Effectiveness of COVID-19 vaccines against delta variant (B.1.617.2): A meta-analysis

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Abstract

Objectives

The highly transmissible COVID-19 *delta variant* (DV) has contributed to the surge in cases and has now been exacerbated the worldwide public health crisis. Several COVID-19 vaccines play a significant role in a high degree of protection against DV. The primary purpose of this meta-analysis is to estimate the pooled effectiveness of the COVID-19 vaccines against DV in terms of risk ratio (RR) among fully vaccinated, compared to unvaccinated populations.

Methods

We carried out a systematic review with meta-analysis of original studies focused on COVID-19 vaccines effectiveness of COVID-19 vaccines against B.1.617.2 clinical perspective among fully COVID-19 vaccinated populations, compared to placebo (unvaccinated populations), published before September 30, 2021. Eleven studies containing data of 17.2 million participants were identified and included in our study. Pooled estimates of COVID-19 vaccines effectiveness (i.e., risk ratio, RR) against delta variant with 95% confidence intervals were assessed using random-effect models. Publication bias was assessed using Egger's regression test and funnel plot to investigate potential sources of heterogeneity and identify any differences in study design.

Results

A total population of 17.2 million (17,200,341 peoples) were screened for the COVID-19 vaccines' effectiveness against delta variant. We found 61.13% of study population were fully vaccinated with 2-dose of COVID-19 vaccines. Weighted pooled incidence of COVID-19 infection was more than double (20.07%) among unvaccinated populations, compared to the fully vaccinated population (8.16%). Overall, the effectiveness of COVID-19 vaccine against DV was 85% (RR = 0.15, 95% CI: 0.07-0.31). The effectiveness of COVID-19 vaccines varied slidably by study designs, 87% (RR = 0.13, 95% CI: 0.06-0.30) and 84% (RR = 0.16, 95% CI: 0.02, 1.64) for cohort and case-control studies, respectively.

Conclusion

Effectiveness COVID-19 vaccines were noted to offer higher protection against delta variant among populations who received two vaccine doses compared with unvaccinated populations. This finding would help efforts to maximise vaccine coverage (i.e., at least 60 to 70% of the population) with two doses among vulnerable populations to have herd immunity to break the chain of transmission and gain greater overall population protection more rapidly.

Introduction

On May 19, 2021, the delta variant (DV) of concern, formerly known as the Indian variant of concern (or B.1.617.2), became the most dominant strain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) ¹. The SARS-CoV-2 DV has been demonstrated in 185 countries ², which is more contagious with higher number of R-naught (R_0 of 5-6), compared to other variants (e.g., Alpha, Beta, Gamma) ³. A significant number of covid-19 new cases caused by the highly transmissible DV is exacerbating the worldwide public health crisis ⁴, and 99% of sequenced, and genotyped cases being related to the DV. The burden of DV has led to considerable demand for herd immunity, and optimal timing of, booster doses for the vaccinated population ⁵. COVID-19 vaccines have been identified as the most effective means of halting the spread of the disease over the world. Several vaccines are currently being administered to people of various ages all around the world. Although the COVID-19 vaccines two doses of vaccines played a significant role in a high degree of protection before delta variant than one dose of vaccination ⁶. Performance of these vaccines are significant still to have herd immunity to break the chain of transmission of delta variant ⁷. A recent study have examined the effectiveness of various COVID-19 immunisation programmes in the real world including the general public and health care settings such as among healthcare and among frontline workers and care home residents ⁸. Emerging evidence suggests the BNT162b2 mRNA vaccine (Pfizer-BioNTech) and the Oxford AstraZeneca adenovirus-vector vaccine, ChAdOx1 nCoV-19 (ChAdOx1) exhibited great efficiency against the Alpha (B.1.1.7) and previous variants in studies before delta variant ⁹⁻¹¹.

