



# Implication of the emergence of the delta (B.1.617.2) variants on vaccine effectiveness

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## Abstract

**Introduction** COVID-19 vaccines have been developed to compact the current SARS-CoV-2 pandemic and have been administered to people all over the world. These vaccines have been quite effective in reducing the possibility of severe illness, hospitalization and death. However, the recent emergence of Variants of Concern specifically the delta variant, B.1.617.2, had resulted in additional waves of the pandemic.

**Methods** We aim to review the literature to understand the transmission and disease severity, and determine the efficacy of the current COVID-19 vaccines. We searched Pubmed, Scopus, and Embase till August 4th 2021, and used the search terms “delta variant”, “vaccinations”, “breakthrough infections”, and “neutralizing antibody”. For the meta-analysis, 21 studies were screened in particular and five articles (148,071 cases) were included in the study, and only four were analyzed in the meta-analysis.

**Results** In this review, both in vitro and in vivo studies showed significant reductions in neutralization rates against delta variants for vaccinated individuals and convalescent patients with prior history of COVID-19. However, There was a lower incidence of infection with SARS-CoV-2 due to Delta variant was found after the second dose of Pfizer-BioNTech, Oxford-AstraZeneca and Moderna vaccines.

**Conclusion** In fully vaccinated individuals, symptomatic infection with the delta variant was significantly reduced, and therefore, vaccinations play an important role to assist the fight against delta variant.

**Keywords** COVID-19 · SARS-CoV-2 · Variants · Delta variant

## Introduction

The emergence of the COVID-19 had shocked the world and affected every nation. Coronaviruses belong to a large family of viruses that have been recognized as large positive-stranded RNA viruses [1]. These viruses are known to have a high predisposition for errors in replication which gives a unique advantage for the virus to increasingly mutate with every replication cycle [2]. These mutations make the virus even more virulent and thereby increase its transmissibility and also evade the host’s natural or acquired immunity [3].

With the continued pandemic, there is a real concern about the effects of emerging variants of the Severe Acute

Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The emergence of these variants had caused concern among the public as well as the healthcare workers (HCWs) [4]. These variants are classified as variants of interest (VOI) and variants of concern (VOC) [5]. VOC refers to variants that have increased transmissibility or virulence, and VOI refers to those with the potential to cause the disease. The first known case of delta variant was first identified in India in late 2020 and ever since has spread worldwide to over 60 countries [6, 7]. Multiple vaccines against SARS-CoV-2 have been authorized and rolled out worldwide, all have been designed based on the original Wuhan SARS-CoV-2 S protein that was first sequenced in January 2020 [8]. Vaccines efficacy depends on stimulating an appropriate antibody and T-cell response to S protein [9]. Efforts to fight the COVID-19 virus have focused on the spike protein which is crucial for the virus to enter the cells [10]. The spike protein is divided into an N-terminal S1 domain

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which allows the virus to attach to the host cells through the angiotensin-converting enzyme (ACE) 2 receptor and a C-terminal S2 domain which allows the virus to adhere to the cell membrane [11, 12]. The S1 domain has two specific domains known as the N-terminal domain (NTD) and a receptor-binding domain (RBD) [13]. Most of the vaccines that have been developed and some monoclonal antibodies that have been used in combatting this virus have specifically focused on the S domain [9, 14].

Despite the vaccinations, the virus evolved due to several mutations that have been appearing on the RBD and the NTD [15] and consequently in VOC and VOI. Out of all the variants that are present at the time of this review, the delta variant B.1.617.2 has become the most concerning of all, due to its high rates of transmission not only in India but also worldwide [16]. The pace at which the delta variant is out-competing other variants can be elucidated from the publicly available data from the COG-UK/ME explorer for the variants of concern in the UK, Scotland, and Northern Ireland. The initial data showed that 47.91% of all the new cases were delta variants and the alpha variant (B.1.1.7.1) comes in a distant second at 0.15% [17]. We intend to discuss the effect of convalescent sera, monoclonal antibodies (mAb), and sera of vaccinated individuals on delta variants based on in vitro tests first and then discuss the effect of vaccination on Delta variants. In addition, we conducted a meta-analysis to evaluate COVID-19 vaccine effectiveness against variants to provide a numeric estimate of the efficacy.

## Methods

We reviewed the literature to understand the transmission and disease severity, and determine the efficacy of the current vaccines. We searched Pubmed, Scopus, and Embase till August 4th 2021, and used the search terms “delta variant”, “vaccinations”, “breakthrough infections”, and “neutralizing antibody”.

