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Clinical manifestations of COVID-19 breakthrough infections: A systematic review and meta-analysis

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Abstract

To provide a comparative meta-analysis and systematic review of the risk and clinical outcomes of coronavirus 2019 (COVID-19) infection between fully vaccinated and unvaccinated groups. Eighteen studies of COVID-19 infections in fully vaccinated ("breakthrough infections") and unvaccinated individuals were reviewed from Medline/PubMed, Scopus, Embase, and Web of Science databases. The meta-analysis examined the summary effects and between-study heterogeneity regarding differences in the risk of infection, hospitalization, treatments, and mortality between vaccinated and unvaccinated individuals. he overall risk of infection was lower for the fully vaccinated compared to that of the unvaccinated (relative risk [RR] 0.20, 95% confidence interval [CI]: 0.19–0.21), especially for variants other than Delta (Delta: RR 0.29, 95% CI: 0.13–0.65; other variants: RR

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0.06, 95% CI: 0.04–0.08). The risk of asymptomatic infection was not statistically significantly different between fully vaccinated and unvaccinated (RR 0.56, 95% CI: 0.27–1.19). There were neither statistically significant differences in risk of hospitalization (RR 1.06, 95% CI: 0.38–2.93), invasive mechanical ventilation (RR 1.65, 95% CI: 0.90–3.06), or mortality (RR 1.19, 95% CI: 0.79–1.78). Conversely, the risk of supplemental oxygen during hospitalization was significantly higher for the unvaccinated (RR 1.40, 95% CI: 1.08–1.82). Unvaccinated people were more vulnerable to COVID-19 infection than fully vaccinated for all variants. Once infected, there were no statistically significant differences in the risk of hospitalization, invasive mechanical ventilation, or mortality. Still, unvaccinated showed an increased need for oxygen supplementation. Further prospective analysis, including patients' risk factors, COVID-19 variants, and the utilized treatment strategies, would be warranted.

KEYWORDS
breakthrough infection, clinical manifestations, COVID-19, Delta variant, vaccine effectiveness

1 | INTRODUCTION

The novel coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), continues to restructure local health systems, disrupt global economies, and pervade all aspects of community life. Due to the universal concerns surrounding the virus and the unsettling nature of its accelerated spread, finding prevention options has become a priority. The development of the coronavirus 2019 (COVID-19) vaccine was a major milestone toward the possible end of the pandemic. However, the ever-evolving nature of the virus through a multitude of mutative evolutionary events has posed a concern for vaccine efficacy due to viral genomic changes. Thus, the questions surrounding the sustainability of the approved COVID-19 vaccines remain a concern against continually rising viral variants.

The more recent variant of concern, the Delta variant, appears to consist of five different sublinegaes to date (B.1.617.2, AY.1, AY.2, AY.3, and AY.3.1).[1] All Delta variant sublineages share the main mutations of concern, T478K and L452R.[1] A recent case in Lombardy, Italy has indicated the presence of the E484K mutation on the B.1.617.2 sublineage causing novel resistance to monoclonal antibody treatment options and a substantial decrease in vaccine efficacy.[1] Due to the widespread convergent evolutionary trends, it can be expected that this mutation will spread through all variant types. Monitoring both emerging variants and viral evolutionary patterns are necessary to understand the current state of the pandemic. Further, it is vital to reevaluate the efficacy of vaccines to improve the prevention protocols in the future.

Previous studies have reported varying clinical outcomes for both vaccinated and unvaccinated groups. In Israel, vaccinations across all ages were observed to be highly effective in preventing both symptomatic and asymptomatic infections, hospitalization, severe disease, and death.[2] Another study found significant decline in vaccine effectiveness with age and with existing comorbidities such as type 2 diabetes, chronic obstructive pulmonary disease, immunosuppression, and cardiac disease.[3] Due to the variability of findings, it is imperative to determine a cohesive view of the clinical outcomes for both vaccinated and unvaccinated individuals.

In this study, we comparatively analyze vaccinated and unvaccinated individuals to understand the effectiveness of COVID-19 vaccination through examining their respective clinical outcomes while including the Delta variant. Through the meta-analysis and systemic review format, numerous scientific publications will be used to provide a comprehensive view of what is known regarding vaccine effectiveness through the Delta variant. It is anticipated that the data derived from this study can be used to drive policy decisions, promote prevention innovations, and contribute toward the end of the pandemic.

2 | METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Supporting Information: Table S1), and this study was not registered with PROSPERO due to concerns about exposure of ideas related to timely and important research topics.