The continued appearance of novel SARS-CoV-2 variations could jeopardise the efficacy of immunisation efforts, especially since in vitro tests suggest that vaccine-elicited antibodies have lower neutralisation activity against emergent variants ^{12,13}. The delta variation (B.1.617.2) is of particular concern, as it has resulted in substantial increases in infections in many countries, including ones with excellent vaccination coverage, such as the United Kingdom (U.K.). In the U.K., after being recognised as a Variant of Concern (VOC) on April 28, 2021, it swiftly became dominant ¹³.

The rapid pace at which data is emerging, as well as heterogeneities in study protocol and design, different socioeconomic and demographic characteristics (i.e., age, sex, ethnicity, comorbidities etc.) and regions and implementation way, make interpreting and assessing the anticipated impact of vaccine campaigns on local epidemics difficult and challenging. Measuring the Effectiveness of COVID-19 vaccines against the most dominant variant (B.1.617.2) can be a basis for accentuating protection in patients with COVID-19 infection. In contrast, there is still a scarcity of real-world data on the effectiveness of vaccines against DV ¹⁴. Therefore, using a systematic review and meta-analysis, we aimed to estimate the pooled COVID-19 vaccines efficacy and effectiveness against DV. This study is important and unlike previous systematic reviews and meta-analyses ¹⁵⁻¹⁷, which focussed on risk assessment, immunogenicity, reactogenicity and efficacy across different vaccine platforms.

We anticipated that our study findings will provide a comprehensive understanding of the effectiveness of COVID-19 vaccines and will inform strategies to promote protection against COVID-19, especially DV. Furthermore, the study provides real-time evidence to boost vaccine confidence. Globally, there has been

unfounded concerns that have affected public confidence in vaccines and boosted vaccine hesitancy which could delay the fight against the pandemic if not urgently addressed^{18,19}.

Methods

Search strategy

We conducted a comprehensive search for academic research studies that reported the effectiveness of coronavirus disease-19 (COVID-19) vaccines against COVID-19 delta variant published May 1, 2021 and September 30, 2021 from the following electronic bibliographic databases: Scopus, EBSCOhost (CINAHL, Medline), PubMed, Web of Science, and the first 20 pages of Google Scholar. The following search terms were used with no language restrictions:

[(“Effectiveness” OR “Efficacy” OR “Security” OR “Safety” OR “Evaluation”) AND (“COVID-19 Vaccines” OR “Coronavirus-19 Vaccines” OR “mDNA COVID-19 vaccines” OR “Moderna” OR “mRAN-1273” OR “Pfizer/BioNTech” OR “BNT162b2” OR “Johnson & Johnson” OR “Ad26.COV2.S” OR “Oxford/AstraZeneca” OR “AZD1222” OR “BBIBP-CorV” OR “Vero Cells” OR “CoronaVac” OR “Vaccines”) AND (“Delta Variant” OR “B.1.617.2” OR “Delta” OR “Alpha Variant” OR “Variant”)]

Study participants

Our study scope comprises of vaccinated or unvaccinated populations that were infected with COVID-19 during delta variant.

Inclusion and exclusion criteria

Eligible studies were selected if they 1) were original articles; 2) published between May1, 2021 and September 30, 2021 (focuses on delta variant); focused on 3) effectiveness of COVID-19 vaccines against delta variant (B.1.617.2) clinical perspective, 4) effectiveness or efficacy of all COVID-19 vaccines, 5) effectiveness or efficacy on fully COVID-19 (i.e., 2-dose) vaccinated compared to placebo (unvaccinated), and 6) reported clinical characteristics of the COVID-19 among infected people. Editorials, letters, perspectives, commentaries, reports, opinion species, reviews, and studies with 'insufficient related data were excluded from our study. The reference lists of studies included were checked for eligible studies. We selected the starting date of date of May 1st 2021 because it marks a period when B.1.617.2 was escalated VOC having been earlier detected in April 2021^{20,21}.

Data extraction

Data were independently extracted into EndNote libraries by three researchers who later compared their results. Emerging differences in the data were discussed and resolved by consensus and where the three researchers could not agree, the fourth and fifth researchers were consulted for adjudication. Extracted data captured author's name, year, settings, design or approach, the overall number of COVID-19 infections, number of vaccinated and unvaccinated participants, and number of participants.