In addition, to examine the effectiveness/efficacy of SARS-CoV-2 vaccines against the Delta [B.1.617.2] variant, we conducted a meta-analysis to evaluate COVID-19 vaccine to provide a numeric estimate. We used a protocol from the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement. Vaccine effectiveness measures of how well a vaccine protects people from infection (e.g., vaccine effectiveness of 88% means that 88% of people will be protected from becoming infected with SARS-CoV-2 and 12% of people will still be at risk of becoming infected with SARS-CoV-2). We also used the risk of bias in non-randomized studies-of interventions (ROBINS-I) tool to evaluate studies with low risk of bias

and high quality [18]. Taking a conservative approach, a random effect with the DerSimonian–Laird model was used [19]. This approach results in wider confidence intervals [CIs] than a fixed-effect model. Statistical heterogeneity was assessed utilizing  $\chi^2$  test and I2 statistics [20]. An I2 value of <40% indicates low heterogeneity, 30–60% moderate heterogeneity, 50–90% substantial heterogeneity, and 75–100% considerable heterogeneity. To detect the source of heterogeneity, subgroup analysis was performed based on vaccine brand administered [Pfizer-BioNTech, Oxford-AstraZeneca, and Moderna]. Publication bias was evaluated using funnel plots and the Egger’s correlation test, with  $p < 0.05$  indicating statistical significance [21]. R version 4.1.0 with the packages metafor and meta was used for all statistical analyses.

## Results

### In vitro tests against the delta variant

#### Convalescent sera

A study evaluated the neutralization ability of the sera against delta variants, and was based on the reduction in titers with a comparison reference to the D614G (B.1 lineage)[22]. There were four-to-sixfold reduction in the neutralization rate against the delta variants [22]. This means that the delta variant is less sensitive to the antibodies produced by natural infection, and thus, there is a possibility of reinfection with the delta variant. This emphasizes the need for vaccinations in people who have already built immunity due to previous exposure to COVID-19.

#### Monoclonal antibodies

A set of monoclonal antibodies (casirivimab, bamlanivimab, imdevimab, and etesevimab) had been approved and all of them target the RBD region. It was shown that all these monoclonal antibodies have reduced sensitivity against the delta variant and that bamlanivimab in specific did not show any antiviral activity [23, 24].

#### Sera of vaccinated individuals

Several studies have been done to evaluate the efficacy of vaccinations on the delta variant. In some studies, the efficacy of the sera against D614G was measured, whereas in other studies, wild type virus was used to test the sensitivity of Delta variant to the sera of vaccinated individuals [22, 25, 26]. In one study, the sera of vaccinated individuals after a

single dose of Pfizer vaccine (BNT162b2) and AstraZeneca vaccine (ChAdOx1 nCoV-19) showed very low levels of neutralizing antibody activity [22]. However, when the sera of vaccinated individuals were used after the completion of two doses of the COVID-19 vaccine, there were higher levels of neutralizing antibodies. The efficacy of two doses of either AstraZeneca vaccine or Pfizer-Biontech was 60% and 88%, respectively [22]. In another study from India, sera collected from patients vaccinated with the BBV152 (COVAXIN) vaccine had neutralizing antibodies against the delta variant, but this was reduced by 1.95 times [16]. In the Legacy study, neutralizing antibodies (NABs) were determined from 149 participants who received one dose (median time of 30 days) and 159 who had two doses (median time = 28 days) of BNT162b2 against multiple SARS-CoV-2 strains including wild-type and B.1.617.2 [25]. Of the group who had two doses, 3% did not have neutralizing antibodies (Nab) against B.1.617.2 and these antibodies were generally 5–8 (95% CI 5.0–6.9) fold less against B.1.617.2 compared to the wild-type [25]. Reduced NAB activity against B.1.617.2 relative to B.1.1.7 strain after one vaccine dose was also related to age and time since the second dose of the BNT162b2 vaccine [25]. In vitro neutralization studies, not yet peer-reviewed at the time of this review, conducted by Moderna (mRNA-1273) also showed that there is a 2.1-fold reduction in neutralizing titers of delta variant [27]. In another study which is yet to be peer-reviewed, it was shown that the single dose of the Johnson & Johnson vaccine (Ad26.COV2.S) had shown low neutralizing antibody titers against the delta variants and thus make the vaccinated individuals vulnerable to breakthrough infections [28]. It, therefore, can be seen that although there has been lower efficacy against delta variant, vaccinations may still play an important role for developing resistance toward the delta variant. In a company-sponsored study, researchers tested 20 volunteers immunized with BNT162b2 from the original clinical trial [29] for neutralization. Serum was taken 2–4 weeks after the second dose showed the following geometric mean neutralization titers (GMT) against spike protein: 502 for USAWA1/2020, 302 for B.1.525, 157 for B.1.617.1, 157 for B.1.617.2, 355 B.1.617.2, 343 for B.1.617.2.v2, and 331 for B.1.618, and these were statistically lower than the wild-type USAWA1/2020 [30]. Thus, neutralization of most of the variants was considerably reduced relative to the wild-type virus. Sera from eight participants of the Ad26.COV2.S COVID-19 vaccine ENSEMBLE trial [31] was collected 71 days post single dose; in comparison to wild type, there was a 1.6-fold reduction in GMT [31]. Another study involving 20 participants who received either one or two doses of Ad26.COV2.S reported a median neutralizing antibody titer of 184 against wild type versus 171 against the B.1.617.1 variant, and 107 against the B.1.617.2 variant [32].