2.1 | Literature search strategy and study selection

We searched Medline/PubMed, Scopus, Embase, and Web of Science databases up to December 7, 2021. The search terms used are described in Supporting Information: Table S2. Three authors (C. L., W. W., A. Y. K.) independently screened title/abstracts and

the fourth author (J. I. S.) resolved any disagreements. The full literature search strategy is presented in Supporting Information: -Figure S1. The eligibility criteria for inclusion were as follows: (1) studies in which SARS-CoV-2 infection among fully vaccinated and unvaccinated individuals were compared; (2) studies about the incidence of infection in individuals according to their vaccination status; (3) a short survey, or monthly report with clinical data for SARS-CoV-2 infection in the fully vaccinated and unvaccinated groups. We excluded (1) studies where partially vaccinated cases were mixed with vaccinated groups; (2) case series and those relating to booster vaccinations; (3) laboratory studies without sufficient data; (4) review articles, letters to the editors, abstracts, articles that did not contain sufficient information on patients; (5) studies with limited information about breakthrough infection; and (6) studies with insufficient clinical data.

2.2 | Data extraction and statistical analysis

Four authors (C. L., W. W., A. Y. K., and J. I. S.) extracted data, including study author, year, country, dates, population, study design, sample size, type of variant, demographic factors (age, gender, race, comorbidity), and clinical outcomes (infection incidence, proportion of asymptomatic infection/hospitalization/patients needing intensive care/mortality). Throughout the article, vaccinated means fully vaccinated individuals who received their primary series of COVID-19 vaccines; for example, persons after 2 weeks from their second dose of a messenger RNA vaccine such as Pfizer-BioNTech or Moderna.

The risks of infection, hospitalization, oxygen requirement, invasive mechanical ventilation, and mortality were expressed as relative risk (RR) and 95% confidence interval (CI). Random effects model was used to demonstrate each comparison between unvaccinated and fully vaccinated groups. Heterogeneity among studies was expressed as I^2 (values over 50% are commonly considered to represent significant heterogeneity). All tests were two-sided; an alpha level of 0.05 was chosen for significance. Statistical analyses were performed using R version 4.1.0 (R Foundation for Statistical Computing) and the Review Manager (RevMan) software version 5.2.3 (The Nordic Cochrane Centre).

3 | RESULTS

The initial search identified 1025 studies which included comparative studies, epidemiology focused studies, infectivity analyses, laboratory studies, modeling studies, and outcome-based studies. We excluded studies with irrelevant data and not responding to inclusion criteria. The PRISMA flow model for study selection is shown in Supporting Information: Figure S1. Finally, 18 studies were included in the synthesis of the meta-analysis and systemic review.[4–21] Findings of each included study are described in Supporting Information: Table S3.

The clinical outcomes according to vaccination status in each study are demonstrated in Tables 1–2. Figure 1A–C examined the risk of SARS-CoV-2 infection among exposed individuals according to vaccination status for the Delta variant, non-Delta variants, and all variants, respectively. Figure 1A (the Delta variant) indicated an RR of 0.29 (95% CI: 0.13–0.65) among the fully vaccinated individuals compared to the unvaccinated ones when exposed to the Delta variant under the random effects model (I^2 = 97%). Figure 1B (other than the Delta variant) indicated an RR of 0.06 (95% CI: 0.04–0.08) under the random effects model (I^2 = 19%). When including all variants (Figure 1C), the risk of infection among the fully vaccinated presented an RR of 0.18 (95% CI: 0.10–0.33) with significant heterogeneity among included studies (I^2 = 99%). Universally, vaccinated individuals were still less likely to be infected when in contact with all variants of SARS-CoV-2. However, the beneficial effect diminished in the Delta variant when compared to others.

The risk of asymptomatic infection according to vaccination status for all variants is shown in Figure 2. The RR was 0.56 (95% CI: 0.27–1.19) under the random effects model (I^2 = 83%) indicating no difference in asymptomatic infection risk between vaccinated and unvaccinated groups. Figure 3 shows the risk of hospitalization according to vaccination status in all variants. The RR was 1.06 (95% CI: 0.38–2.93) in the fully vaccinated when compared to the unvaccinated group under the random effects model (I^2 = 100%).