Study screening and selection

The screening and selection of studies followed a three-stage screening procedure. The first stage involved screening studies by title to eliminate duplicates. The second stage required reading of abstracts to determine their relevance to our study. The third stage necessitated reading of full texts of the retained studies and those that met the set criteria were retained for our study as reflected in Fig. 1. RAM carried out and recorded the above process and shared the record with other two authors (RAM and MAR) for verification. Discrepancies were discussed and resolved by consensus.

Quality assessment

Quality assessment was independently conducted by two authors who applied four quality assessment tools due to the heterogeneity of included studies designs. Discrepancies in the two author's quality assessments were referred to the other authors for adjudication. The included studies designs were cohort, case series, and case controls. The three critical appraisal tools applied were from the Joanna Briggs Institute (JBI). The JBI tools have been used widely in academic studies^{22,23}. The tools provide a subjective assessment of risk of bias (ranked as low, moderate, or high)²⁴. Higher quality indicates greater confidence that future research is unlikely to change or contradict the results, while lower quality indicates higher likelihood that future research may not affirm the study results. The first JBI tool used was the checklist for cohort studies which we applied to four studies^{25–28} included in this systematic review and meta-analysis. The checklist assesses critical areas of studies' methodologies for biasness in design, implementation, and analysis (*Appendix Table A1*). The second tool of quality assessment used was the JBI checklist for analytical case control studies which we applied to six case control studies^{6,29–33} included in this review. The checklist consists of ten items that enables the critical appraisal of studies for potential biasness (*Appendix Table A2*). The third and last tool used was the JBI checklist for case series study and was applied to one study included³⁴ in our review (*Appendix Table A3*). The checklist comprises of ten items measuring comparability of study groups, matching of cases and controls, identification criteria for cases and controls, reliability and validity of exposure measurement, similarities in exposure measurement for case and control, identification of confounding factors, addressing the confounding factors, assessment of outcomes, length of exposure period and statistical analysis.

Data analysis

Given the high heterogeneity between studies ($I^2 > 50\%$)³⁵, we used random effects meta-analysis models to obtain pooled 2-dose COVID-19 vaccines effectiveness (VE) estimates against Delta variant (B.1.617.2) complemented with a sensitivity analysis to examine the effects of outliers. VE was calculated as $1 - \text{risk ratio (RR)}$.

$$VE = \frac{(\text{Riskamongunvaccinatedgroup} - \text{riskamongvaccinatedgroup})}{\text{Riskamongunvaccinatedgroup}}$$

$$\text{Alternatively, } VE = 1 - \text{riskratio(RR)}$$

For 2-dose VE, we calculated pooled estimate of VE against delta variant and by study design. We assessed residual heterogeneity between studies by calculating the I^2 statistic³⁵. The I^2 statistic enabled us to determine whether the percentage of variance was attributable to the heterogeneity of the data in studies included using the random-effects model. We used forest plots to show the distribution of risk ratio of COVID-19 infection during the delta variant. Subgroup analysis based on the vaccine phases significantly decreased the heterogeneity in the high heterogeneity cases. The presence and effect of publication bias were assessed by using Egger's regression test³⁶ and funnel plot³⁷, to investigate potential sources of heterogeneity and identify any differences study design. All analyses, two-tailed statistics and a significance level of less than 0.05 were considered. All statistical analyses were performed by STATA/SE version 15.0.

Results

Description of studies included

A total of 17.2 million peoples were screened for the COVID-19 vaccines' effectiveness against delta variant. Our primary search of databases yielded 753 studies of which 11 met criteria (i.e., six studies were case-control^{6,29-33}, four studies were cohort design²⁵⁻²⁸ and one study was case-case design³⁴ which were included in this study (Fig. 1). The included studies had a total sample of 17.2 million (N = 17,200,341) and of these, 61.13% of were fully vaccinated (n = 10,514,132) with 2-dose COVID-19 vaccines. The COVID-19 infection was more than double (21.61%, 95% CI: 8.50%-34.72%) among unvaccinated population, compared to the fully population vaccinated (8.88%, 95% CI: 0.18%-17.95%) population.