### **Effect of vaccinations on delta variant in vivo**

The emergence of significant mutations on the spike protein like D614G, L452R, T19R, dell157-158, T478K, D614G, P681R, and D950N had been well documented [33]. The mutations called 452R and 478 K have allowed the virus to replicate at a faster pace, which in turn contributes to higher transmissibility [34].

A test-negative case–control study compared vaccination status in persons with symptomatic COVID-19 with BNT162b2 or ChAdOx1 nCoV-19 vaccines. The study included 14,837 with alpha variant and 4272 with delta variants. In the pooled analysis of all vaccinated individuals, one dose of the vaccine was less effective against the delta variant (30.7%; 95% CI 25.2–35.7) than the alpha variant (48.7%; 95% CI 45.5–51.7) [35]. Two doses of any of the vaccines showed the effectiveness of 87.5% (95% CI 85.1–89.5) against the alpha variant and 79.6% (95% CI 76.7–82.1) against the delta variant [35]. For BNT162b2, there was a small difference in the effectiveness against the different variants with 93.7% (95% CI 91.6–95.3) for the alpha variant and 88.0% (95% CI 85.3–90.1) for the delta variant [35]. However, ChAdOx1 nCoV-19 was 74.5% [95% CI 68.4–79.4] effective against alpha and only 67.0% [95% CI 61.3–71.8] against delta [35]. The study did not have enough number of cases nor did it account for sufficient time for follow-up, to evaluate the effectiveness in terms of hospitalizations or deaths [35]. The effectiveness with heterologous vaccinations (meaning one dose being BNT162b2 and the other being ChAdOx1 nCoV-19) was found to be 79.6%. This study is specifically important for the countries to change their policies with regards to the vaccination strategies. There was a consensus earlier that increasing the dosing intervals between the two shots would increase the efficacy of the vaccine and also increase the possibility of a larger population being vaccinated [36]. This policy with the ever-increasing spread of delta variant would not be productive as a single dose of the vaccination could put these populations at risk. However, in another study, a single shot of ChAdOx1 nCoV-19 for residents in a care home that was exposed to delta variant did not need any hospitalizations [37]. This might be because the second dose of the vaccine was given on the same day of exposure to the delta variant.

Protection from B.1.617.1 (Kappa) (with L452R and E484Q mutations in RBD) and B.1.617.2 (Delta) (with RBD L452R and T478K mutations in RBD) by vaccines has been of concern. Liu et al. tested neutralization activity against the latter variants from 25 individuals who received two doses of BNT162b2 vaccine, administered 3 weeks apart, with serum taken 4–14 days after the second dose. The neutralization titers against B.1.617.1 and B.1.617.2 were reduced 2.7-fold ( $p < 0.0001$ ) and 2.5-fold ( $p < 0.0001$ ) respectively, relative to a Wuhan-related strain

(isolated early in the pandemic from Australia). Additionally, neutralization was tested from another 25 individuals who received two doses of ChAdOx1nCoV-19 administered 8–14 weeks apart, with serum taken 14–28 days after the second dose. The neutralization titers against B.1.617.1 and B.1.617.2 were reduced 2.6-fold ( $p < 0.0001$ ) and 4.3-fold ( $p < 0.0001$ ), respectively, relative to the Wuhan-related strain. Finally, they tested 20 volunteers 10 weeks after a single dose of BNT162b2 and found a complete absence of neutralization [38].

