]. The inactivated vaccine BBV152 developed in India showed an overall protection rate of 77.8% against symptomatic disease in Phase III clinical research and 65.2% against the Delta variant, while the overall protection rate for severe cases, including Delta variant infection, was 93.4% [14].

According to reported data, BNT162b2, mRNA-1273, ChAdOx1, and other widely used vaccines in Europe and the United States as well as inactivated vaccines developed and applied in China and India still have certain protective effects against the Delta variant, especially against severe cases and

Table 2. Vaccine efficacy against the Delta variant.

No.	Vaccine	Data Source	Country/ Region	Age	No. of participants (total)	No. of positive cases	Dose	Vaccine Efficacy (%)	Reference
1	BNT162b2	real world	Canada	≥16	421,073 (Symptomatic infection)	506(non-VOC); 3905(Alpha); 305 (Beta/Gamma); 277(Delta)	1	61 (non-VOC); 66 (Alpha); 60 (Beta/Gamma); 56 (Delta)	[15]
						18 (non-VOC); 92(Alpha); 9 (Beta/Gamma); 6 (Delta)	2	93 (non-VOC); 89 (Alpha); 84 (Beta/ Gamma); 87 (Delta)	
	mRNA-1273					91 (non-VOC); 695 (Alpha); 58 (Beta/Gamma); 56 (Delta)	1	54 (non-VOC); 83 (Alpha); 77 (Beta/ Gamma); 72 (Delta)	
						≤5 (non-VOC); 12 (Alpha); 0 (Beta/Gamma); ≤5 (Delta)	2	89 (non-VOC); 92 (Alpha)	
	ChAdOx1					25 (non-VOC); 647 (Alpha); 62 (Beta/Gamma); 22 (Delta)	1	67 (non-VOC); 64 (Alpha); 48 (Beta/ Gamma); 67 (Delta)	
						0 (non-VOC); ≤5 (Alpha); 0 (Beta/Gamma); 0 (Delta)	2	/	
	BNT162b2			≥16	14,168 (Hospitalization/ death)	107 (non-VOC);1122(Alpha); 127 (Beta/Gamma); 50 (Delta)	1	68 (non-VOC); 80 (Alpha); 77 (Beta/ Gamma); 78 (Delta)	
						≤5 (non-VOC); 26 (Alpha); ≤5 (Beta/Gamma); ≤5 (Delta)	2	96 (non-VOC); 95 (Alpha); 95 (Beta/ Gamma);	
	mRNA-1273					74 (non-VOC); 211 (Alpha); 18 (Beta/Gamma); 50 (Delta)	1	57 (non-VOC); 79 (Alpha); 89 (Beta/ Gamma); 96 (Delta)	
						≤5 (non-VOC); 17 (Alpha); ≤5 (Beta/Gamma); ≤5 (Delta)	2	96 (non-VOC); 94 (Alpha)	
	ChAdOx1					≤5 (non-VOC); 142 (Alpha); ≤13(Beta/Gamma); ≤5 (Delta)	1	85 (Alpha); 83 (Beta/Gamma); 88 (Delta)	
						0 (non-VOC); ≤5(Alpha); 0 (Beta/Gamma); ≤5 (Delta)	2	/	
2	BNT162b2	real world	UK	≥16	7429	344 (Alpha); 49 (Delta)	1	49.2(Alpha); 33.2 (Delta)	[55]
					6453	28 (Alpha); 13 (Delta)	2	93.4(Alpha); 87.9 (Delta)	
	ChAdOx1				27,034	1137 (Alpha); 230 (Delta)	1	51.4(Alpha); 32.9 (Delta)	
					2131	46 (Alpha); 14 (Delta)	2	66.1(Alpha); 59.8 (Delta)	
3	BNT162b2	real world	Scotland	≥5	265,220	14,324 (Alpha); 14,214 (Delta)	1	38 (Alpha); 30 (Delta)	[56]
					343,936	53,575 (Alpha); 53,679 (Delta)	2	92 (Alpha); 79 (Delta)	
	ChAdOx1				266,682	15,137 (Alpha); 14,863 (Delta)	1	37 (Alpha); 18 (Delta)	
					301,989	32,588 (Alpha); 32,719 (Delta)	2	73 (Alpha); 60 (Delta)	
4	BNT162b2	real world	Israel	/	/	/	/	64 (total); 93.4 (severe cases/hospitalization)	[59]
5	BNT162b2	real world	Israel	/	/	/	/	39 (total);88 (hospitalization); 91.4 (severe cases)	[13]
7	BBV152	Phase III clinical trial (NCT04641481)	India	18–99	25,798	8471(Delta); 8471(Kappa)	2	65.2 (Delta); 90.1 (Kappa)	[14]

deaths. It should be noted that the rates of protection against various SARS-CoV-2 strains, including the Delta variant, were significantly better after two shots than after one shot. To effectively limit the spread of SARS-COV-2 globally, in addition to expanding the vaccinated population, it is critical to increase the proportion of fully vaccinated individuals.

6. Expert opinion

As the world was gradually emerging from the shadow of the pandemic caused by the Alpha variant, the number of new cases in many countries decreased, and lockdowns were gradually lifted, the Delta variant caused a second outbreak in India and spread to the surrounding countries and then globally. The epidemic has returned in many countries, with increases in the numbers of cases in countries with good vaccination coverage. Affected by the rapid spread of the Delta variant, the world is now in the early stage of the third round of the epidemic. Its high infectivity means that a higher proportion of the population needs to be vaccinated to reduce the disease burden therefore, the Delta variant poses a greater challenge for the elimination of SARS-CoV-2.

The Delta variant is more infectious than other VOCs and has immune evasion characteristics, to some extent. After the completion of the two-shot Pfizer vaccine, the rate of protection against the Delta variant was 79–87%, while that of the AstraZeneca vaccine was 60%, both of which were lower than those against the Alpha variant. Real-world data from different countries have shown that current vaccination procedures cannot prevent Delta variant infection and morbidity; however, they effectively protect against severe illness and death.

To cope with the high prevalence of the Delta variant, vaccination against COVID-19 should be accelerated globally. Increasing vaccine coverage is the most important measure to prevent and control the spread of the Delta variant. In countries with high vaccination rates, such as the United Kingdom, the fatality rate has not increased with surging cases, while in countries with low vaccination rates, such as Indonesia and Thailand, the epidemic is more serious. New cases in the United States are also mainly concentrated in the unvaccinated population. Therefore, accelerating vaccination, with a focus on providing vaccines to vaccine-deficient countries, is key to controlling the global epidemic. The experience in the prevention and control of the Delta variant epidemic in Guangdong Province, China suggests that the establishment of appropriate lockdown measures on the basis of vaccination is an effective means to reduce the transmission rate and control the epidemic. In view of the high infectivity of the Delta variant and the difficulty in improving vaccine coverage to achieve group immunization in a certain period of time, intervention measures such as wearing masks, maintain social distance, and lockdown in high incidence/ongoing transmission areas are necessary to control the spread of the epidemic. In addition, the immunization should be strengthened for people with low immunity.

The development of vaccines is of great significance to controlling the prevalence of the Delta variant and subsequent variants. Based on close monitoring of SARS-CoV-2 mutations, it is necessary to accelerate vaccine research and development. The WHO, FDA, EMA and UK have all put forward technical guidelines for vaccine research and development focused on variants. According to modified vaccine guidelines, through non-inferiority trials, the review and approval as well as clinical research progress of anti-variant vaccines can be accelerated, and research and development as well as the application of anti-variant vaccines can be promoted.

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Declaration of interest

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Author contributions

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