<Insert Fig. 1 here>

Table 1
Characteristics of selected studies

Study	Country	Design	Fully vaccinated group		Unvaccinated group	
			Number of infected persons, n (%)	Total vaccinated population	Number of infected persons, n (%)	Total unvaccinated population
Bernal et al. (2021) ³¹	United Kingdom	Case-control	143 (0.60)	23,993	7,313 (7.59)	96371
Fowlkes et al. (2021) ²⁵	USA	Cohort study	34 (1.14)	2,976	194 (4.69)	4136
Grannis et al. (2021) ²⁶	USA	Cohort study	134 (2.94)	4,551	1,185 (20.76)	5708
Barlow et al. (2021) ⁶	USA	Case-control	145 (29.00)	500	279 (55.80)	500
Hu et al. (2021) ³⁰	China	Case-control	187 (39.29)	476	184 (38.66)	476
Jara et al. (2021) ²⁷	Chile	Cohort study	12286 (0.29)	4,173,574	185,633 (3.39)	5471728
Kislaya et al. (2021) ³⁴	Portugal	Case-case study	162 (11.89)	1,363	777 (46.00)	1689
Li et al. (2021) ²⁹	China	Case-control	12 (12.37)	97	37 (34.58)	107
Nanduri et al. (2021) ²⁸	USA	Cohort study	2999 (0.06)	5,011,746	1,397 (0.15)	953861
Nasreen et al. (2021) ³³	Canada	Case-control	10 (0.12)	8,461	6,325 (22.03)	28705
Tang et al. (2021) ³²	Qatar	Case-control	249 (0.02)	1,286,395	4,993 (4.06)	122928
Total, n = 12			N = 16,361 (0.16)	N = 10,514,132	N = 208,317 (3.12)	N = 6,686,209
Weighted pooled incidence of COVID-19 infection.			8.88% (95% CI: 0.18-17.95)		21.61% (95% CI: 8.50-34.72)	

Effectiveness of the COVID-19 vaccines against delta variant

Figure 2 shows the effectiveness of the COVID-19 vaccines against delta variant after two doses. All four cohort studies showed vaccines played a significant role in reducing the risk of COVID-19 infections among fully vaccinated populations, compared to unvaccinated populations. The pooling of four cohort studies^{25–28} showed vaccines significantly lowered the risk (RR = 0.20, 95% CI: 0.07–0.54) of exposure against delta variant (B.1.617.2) among fully vaccinated (i.e., 2 doses) populations by 80% compared to unvaccinated populations. Pooled estimates for six case-control studies, except one study, showed significantly lower risk of having COVID-19 infection (90%) [RR = 0.10, 95% CI: 0.01–0.80] against delta variant among fully vaccinated populations than unvaccinated populations (Figure 2). Overall, the effectiveness of COVID-19 vaccine against delta variant was 86% (RR = 0.14, 95% CI: 0.07–0.54). The funnel plot shows some asymmetry (Figure 3); however, this is not significant for Begg's regression test (p = 0.481 for five case-control studies and p = 0.314 for five cohort studies) (Table 2), denoting absence of publication bias. Therefore, we included all 11 studies in the meta-analysis. There was statistically significant heterogeneity ($I^2 = 99.9\%$, $p < 0.001$ for six case-control studies and $I^2 = 99.8\%$, $p < 0.001$ for four cohort studies, $I^2 = 99.8\%$, $p < 0.001$) (Figure 2).