### The effectiveness of available SARS-CoV-2 vaccines against the variant of concern Delta [B.1.617.2]

Our literature search revealed 21 articles and after full-text screening we identified five articles (148,071 cases), and only four were included in the meta-analysis (Fig. 1). The key findings of vaccine effectiveness against variants of concern (Delta) are presented in Table 1. Overall, there was low certainty of evidence that one dose of Pfizer-BioNTech prevented symptomatic infection from the Delta variant (range of mean estimates: 79–88%) [35, 39]. There was a moderate certainty of evidence that two doses of Pfizer-BioNTech prevented symptomatic infection from the Delta variant (range of mean estimates: 87–96%) [40–42]. There was also low certainty of evidence that one dose of Oxford-AstraZeneca prevented symptomatic infection from the Delta variant (range of mean estimates: 60–67%); and a moderate certainty of evidence that two doses of ChAdOx1 vaccine prevented symptomatic infection from the Delta variant (range of mean estimates: 59.8–92%) [40, 42]. There was moderate certainty of evidence that Moderna prevented symptomatic infection and hospitalization from the Delta variant (72% and 96%, respectively) [41]. Of the 152,752 COVID-19 vaccine recipients who received the first dose and included in the meta-analysis, the overall pooled proportion who had a laboratory-confirmed SARS-CoV-2 infection with Delta variant after Pfizer-BioNTech vaccination was 42.4% (95% CI 0.0–54.5,  $n = 30,882$ , 4 studies,  $I^2 = 99%$ ,  $p < 0.01$ ), while 19.4% (95% CI 0.0–30.7,  $n = 120,879$ , 4 studies,  $I^2 = 99%$ ,  $p < 0.0001$ ) suffered infection with SARS-CoV-2 due to Delta variant after Oxford-AstraZeneca and 56.5% (95% CI 30–83,  $n = 991$ , 1 study) after Moderna vaccination (Fig. 2). As expected, lower incidence of infection with SARS-CoV-2 due to the Delta variant was found after the second dose of Pfizer-BioNTech (4.8, 95% CI 0.0–9.3,  $I^2 = 93%$ ), Oxford-AstraZeneca (9.7, 95% CI 0.0–14.1,  $I^2 = 99%$ ), and Moderna (5.0, 95% CI – 4.6 to 14.7) vaccination (Fig. 3). Funnel plots for possible publication bias for the pooled effect size to determine the prevalence of infections in SARS-CoV-2 patients with Delta variant appeared asymmetrical on visual inspection, and Egger's tests showed asymmetry ( $p$  values  $< 0.05$ ).

### Delta variant effect in high-risk activities

High-risk activities or performance sports put people in close quarters and there are low chances of people to socially distance themselves or adhere to wearing masks while performing such activities. A recent report showed two cases of trekkers who were fully vaccinated with both Moderna and AstraZeneca test positive for delta variants [43]. The trekker with the AstraZeneca vaccine developed severe pneumonia and the other trekker had mild sore throat and congestion. Both the trekkers eventually got better. In a similar context, a recent outbreak that happened in a gymnastics facility highlights how easily a single infected case of the delta variant can spread quickly in the facility and the community, as well [44]. Among the 47 cases that had the delta variant, only two needed hospitalization and they both happened among unvaccinated individuals.

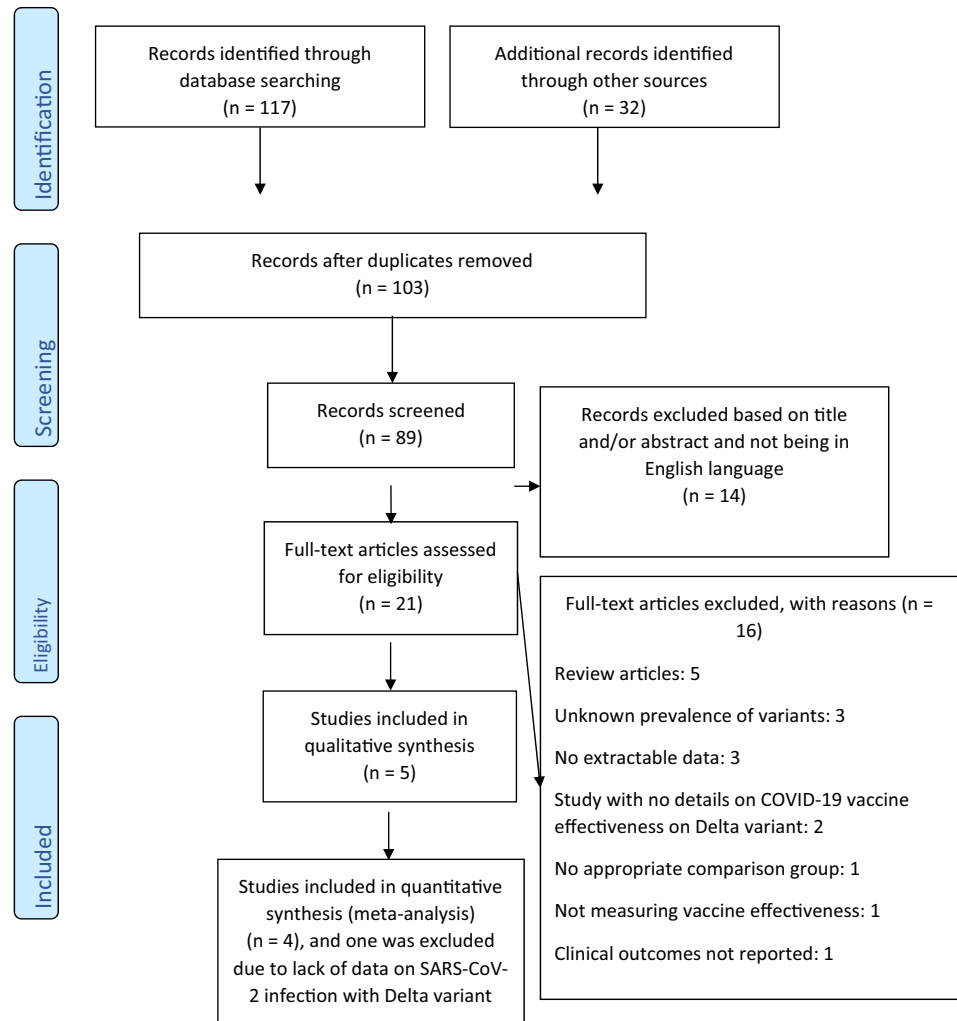
### Delta variant effect on fully vaccinated individuals at large social events