After being hospitalized, the risk of oxygen requirement in unvaccinated patients was 1.40 (95% CI: 1.08–1.82) under the random effects model (I^2 = 73%) (Figure 4). Note, Chia et al.[22] and Bierle et al.[23] only contributed Delta variant data sets to this figure. Figure 5 described the risk of invasive mechanical ventilation among the unvaccinated (RR 1.65 [95% CI: 0.90–3.06], I^2 = 54%), which seemed marginally significant. Notably, the mortality risk in the unvaccinated after being hospitalized presented a RR of 1.19 (95% CI: 0.79–1.78) as shown in Figure 6. Heterogeneity was measured at I^2 = 0% indicating consistent findings within studies included for this analysis. In partially vaccinated patients, the risk of supplemental oxygen treatments (RR 1.00 [95% CI: 0.95–1.05], I^2 = 0%) and mortality (RR 0.78 [95% CI: 0.21–2.88], I^2 = 74%) was not different compared to unvaccinated (Supporting Information: Table S4 and Figures S2,3).

Table 3 describes the demographic characteristics of the patients included in each study. Significant differences between vaccinated and unvaccinated patients were found except for the study by Butt et al.[17] in which the propensity score was matched for demographic variables. The average median age range of patients in vaccinated and unvaccinated groups were between 45 and 70.3 and 39.5–59.6 years, respectively. The proportion of male in infected patients were similar between fully vaccinated and unvaccinated (Supporting Informaion: Figure S4). The race of participants found within both vaccinated and unvaccinated cohorts included Hispanic, Black, White, and other unnamed groups. Underlying health conditions were also assessed including hypertension, diabetes, chronic lung disease, immunosuppression, and transplantation. In addition, the information regarding seropositivity only from three available studies

TABLE 1 The number of infected cases and asymptomatic infection according to the vaccination status

Author	Country	Study type	Variants	Vaccine types	Infected cases				Asymptomatic/infected	
					Breakthrough		Unvaccinated			
					Delta	Others	Delta	Others	Breakthrough	Unvaccinated
Bosch	USA	Retrospective	Delta, pre-Delta[¶]	mRNA, J&J	1089	31	5041			
Naito	Japan (HW)	Prospective cohort	Delta, pre-Delta[¶]	mRNA	3/2809	0/2809	19/5883	13/5883		
Fowlkes	USA	Prospective cohort	Delta, pre-Delta[¶]	mRNA, J&J	24/2352	10/2875	19/488	175/4137		
Sheikh	Scotland	Prospective cohort	Delta, pre-Delta[¶]	BNT162b2	BNT162b2:	BNT162b2:	3672/117 263	5828/119 419		
					208/53 679	104/53 575				
				ChAdOx1	ChAdOx1:	ChAdOx1:				
					231/32 719	100/32 588				
Ghosh	India	Prospective cohort	Beta	ChAdOx1	2512/1 312 938		10 061/1 595 630			
Waldman	USA (HW)	Cross-sectional	Delta	mRNA, J&J	309/72 624		131/15 946			
Taylor	USA	Cross-sectional	Delta	mRNA. J&J						
Tenforde	USA	Case-control	Alpha, Delta and others	mRNA						
Bahl	USA	Observational cohort study	Alpha	mRNA. J&J		129		10 880		
Liu	USA	Observational, retrospective	Not specified	mRNA	198/14 362		3902/37 752			
Chia	Singapore	Retrospective	Alpha, Beta, Delta, Gamma	mRNA	71		130		20/71	12/130
Thangaraj	India	Prospective cohort	Delta, Kappa, Alpha, Beta	ChAdOx1 COVAXIN	84	3	134	17	12/104	10/176
Butt	Qatar	Case-control	Delta and Beta	BNT162b2		456		456	216/456[α]	204/456[α]
Shamier	Netherland	Retrospective	Alpha, Beta, Delta and Gamma	mRNA	114	47			21/157	
				Astra						
				J&J						
Butt	USA	Case-control	Alpha, Beta and Delta	mRNA		250		250		
Aslam	USA	Retrospective cohort	Not specified	mRNA		4/912		59/1151		
				J&J						
Christensen	USA	Retrospective	Delta and Alpha	mRNA	3088	258	9483	3509		
				J&J						
Bierle	USA	Retrospective[δ,α]	Delta	mRNA	201		429			
				J&J						

Note: All data are expressed as n, n/N.

Abbreviations: ECMO, extracorporeal membrane oxygenation; HW, healthcare workers; IMV, invasive mechanical ventilation; NIPPV, noninvasive positive pressure ventilation.

[¶]Pre-Delta means any variant other than the Delta variant that was dominant before the Delta variant was most likely.

[δ]Variants other than delta.

[α]Data from delta variant only.