<Insert Figure 2 and Figure 3 here>

Table 2
Assessing publication bias

Study design	Number of studies	Egger's regression test			Small-study effect (p-value)	
		RR, (95% CI)	p-value	Bias (RR), 95% CI	p-value	
Case-control	6	0.61 (0.02, 5.53)	0.224	30.53 (0.89, 51.45)	0.481	p-value = 0.685
Cohort study	4	0.09 (0.04, 0.17)	0.015	13.32 (0.98, 45.47)	0.390	P-value = 0.390
Case-case study	1	-	-	-	-	-

RR = risk ratio, p-value = probability value

Quality of included studies

Our findings suggest that five (n = 5) of the included studies^{6, 29–31, 34} were of high quality implying that they were robust studies; six of the studies^{25, 26, 28, 30, 32, 33} were ranked as medium quality implying that their methods were of moderate quality based on the JBI quality assessment criteria. There was no study excluded based on poor scoring on the quality assessment scales. Notably, one (n = 1) cohort study²⁷ was assessed as high on the JBI tools; the rest (n = 3) cohort studies were found to be of medium quality on the same scale^{25, 26, 28}. Three out of six (n = 3/6) case-control studies included^{6, 29, 31}, were found to be of high quality based on the JBI quality assessment scale for case-control studies; the rest (n = 3) of the studies^{30, 32, 33} were found to be of medium quality on the same scale. Lastly, the only one case–series study³⁴ included in our review was found to be of high quality on the JBI quality assessment scale of case controls.

Discussion

In this catastrophic situation, several vaccines, including Pfizer-BioNTech, Moderna, AstraZeneca, protect against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). These vaccines teach our cells how to make a protein (or even just a piece of a protein)—that triggers an immune response inside our bodies. Theoretical benefits of these vaccines are that those vaccinated gain protection without ever having to risk the serious consequences of getting sick and or die of COVID-19. Several studies found that these vaccines trigger an immune response against the virus^{27, 38, 39}. These vaccines have been approved for clinical use by the World Health Organization based on comprehensive assessments of non-clinical, laboratory confirmation, clinical utility, and manufacturing data provided by manufacturers to respective regulatory bodies (i.e., U.S. Food and Drug Administration (FDA) and the Department of Health and Human Services or related institutes). Though these vaccines' efficacy and side effects have not yet been widely discussed, numerous claims have been made by popular media and politicians^{40, 41}. During this process, respective government bodies examine the quality and consistency of the vaccine so that the potential benefits offset the potential adverse effects of the vaccine. Despite unsubstantiated claims on the COVID-19 vaccines efficacy and associated side effects, there is a lack of accumulated evidence on the effectiveness of this vaccine²⁷. However, among different variants of SARS-CoV-2, the delta variant has significantly increased virulence and transmission capacity⁴². In addition, recent evidence indicates that the vaccine's effectiveness declined with the emergence and promotion of the delta variant⁶. Therefore, this meta-analysis presents a piece of systematic and evidence-based information regarding the effectiveness of different COVID-19 vaccines against specific delta variant (B.1.617.2).

The B.1.617.2 has seen a sharp rise in infections and mortality in 186 countries², including those with relatively high vaccine coverage and increased hospitalization and mortality in the U.K.^{20, 43}. The high transmissibility of SARS-CoV-2 mainly of delta variant is a considerable socioeconomic global burden. Previous evidence on vaccine effectiveness reported reduced protection against the delta variant compared to the Alpha variant^{1, 31}. Even the efficacy of the 2-dose ChAdOX1 vaccine decreased by 59.8% after exposure to B.1.617.2³¹. Recent reports determined a higher vaccine breakthrough infection in terms of reduced prophylactic vaccine effectiveness against the SARS-CoV-2 delta variant (B.1.617.2)^{1, 31}. While more contributing factors may reduce immunity, a recent Israeli study has found higher infection rates even among the earliest vaccinated individuals⁴⁴. Another study among nursing home residents found the effectiveness of the mRNA vaccine as 74.7% against infection, but the efficiency decreased significantly by 53.1% when the B.1.617.2 circulation predominated²⁸. The interpretation of this report is complex due to the bias of the methodology, research population, care settings, immunisation timeline and