Social events are places that bring people in close proximity and can produce high chances of transmission for the delta variants. A recent wedding event had a small outbreak of delta variant infection among the attendees [45]. The significant difference here was the fact that all six individuals were fully vaccinated. Among them, one of the individuals who was vaccinated with BBV152(COVAXIN) died, whereas the other individual vaccinated with Pfizer (BNT162b2) needed monoclonal antibody infusion. This shows a distinct case of vaccine breakthrough where the person's immune system might have not generated the necessary immunological response to the vaccinations or maybe that immunity started to wane over time.

### Delta variant effect on health care workers

In a recent outbreak in a hospital in Finland, it can be seen how the delta variant could spread so quickly among patients and health care workers (HCWs) [46]. Among the 58 patients (mean age 80 years) who were infected, there were 18 deaths. Among these 18 patients, only one patient who died was fully vaccinated, 11 were vaccinated with one dose and 6 were unvaccinated individuals. The age of the patients and any underlying comorbidities might have some effect, but a majority of the deaths were due to the delta variant. Among HCWs, there were about 45 cases of infections, but no deaths, and the mean age among the HCWs was 38 years. These HCWs also contributed further to secondary infections in the community with whom they were in close contact. This highlights the presence of breakthrough

**Fig. 1** Flow diagram of studies included in the systematic review and meta-analysis



infections with the delta variant, even in individuals who are fully vaccinated.

Despite the availability of vaccines worldwide, there has been an overwhelming vaccine hesitancy [38]. In the Kingdom of Saudi Arabia, the initial willingness of the HCWs to receive the ChAdOx1 nCoV-19 and RNA BNT162b2 vaccines were 24.4%, and 20.9%, respectively [47]. In USA, for example, the vaccination rates can range from 44.8% in Mississippi and 75.4% in Vermont [48]. This is a worrying trend, since in a matter of a month (July 13th–August 13th, 2021), the 7 day moving average in the USA had increased by 350% [48]. This just shows how fast the delta variant can transmit and cause disruptions not only in the USA but also worldwide. It is highly imperative that it is time for the unvaccinated HCWs to understand the situation and make informed decisions to get vaccinated. There is also a need for additional doses for immunocompromised individuals and booster doses for other individuals overtime. It is also important that administration of booster doses follow the order of priority and be given to older age groups

followed by younger age groups. This is because historically it had been shown that vaccine efficacy decreases with age, and that innate immunity shows a decline with the age [49, 50]. Few studies had shown that the heterologous vaccinations (BNT162b2 and ChAdOx1 nCoV-19), may results in a strong immune response [51, 52]. In the meantime, there is a continued need to focus on wearing masks, practice hand hygiene and cough etiquette, and to observe social distancing to end this pandemic.

In conclusion, SARS-CoV-2 seems to be constantly outsmarting us and trying to survive by mutating in ways that gives it a significant advantage to bypass the immune system. The delta variant, at this time, is the most concerning among the variants given its higher rate of transmission and the reduced neutralizing activities. The only way to slow down its spread is through complete vaccinations and following health protocols that are in place. Also, it is important to have policies for preparing health systems (both supplies and personnel), identifying populations at risk, following vaccination shortfalls and expanding vaccination



**Table 1** Summary of the characteristics of the included studies with evidence on the effectiveness of available COVID-19 vaccines for Delta variant [B.1.617.2] of the SARS-CoV-2 ( $n=5$ ), 2021