TABLE 2 Comparison of Clinical outcome and severity according to the vaccination status

Author	Country	Variants	Vaccine types	Hospitalization/infected				Oxygen treatment				Intensive care/hospitalized				Mortality/hospitalized			
				Breakthrough		Unvaccinated		Breakthrough		Unvaccinated		Breakthrough		Unvaccinated		Breakthrough		Unvaccinated	
				Delta	Others	Delta	Others	Delta	Others	Delta	Others	Delta	Others	Delta	Others	Delta	Others	Delta	Others
Bosch	USA	Delta, pre-Delta[¶]	mRNA, J&J	119/1089	7/31	505	334												
Naito	Japan (HW)	Delta, pre-Delta[¶]	mRNA																
Fowlkes	USA	Delta, pre-Delta[¶]	mRNA, J&J																
Sheikh	Scotland	Delta, pre-Delta[¶]	BNT162b2 ChAdOx1	Alpha: 223/9996 infected Delta: 134/7723 infected															
Ghosh	India	Beta	ChAdOx1													7/2512 infected		37/10061 infected	
Waldman	USA (HW)	Delta	mRNA, J&J																
Taylor	USA	Delta	mRNA. J&J	393	389	1145	4896												
Tenforde	USA	Alpha, Delta and others	mRNA	191	123	666	1003	98/142		889/1055		**35/142** IMV 11/142 NIPPV 20/142 ECMO 1/142		**423/1055** IMV 243/1055 NIPPV 182/1055 ECMO 39/1055		9/142		91/1055	
Bahl	USA	Alpha	mRNA. J&J		95/129		5250/10 880	64/95[α]		4042/5250[α]		IMV 6/95[α,¶] NIPPV 10/95[α] ECMO 0/95[α]		IMV 395/5250[α] NIPPV 428/5250[α] ECMO 4/5250[α]		8/95[α]		379/5250[α]	
Liu	USA	Not specified	mRNA	120/121		3031/3037						IMV 9/121		IMV 249/3037		5/121		157/3037	
Chia	Singapore	Alpha, Beta, Delta, Gamma	mRNA					2/71[δ]		27/130[δ]		0/71 (IMV 0/71)[δ]		7/130 (IMV 2/130)[δ]		0/71[δ]		2/130[δ]	
Thangaraj	India	Delta, Kappa, Alpha, Beta	ChAdOx1 COVAXIN					7/104		34/176						0/104		7/176	
Butt	Qatar	Delta and Beta	BNT162b2													Severe+ death: 48/456[α]		Severe + death: 121/456[α]	
Shamier	Netherland	Alpha, Beta, Delta and Gamma	mRNA Astra J&J	0/161				0/161				0/161				0/161			
Butt	USA	Alpha, Beta and Delta	mRNA													Severe+ death: 50/250[α]		Severe+ death: 53/250[α]	
Aslam	USA	Not specified	mRNA													0/4 infected[α]		2/59 infected[α]	

TABLE 2 (Continued)

Author	Country	Variants	Vaccine types	Hospitalization/infected				Oxygen treatment				Intensive care/hospitalized				Mortality/hospitalized			
				Breakthrough		Unvaccinated		Breakthrough		Unvaccinated		Breakthrough		Unvaccinated		Breakthrough		Unvaccinated	
				Delta	Others	Delta	Others	Delta	Others	Delta	Others	Delta	Others	Delta	Others	Delta	Others	Delta	Others
			J&J																
Christensen	USA	Delta and Alpha	mRNA	800/3088	96/258	6406/13 619													
			J&J																
Bierle	USA	Delta	mRNA	23/201[δ]		53/429[δ]		11/201[δ]		38/429[δ]									
			J&J																

Note: All data are expressed as n, n/N.

Abbreviations: ECMO, extracorporeal membrane oxygenation; HW, healthcare worker; IMV, invasive mechanical ventilation; NIPPV, noninvasive positive pressure ventilation.

[¶]Pre-Delta means any variant other than the Delta variant that was dominant before the Delta variant was most likely.

[α]Variants other than delta.

[δ]Data from delta variant only.

was described in Supporting Informaion: Table S5. These differences might explain the heterogeneity observed among studies.

4 | DISCUSSION

The implementation of public health policies and rapid vaccination programs have proven to substantially diminish the spread of COVID-19. However, due to mutative evolutionary events, the virus has found ways to accelerate its spread despite these safety measures in place. More alarmingly, the COVID-19 vaccine has shown a reduction in efficacy against both time and ever-evolving variants. Therefore, it is imperative to consider the clinical outcomes of both vaccinated and unvaccinated groups to determine COVID-19 vaccine effectiveness against the current state of the pandemic.