the potential selection and case diagnosis⁶. Our study found that the effectiveness of COVID-19 vaccine was 80% more protective among those vaccinated with the delta variant (RR = 0.20, 95% CI: 0.07-0.54), compared to unvaccinated populations. A previous study also found a higher rate of vaccine infection breakthrough, indicating lower effectiveness of vaccines in protecting infection with the delta variant³⁴. Another study also argued that infections with delta variant that are transmitted despite the vaccine carry a similar viral burden for people who have not been vaccinated¹⁴. Though the effectiveness of vaccines is lower among delta cases, completing the second dose of vaccines reduces the complication among those vaccinated⁶. In addition, a growing number of cases detected after one or two doses of vaccination are more likely to be infected with B.1.617.2 than other variants¹². Since the efficacy of the vaccines against the B.1.617.2 is lower, several studies recommended an additional dose to curtail the infection of the variant and optimise the immune response^{12,28}. Single-dose vaccine recipients with high infection rates of B.1.617.2 or who have been infected before with another variant can risk vaccine-adapted forms of evolution¹². We argue that the population should be vaccinated as much as possible since those who have not been vaccinated cannot be protected by a significant reduction in the number of vaccinated populations as seen by other infections, making herd immunity could be unachievable due to emerging variants¹⁴.

Our study is unique with several strengths. *Firstly*, this meta-analysis study that provides evidence-based data on vaccines' effectiveness against the B.1.617.2 variant. *Secondly*, we only considered the studies that provide symmetrical information of individuals vaccinated with two doses. Finally, a large population was considered in this study that yields a piece of adequate evidence on this topic. However, we acknowledge some limitations with our study design and selection of published studies. Effectiveness of vaccines (e.g., BNT162b2 or ChAdOx1 nCoV-19) after one dose was significantly lower among population with the B.1.617.2 variant (30.7%) than among those with the alpha variant (48.7%)³¹. Studies on single-dose vaccination and its efficacy were excluded in this meta-analysis due to lack of reported data, lower effectiveness with the delta variant, insufficient number of studies, and we did not employ any analysis considering the sub-groups of different types of vaccines due to insufficient number of studies and reported combined results with more than one vaccine.

Nonetheless, our study provides valuable insights into the effectiveness of the vaccines against the delta variant since there is a dearth of information on this topic. Depending on the predominance of the delta variant, the findings of this study may help policy-makers take action or control measures, and coordinate vaccination effects. Recently, caution has been elevated that vaccine performance may diminish in the future, considering the possibility of a series of potential viral genetic drift⁶. These claims highlight the importance of both pharmaceutical and non-pharmaceutical interventions in tandem to reduce SARS-CoV-2 infection. Future research can examine the combined efficacy of mass vaccination, contact tracing and social distancing measures in minimising the socioeconomic burden arising from COVID-19. Our study's practical implication is that taking the mounting evidence on the efficacy of pharmaceutical intervention into account, mass vaccination against should be continued in a planned manner to lessen the socioeconomic burden of COVID-19. To do so, COVID-19 vaccines should be categorised as a global humanitarian good emphasising the optimisation of production and equal distribution.

On the other hand, the demand side should target reducing vaccine hesitancy so that more vulnerable populations are adequately covered. The effectiveness of COVID-19 vaccines was noted with the delta variant among populations after receiving two vaccine doses as compared with unvaccinated populations. This finding would help efforts to maximise vaccine coverage with two doses among vulnerable populations.

Declarations

Competing interests

The authors declare that they have no competing interests.

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No funding was received for conducting this study.

Author contributions

RAM conceptualised the systematic review and meta-analysis. RAM, MAA, SK and MAR conducted the search, data extraction, under the supervision of AMNR. RAM performed meta-analysis. All authors contributed to finalise the draft paper. RAM, MAA, SK, MAR, JKK and AMNR contributed to revision and approval for submission.