Author, year, study location	Study design, setting <sup>a</sup>	Age (years) <sup>b</sup>	Male, (%)	Assessment of study risk of bias (tool used; finding)	Notes	Vaccine and dose	Findings
Bernal et al. 2021 [35], England	Retrospective, test-negative case-control, multi-center	Alpha group: 16–29 (35.9%); 30–39 (28.3%); and 40–49 (19.7%) and delta group: 16–29 (36.8%); 30–39 (27.2%); and 40–49 (19.5%)	Alpha group: (48.2) and delta group: (52)	ROBINS-I, low risk of bias	Sequenced cases 19,109: 14,837 alpha and 4272 delta	Pfizer-BioNTech OR Oxford-AstraZeneca	Protection $\geq 21$ days after 1st dose against symptomatic infection: • [delta: 30.7% (95% CI 25.2–35.7)] vs [alpha: 48.7% (95% CI 45.5–51.7)] against symptomatic infection  Pfizer-BioNTech Protection against symptomatic infection $\geq 14$ days after 2nd dose: • [delta: 88.0% (95% CI 85.3–90.1)] vs [alpha: 93.7% (95% CI 91.6–95.3)]  Oxford-AstraZeneca Protection $\geq 14$ days after 2nd dose for symptomatic infection: • [delta: 67.0% (95% CI 61.3–71.8)] vs [alpha: 74.5% (95% CI 68.4–79.4)]

**Table 1** (continued)

Author, year, study location	Study design, setting <sup>a</sup>	Age (years) <sup>b</sup>	Male, (%)	Assessment of study risk of bias (tool used; finding)	Notes	Vaccine and dose	Findings
Bernal et al. 2021 [40], England	Retrospective, test-negative case-control, multi-center	Alpha group: 16–29 (34.5%); 30–39 (28.2%); and 40–49 (20.3%) and delta group: 16–29 (35.3%); 30–39 (25.0%); and 40–49 (20.5%)	Alpha group: (48.4) and delta group: (55)	ROBINS-1, moderate risk of bias	Sequenced cases 12,675: 11,621 alpha and 1,054 delta. Positive cases after 1st or 2nd doses were more likely to be due to variant Delta (OR 1.40, 95% CI 1.13–1.75)	Pfizer-BioNTech OR Oxford-AstraZeneca	Protection against symptomatic infection ≥ 21 days after 1st dose: <ul style="list-style-type: none"> <li>• [delta: 33.5% (95% CI 20.6–44.3)] vs [alpha: 51.1% (95% CI 47.3–54.7)]</li> </ul> Protection against symptomatic infection ≥ 14 days after 2nd dose: <ul style="list-style-type: none"> <li>• [delta: 87.9% (95% CI, 78.2–93.2)] vs [alpha: 93.4% (95% CI 90.4–95.5)]</li> </ul> Protection against symptomatic infection ≥ 14 days after 2nd dose: <ul style="list-style-type: none"> <li>• [Delta: 59.8% (95% CI 28.9–77.3)] vs [alpha: 66.1% (95% CI 54.0–75.0)]</li> </ul>

**Table 1** (continued)

Author, year, study location	Study design, setting <sup>a</sup>	Age (years) <sup>b</sup>	Male, (%)	Assessment of study risk of bias (tool used; finding)	Notes	Vaccine and dose	Findings
Sheikh et al. 2021 [39], Scotland	Retrospective, test-negative case-control, multi-center	Not reported	Not reported	ROBINS-I, low risk of bias	Risk of COVID-19 hospital admission was approximately doubled in those with the delta variant when compared to the Alpha variant [rate per 100 person-years: 62.4 vs 36.2]; risk of admission increased in those with ≥ 5 comorbidities [hazard ratio: 6.51, 95% CI 3.52–12.01]	Pfizer-BioNTech  Oxford-AstraZeneca  Pfizer-BioNTech  Oxford-AstraZeneca	Protection against symptomatic infection ≥ 28 days after 1st dose: • [delta: 30% (95% CI 17–41)] vs [alpha: 38% (95% CI 29–45)] Protection against symptomatic infection ≥ 28 days after 1st dose: • [delta: 18% (95% CI 9–25)] vs [alpha: 37% (95% CI 32–42)] Protection against symptomatic infection ≥ 14 days after 2nd dose: • [delta: 79% (95% CI 75–82)] vs [alpha: 92% (95% CI 90–93)] Protection against symptomatic infection ≥ 14 days after 2nd dose: • [delta: 60% (95% CI 53–66)] vs [alpha: 73% (95% CI 66–78)]