The present study focused on comparing clinical outcomes in both vaccinated and unvaccinated individuals in two phases—risk of infection and hospitalization. This study presents itself as the first meta-analysis and systemic review to date focused on comparing vaccinated and unvaccinated individuals during the Delta variant dominant period. Our comparative analysis will determine the true effectiveness of the COVID-19 vaccine through their respective clinical outcomes.

Compared to other variants of concern, the Delta variant presents itself as highly transmissible, easily contractible, and moderately resistant to vaccination. The emergence of the Delta variant has resulted in an estimated 76% transmission advantage over the Alpha variant leading to major public health concerns.[24] The substantially higher risk ratio of 0.29 found in Figure 1A compared to the 0.05 and 0.20 risk ratios found in Figure 1B,C, respectively indicate a greater risk of infection for vaccinated individuals when exposed to the Delta variant. Supporting the higher risk of infection when exposed to the Delta variant even in vaccinated groups is congruent with a study finding smaller reductions in vaccine-associated transmission when comparing the Delta and Alpha variants.[25] Despite this, there is still a minimal risk of transmission between symptomatic breakthrough cases to close household contacts.[26] Further, evidence points toward a faster mean rate of viral load decline among vaccinated individuals infected with the Delta variant compared to unvaccinated individuals infected with pre-Alpha, Alpha, or the Delta variant alluding to vaccine efficacy.[27] Nevertheless, unvaccinated individuals are still more vulnerable to infection compared to their vaccinated counterparts.

COVID-19 infection can be classified as asymptomatic and symptomatic cases. The minimal difference found in Figure 2 between vaccinated and unvaccinated groups in terms risk of asymptomatic infection allude to no effect of vaccination status in this case. However, a Delta variant specific study conducted in Guangzhou, China found milder clinical symptoms in partially and fully vaccinated individuals compared to unvaccinated individuals.[28] Further supporting this study, higher vaccine effectiveness against serious COVID-19 disease such as symptomatic cases have been

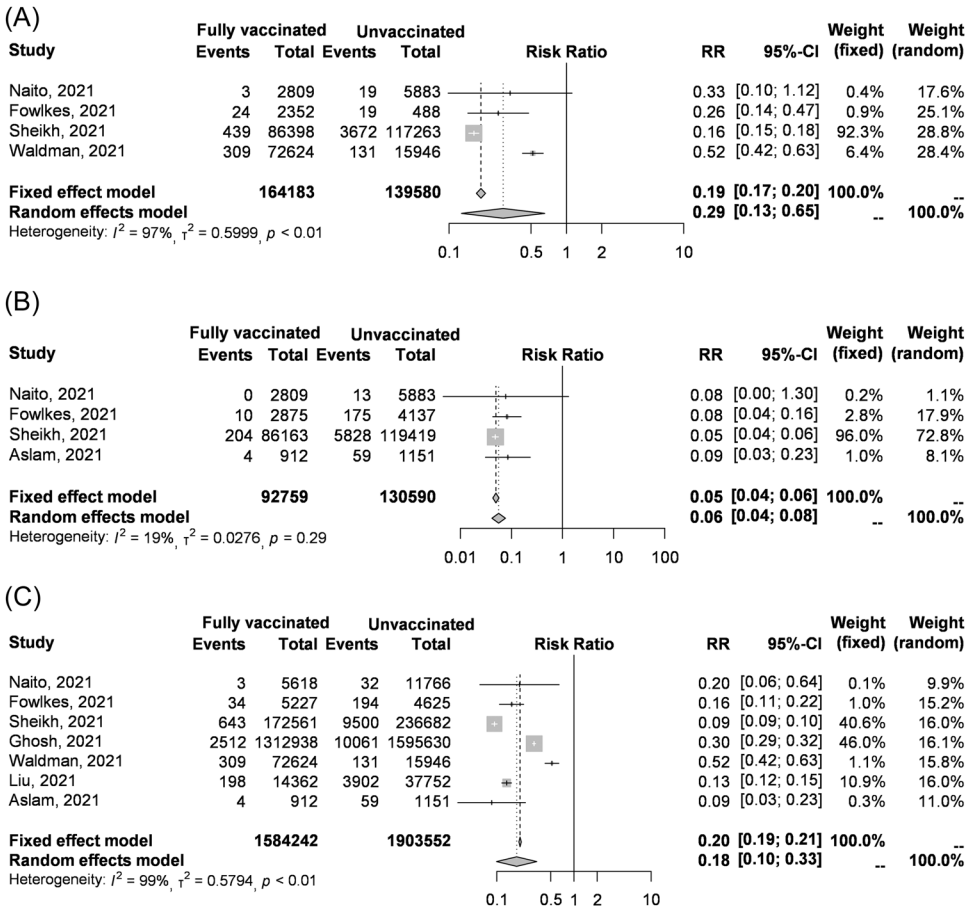
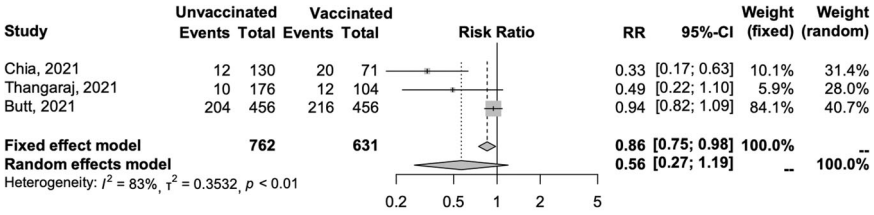
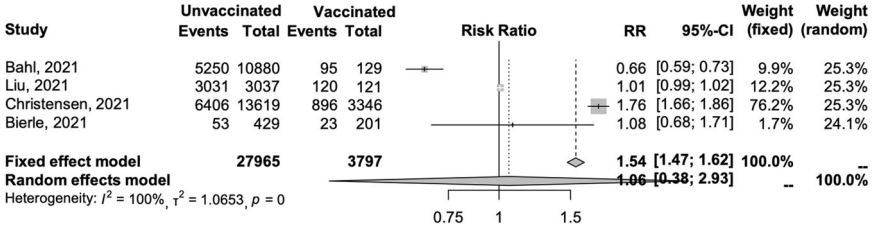