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Appendix Tables

Appendix Table A1. Quality score assessment for cohort study

#	Quality assessment indicators	Selected cohort studies			
		Fowlkes et al. (2021) ²⁵	Grannis et al. (2021) ²⁶	Jara et al. (2021) ²⁷	Nanduri et al. (2021) ²⁸
Q1	Were the two groups similar and recruited from the same population?	✓	✓	✓	✓
Q2	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	✓	✓	✓	✓
Q3	Was the exposure measured in a valid and reliable way?	✓	✓	✓	✓
Q4	Were confounding factors identified?	✓	✓	✓	✓
Q5	Were strategies to deal with confounding factors stated?	✓	✓	✓	✓
Q6	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	✓	✓	✓	✓
Q7	Were the outcomes measured in a valid and reliable way?	✓	✓	✓	✓
Q8	Was the follow-up time reported and sufficient to be long enough for outcomes to occur?	®	®	✓	®
Q9	Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?	␣	␣	®	␣
Q10	Were strategies to address incomplete follow-up utilized?	␣	␣	␣	␣
Q11	Was appropriate statistical analysis used?	✓	✓	✓	✓
Overall quality score		8.5 (medium)	8.5 (medium)	9.5 (high)	8.5 (medium)
Overall appraisal		Included	Included	Included	Included

Note ✓ = yes (= 1), ␣ = no (= 0), ® = unclear (= 0.5); quality assessment decision rules for 11 scales [(i) poor if the overall score ≤ 5, (ii) medium if overall scores is 6 to 9, and (iii) high if the overall score > 9],

Appendix Table A2. Quality score assessment for case-control

#	Quality assessment indicators	Selected case-control studies					
		Barlow et al. (2021) ⁶	Li et al. (2021) ²⁹	Hu et al. (2021) ³⁰	Bernal et al. (2021) ³¹	Tang et al. (2021) ³²	Nasreen et al. (2021) ³³
Q1	Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	✓	✓	✓	✓	✓	✓
Q2	Were cases and controls matched appropriately?	✓	✓	✓	✓	✓	✓
Q3	Were the same criteria used for identification of cases and controls?	✓	✓	✓	✓	✓	✓
Q4	Was exposure measured in a standard, valid and reliable way?	✓	✓	✓	✓	✓	✓
Q5	Was exposure measured in the same way for cases and controls?	✓	✓	✓	✓	✓	✓
Q6	Were confounding factors identified?	✓	✓	✓	✓	✓	✓
Q7	Were strategies to deal with confounding factors stated?	✓	␣	␣	✓	␣	␣
Q8	Were outcomes assessed in a standard, valid and reliable way for cases and controls?	✓	✓	✓	✓	✓	®
Q9	Was the exposure period of interest long enough to be meaningful?	®	␣	␣	␣	␣	®
Q10	Was appropriate statistical analysis used?	✓	✓	✓	✓	✓	✓
Overall quality score		9.5 (high)	8 (high)	8 (medium)	9 (high)	8 (medium)	8 (medium)
Overall appraisal		Included	Included	Included	Included	Included	Included

Note ✓ = yes (= 1), ␣ = no (= 0), ® = unclear (= 0.5); quality assessment decision rules for 10 scales: (i) poor if the overall scores < 6, (ii) medium if the overall scores is 6 to 8, and (iii) high if the overall scores > 8

Appendix Table A3. Quality score assessment for case-series study

#	Quality assessment indicators for case-series study	Kislaya et al. (2021) ³⁴
Q1	Were there clear criteria for inclusion in the case series?	✓
Q2	Was the condition measured in a standard, reliable way for all participants included in the case series?	✓
Q3	Were valid methods used for identification of the condition for all participants included in the case series?	✓
Q4	Did the case series have consecutive inclusion of participants?	✓
Q5	Did the case series have complete inclusion of participants?	®
Q6	Was there clear reporting of the demographics of the participants in the study?	✓
Q7	Was there clear reporting of clinical information of the participants?	✓
Q8	Were the outcomes or follow-up results of cases clearly reported?	✓
Q9	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	✓
Q10	Was statistical analysis appropriate?	✓
Overall quality score		9.5 (high)
Overall appraisal		

Note ✓ = yes (= 1), ® = no (= 0), ® = unclear (= 0.5); quality assessment decision rules for 10 scales: (i) poor if the overall scores <6, ii) medium if the overall scores is 6 to 8, and (iii) high if the overall scores >8

Figures

Figure 1

Steps of study selection procedures

Effectiveness of COVID-19 vaccines against the delta variant

%

Figure 2

Effectiveness of COVID-19 vaccines against delta variant

Figure 3

Funnel plot with pseudo 95% confidence intervals