**Table 1** (continued)

Author, year, study location	Study design, setting <sup>a</sup>	Age (years) <sup>b</sup>	Male, (%)	Assessment of study risk of bias (tool used; finding)	Notes	Vaccine and dose	Findings
Stowe et al. 2021 [42], England	Retrospective, test-negative case-control, multi-center	Not reported	Not reported	ROBINS-I, moderate risk of bias	Same cohort as Bernal [40] with an extended time frame for symptomatic infection. The highest proportion of hospital admissions were in the 70–79 age group for the alpha variant (5/146) and 80 years and over for the delta variant (3/48)	Pfizer-BioNTech  Oxford-AstraZeneca  Pfizer-BioNTech	Protection against hospitalization ≥ 21 days after 1st dose: <ul style="list-style-type: none"> <li>[delta: 94% (95% CI 46–99)] vs [Alpha: 83% (95% CI 62–93)]</li> </ul> Protection against hospitalization ≥ 21 days after 1st dose: <ul style="list-style-type: none"> <li>[delta: 71% (95% CI 51–83)] vs [alpha: 76% (95% CI 61–85)]</li> </ul> Protection against hospitalization ≥ 14 days after 2nd dose: <ul style="list-style-type: none"> <li>[delta: 96% (95% CI 86–99)] vs [Alpha: 95% (95% CI 78–99)]</li> </ul> Protection against hospitalization ≥ 14 days after 2nd dose: <ul style="list-style-type: none"> <li>[delta: 92% (95% CI, 75 to 97)] vs [alpha: 86% (95% CI 53–96)]</li> </ul> Protection against hospitalization ≥ 7 days after 2nd dose: <ul style="list-style-type: none"> <li>[delta: 87% (95% CI, 64 to 95)] vs [alpha: 89% (95% CI 86–91)] vs [beta/gamma: 84% (95% CI 69–92)] from symptomatic infection</li> <li>[Delta: 78% (95% CI, 65 to 86)] vs [alpha: 95% (95% CI 92–97)] vs [beta/gamma: 95% (95% CI 81–99)] from hospitalization</li> </ul>
Nasreen et al. 2021 [41], Canada	Retrospective, test-negative case-control, multi-center	Alpha group: 16–29 (29.8%); 30–39 (20.8%); and 40–49 (19.1%) delta group: 16–29 (33.0%); 30–39 (24.7%); and 40–49 (16.3%) beta/gamma group: 16–29 (28%); 30–39 (19.7%); and 40–49 (19.6%)	Alpha group: (49.6) delta group: (50.4) and beta/gamma group: (50.3)	ROBINS-I, moderate risk of bias	Vaccine effectiveness after partial vaccination tended to be lower against delta than Alpha for Pfizer-BioNTech and Moderna, but was similar to Alpha for Oxford-AstraZeneca	Pfizer-BioNTech	Protection against hospitalization ≥ 14 days after 2nd dose: <ul style="list-style-type: none"> <li>[delta: 92% (95% CI, 75 to 97)] vs [alpha: 86% (95% CI 53–96)]</li> </ul> Protection against hospitalization ≥ 7 days after 2nd dose: <ul style="list-style-type: none"> <li>[delta: 87% (95% CI, 64 to 95)] vs [alpha: 89% (95% CI 86–91)] vs [beta/gamma: 84% (95% CI 69–92)] from symptomatic infection</li> <li>[Delta: 78% (95% CI, 65 to 86)] vs [alpha: 95% (95% CI 92–97)] vs [beta/gamma: 95% (95% CI 81–99)] from hospitalization</li> </ul>

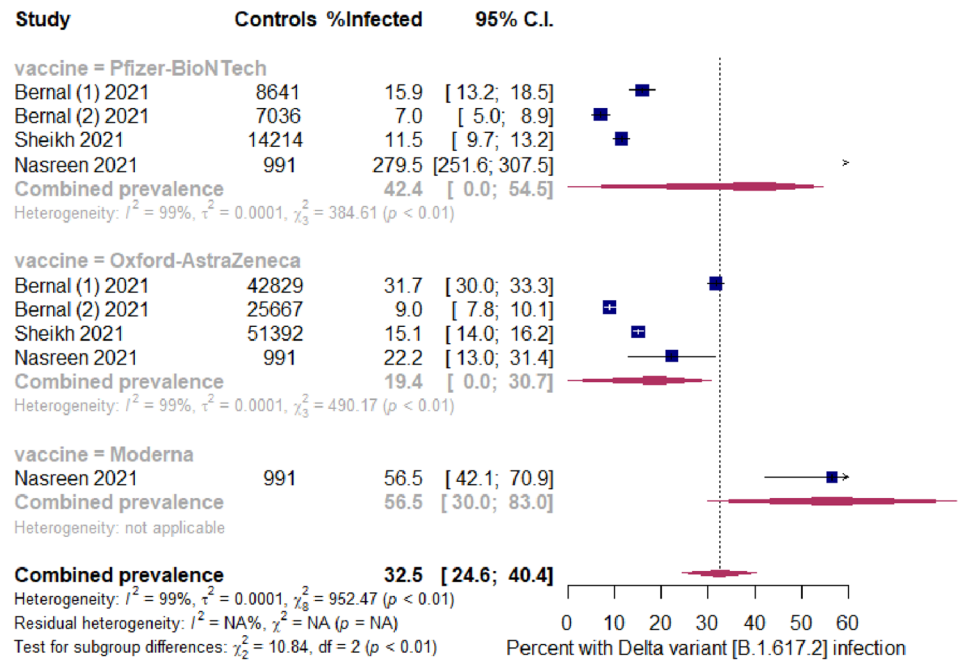
Author, year, study location	Study design, setting <sup>a</sup>	Age (years) <sup>b</sup>	Male, (%)	Assessment of study risk of bias (tool used; finding)	Notes	Vaccine and dose	Findings
						Moderna	Protection $\geq$ 14 days after 1st dose: <ul style="list-style-type: none"> <li>• [Delta: 72% (95% CI 57–82)] vs [Alpha: 92% (95% CI 86–96)] vs [beta/gamma: 77% (95% CI 63–86)] from symptomatic infection</li> <li>• [Delta: 96% (95% CI 72–99)] vs [Alpha: 94% (95% CI 89–97)] vs [beta/gamma: 89% (95% CI 73–95)] from hospitalization</li> </ul>
						Oxford-AstraZeneca	Protection $\geq$ 14 days after 1st dose: <ul style="list-style-type: none"> <li>• [Delta: 67% (95% CI 44–80)] vs [Alpha: 64% (95% CI 60–68)] vs [beta/gamma: 48% (95% CI 28–63)] from symptomatic infection</li> <li>• [Delta: 88% (95% CI 60–96)] vs [alpha: 85% (95% CI 81–88)] vs [Beta/gamma: 83% (95% CI 66–92)] from hospitalization</li> </ul>