FIGURE 1 (A) The risk of SARS-CoV-2 infection among exposed people according to vaccination status (Delta Variant). (B) The risk of SARS-CoV-2 infection among exposed people according to vaccination status (Other Variants). (C) The risk of SARS-CoV-2 infection among exposed people according to vaccination status (all variants). CI, confidence interval; RR, relative risk; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.



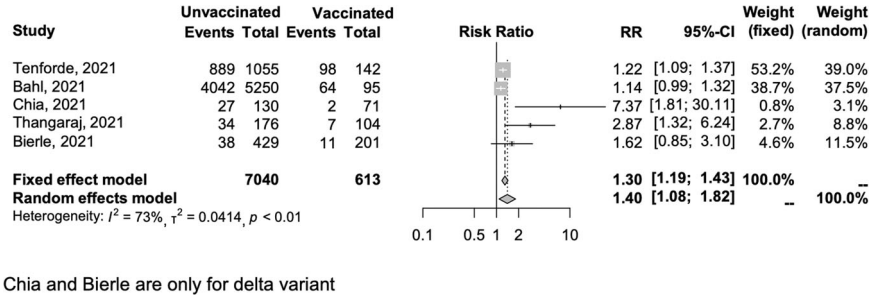
Butt et al. is only for alpha variant.

FIGURE 2 The risk of asymptomatic infection according to vaccination status (all variants). CI, confidence interval; RR, relative risk.



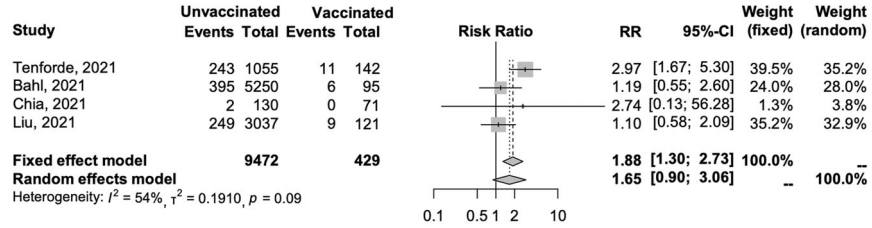
Bierle et al. is only for delta variant

FIGURE 3 The risk of hospitalization according to vaccination status (all variants). CI, confidence interval; RR, relative risk.



Chia and Bierle are only for delta variant

FIGURE 4 The risk of oxygen requirement among hospitalized SARS-CoV-2 patients (all variants). CI, confidence interval; RR, relative risk; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.