*ARDS* acute respiratory distress syndrome; *CI* confidence interval; *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2; *ROBINS-I* risk of bias in non-randomized studies-of interventions

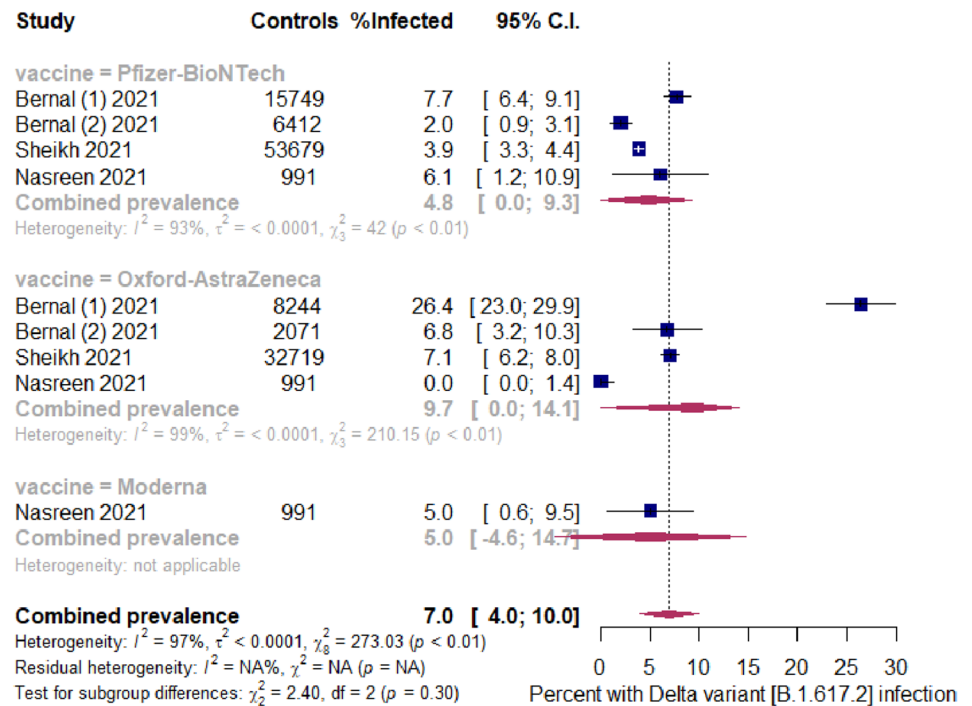
<sup>a</sup>A test-negative case-control design was used in all included studies to estimate vaccine effectiveness against symptomatic disease caused by the SARS-CoV-2 delta variant, as compared with the other COVID-19 variants [i.e., Alpha and Beta/Gamma], over the period that the delta variant has been circulating. This approach has been described in detail elsewhere [53]. Vaccination status was compared among those with symptomatic SARS-CoV-2 and those who had symptoms but had a PCR negative test (controls)

<sup>b</sup>Data are presented as number (%)

**Fig. 2** Pooled estimate for the prevalence of SARS-CoV-2 symptomatic infection with Delta variant [B.1.617.2] after the first dose of COVID-19 immunization stratified by the vaccine type



**Fig. 3** Pooled estimate for the prevalence of SARS-CoV-2 symptomatic infection with Delta variant [B.1.617.2] after the second dose of COVID-19 immunization stratified by the vaccine type



coverage, and early detection and quarantine of COVID-19 cases, must be set forth at local levels. It is important to have further research on variants and to develop vaccines that can tackle the variants that exist currently and those that might emerge in the future.

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## Declarations


**Conflict of interest** All authors have no conflict of interest to declare.

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