Bhal is only for alpha variant

FIGURE 5 The risk of invasive mechanical ventilation among hospitalized SARS-CoV-2 patients (all variants). CI, confidence interval; RR, relative risk; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

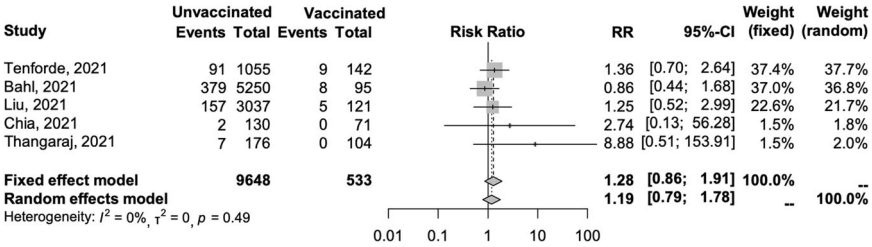


FIGURE 6 The risk of mortality among hospitalized SARS-CoV-2 patients (all variants). CI, confidence interval; RR, relative risk; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

observed against Alpha and Beta variants.[29] Despite this, negligible differences were found between vaccinated and unvaccinated groups for risk of asymptomatic cases for all variants in this study.

The risk of hospitalization, oxygen requirement, invasive mechanical ventilation, and mortality were all considered to be measures of disease severity when comparing infected vaccinated and unvaccinated individuals in our study. Figure 3 showed no difference in risk of hospitalization for all variants when comparing vaccination status thereby indicating negligible vaccine efficacy in this regard. However, according to Figure 4, risk of oxygen requirement was higher in unvaccinated individuals when compared to vaccinated individuals. Clinical severity in unvaccinated groups compared to vaccinated groups have been examined in terms of risk of febrile symptoms and illness duration in a previous study. It was found that among infected individuals, the risk of febrile symptoms was 58% lower and the duration of illness was shorter with 2.3 fewer days spent in bed when comparing vaccinated individuals to the unvaccinated ones.[30] Similarly to Figures 3,4 showed negligible differences in risk of invasive mechanical ventilation when comparing for vaccination status. Lastly, the risk of mortality when comparing vaccinated and unvaccinated groups remained nonsignificant as shown in Figure 6. In the Yogyakarta and Central Java provinces in Indonesia, related findings were found indicating no significant difference in the hospitalization and mortality rates of patients infected with the Delta and non-Delta variants.[31] Nevertheless, the Delta variant still presents itself as a more severe infection when compared to the Beta variant, however, evidence alludes to a protective nature of vaccination against severe outcomes for both variants of concern supporting claims of vaccine efficacy[33,34,.35]

This study also examined the role of comorbidities including hypertension, diabetes, chronic lung disease, immunosuppression, and transplantation on risk of infection and clinical severity. As Table 3 demonstrated the median or mean age of included studies ranged from 45 to 70.3 and the proportion of patients with hypertension was also different (range: 19.7%–75.2%). Other than this, the variable medical conditions in each study should be considered in interpreting the result. Another study reported that vaccine breakthrough infections with the Alpha and Delta variants were associated with comorbidities such as hypertension, immunosuppression, cancer, and coronary heart disease.[36] Further, the rate of severe or critical disease has been found to be higher among older individuals with comorbidities in previous studies alluding to the importance of underlying patient health and well-being when concerned with COVID-19 infection.[37] In a recently published study,

TABLE 3 Patients' demographic in included studies

Author	Category	Gender(Male)[§]		Age		Race		Hypertension		Diabetes		Chronic lung disease		Immunosuppressed		Transplants	
		Break-through	Unvaccinated	Break-through	Unvaccinated	Break-through	Unvaccinated	Break-through	Unvaccinated	Break-through	Unvaccina-ted	Break-through	Unvaccina-ted	Break-through	Unvaccinate-d	Break-through	Unvaccina-ted
Bosch	Hospitalized patients	82/126	499/839	69.1 ± 13.9	59.6 ± 16.0	Hispanic 6/126	Hispanic 55/839	80/126	433/839	39/126	190/839	93/126	586/839	42/126	128/839	28/126	57/839
Tenforde	Hospitalized	176/314	838/1669	67 (55–74)	53 (40–63)	Hispanic 55/314 black 55/314 white 201/314 other 14/314	Hispanic 381/1669 black453/1669 white 17/1669 other 118/1669	236/314[¶]	814/1667[¶]	112/314	425/1667	100/314	327/1667	128/314[†]	191/1667[†]		
Chia	Infected	27/71	67/130	56 (39–64)	39.5 (30–58)			14/71	28/130	5/71	28/130						
Thangaraj	Infected	66/113	109/185	54 (42–64) *n* = 113	47 (33–57) *n* = 185			50/112[**]	71/182[**]								
Bahl	Infected	60/129	5130/10 880	70.3 ± 16.4	52.1 ± 18.2	Black 13/129 White 108/129	Black 3452/10 880 White 6467/10 880										
Butt[‡]	Infected	277/456	277/456	45 (36–59.8)	45 (36–59.8)	Qatari 144/456	Qatari 144/456	140/456	114/456	116/456	108/456	30/456	23/456	20/456	5/456	8/456	4/456
Aslam	Infected	587/912	802/1239	59.4 ± 13.8	55.3 ± 13.8												
Liu	Infected	88/198	5153/14 164	58.5 ± 20.34	59.1 ± 18.86	black 30/198 white 88/198 Hispanic 58/198	black1851/14 164 white 325/14 164 hispanic3932/14 164							90/198	5133/14 164	10/198	366/14164

[¶]Cardiovascular disease: Hypertension, heart failure, peripheral vascular disease, prior myocardial infarction, cardiac arrhythmias, valvular heart disease.

[†]Active solid organ cancer, active hematologic cancer HIV infection without AIDS, AIDS, congenital immunodeficiency syndrome, previous splenectomy, previous solid organ transplant, immunosuppressive medication, systemic lupus erythematosus, rheumatoid arthritis, psoriasis, scleroderma, or inflammatory bowel disease, including Crohn disease or ulcerative colitis.

[**]Any comorbid condition.

[‡]Propensity score matched study (age, gender, race, comorbidity, reason for testing).

[§]The proportion of male patinets were expressed, for instance, '82/126 in Bosch et al. in breakthrough infection means 82 male among 126 total patients'. All data were presented as n, n/M, median (interquartile range) or mean (±standard deviation).

the role of gender was stressed as a predictor for breakthrough infection[37] and there were several plausible explanation describing gender-related difference in angiotensin-converting-enzyme-2 expression,[38,39] estrogen, X-chromosome,[40,41] and behavioral patterns in precautionary measures for COVID-19 prevention.[42,43] As the virus continues to mutate, it is important to monitor, understand and further analyze the respective clinical outcomes of both vaccinated and unvaccinated groups for future variants to come.

There are several limitations to this study. First, the high level of heterogeneity found in this study indicates inconsistencies within included studies. Due to the limited number of studies, we could not compare the results according to study design such as prospective or cross-sectional studies. Therefore, cautious interpretation of the results would be warranted. Additionally, the conflicting findings found within included studies make it harder to justify conclusions being made within the study. Second, some of the included studies examined specific variants thereby skewing the findings to one variant of concern. This unbalanced representation makes it harder to generalize conclusions for all variants of concern. Third, we could not match the differences in patient demographics or risk factors for SARS-CoV-2 infection. Since heterogeneity was present in comorbidities, we could not adjust these parameters when comparing clinical outcomes. Only one study provided substantial results after adjustments. Specifically, seropositivity data were not accessible in most studies. The different positivity in IgG antibody against COVID-19 could affect the results in clinical outcome. Therefore, further prospective studies which adjust for the baseline characteristics of patients would be necessary to evaluate vaccine efficacy more precisely. Additionally, this study is limited to deliver significant meaning in partially vaccinated patients as only two available data sources were integrated in the meta-analysis.

5 | CONCLUSION

This study is the first meta-analysis and systematic review focused on comparing the clinical outcomes of vaccinated and unvaccinated individuals within the Delta dominant period to date. The study findings indicated greater risk of unvaccinated individuals for SARS-CoV-2 infection and oxygen requirement compared to vaccinated individuals and negligible differences between groups for risk of asymptomatic infection, hospitalization, invasive mechanical ventilation, and mortality. Due to limited patient information and the heterogeneity among included studies, further prospective well-adjusted studies are necessary to evaluate vaccine efficacy against variants of concern to come.

AUTHOR CONTRIBUTIONS

Christine J. Lee: Conceptualization, methodology, data curation, formal analysis, resources, investigation, writing—original draft, writing—review & editing. **Wongi Woo:** Conceptualization, methodology, data curation, formal analysis, investigation, software, writing—original draft, writing—review & editing. **Ah Young Kim:** Conceptualization, methodology, data curation, formal analysis, writing—original draft, writing—review & editing. **Dong Keon Yon:** Writing—review & editing. **Seung Won Lee:** Writing—review & editing. **Ai Koyanagi:** Writing—review & editing. **Min Seo Kim:** Writing—review & editing. **Sungsoo Lee:** Writing—review & editing. **Jae Il Shin:** Conceptualization, methodology, validation, supervision, project administration writing—review & editing. **Smith Lee:** Writing—review & editing.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared by the corresponding author on reasonable request.

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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