Preplanned Studies

Protection of Omicron Sub-Lineage Infection Against Reinfection with Another Omicron Sub-Lineage: Systematic Review, Meta-Analysis, and Meta-Regression — Worldwide, 2022–2023

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Summary

What is already known about this topic?

Both the decline in immunity over time and the evolution of the virus play a role in the level of protection offered by a prior infection.

What is added by this report?

Point estimates indicated variations in protection levels based on the initial infecting variant and the reinfecting variant. There was a consistent correlation between real-world protection, antigenic distance, and humoral immunity levels. Specifically, shorter antigenic distances and higher humoral immunity levels corresponded to enhanced real-world protection.

What are the implications for public health practice?

Our findings suggest that virological and immunological studies could help identify and assess the epidemic risk posed by new variants before they become dominant. Prompt incorporation of the latest variants into the antigen components of the coronavirus disease 2019 (COVID-19) vaccines can significantly contribute to effective epidemic prevention and control measures.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variant has infected over 90% of the global population at least once (*1*). The protection conferred by previous infections is gradually becoming a crucial factor in controlling the pandemic (*2*). Our research used systematic reviews and meta-analyses to estimate the degree and longevity of protection against reinfection by another Omicron sub-lineage, relative to uninfected individuals, under a similar vaccination status. Out of 14,105 publications, we selected 10 studies that had either a cohort, test-negative design, or case-control approach, and utilized their data for a statistical analysis. Our findings indicate that the immunity provided against reinfection tends to vary based on the previous variant encountered and the variant causing reinfection. Moreover, protection offered by Omicron sub-lineage infection against reinfection with another Omicron sub-lineage tends to decrease over time. The degree of protection from a prior infection increases with more closely related antigenic distance and higher humoral immunity levels.

We employed three-level meta-analytic models using the 'metagen' function of the 'meta' package (version 6.3) in R (version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria) for consolidating protection data. We extracted multiple protection data points from a single study, incorporating all in the meta-analyses. Three-level meta-analyses permit the explicit modeling of nested data structures, such as when individual studies provide multiple estimates for varying subgroups or time points. These models yield more valid and reliable estimates than traditional fixed and random-effect models under such conditions (*3*). For research data specifying time from initial infection, we applied a meta-regression of the log odds to approximate the waning of protection over time, assessing at 1-month intervals. We performed meta-analysis and meta-regression only on groups comprising more than two articles with verifiable extracted data. Database searches covered PubMed, the World Health Organization (WHO) coronavirus disease 2019 (COVID-19) database, SSRN, MedRxiv, Embase, and the WanFang Database. We searched for cohort, test-negative design, and case-control studies published on or before October 24, 2023, using keywords related to reinfection, prior infection, and Omicron (Supplementary Table S1, available at https://weekly.chinacdc.cn/). Included studies were those that considered the protective effect of prior Omicron infection in individuals against those who were infection-naïve and had comparable vaccination status. We evaluated the risk of bias using the ROBINS-I tool (Supplementary Table S4, available at https://weekly.chinacdc.cn/). Our study, which

complies with PRISMA, was registered with PROSPERO (CRD42023466200). Supplementary Materials (available at https://weekly.chinacdc.cn/) provide detailed methodology.

We reviewed the titles and abstracts of 14,105 articles, of which 491 passed our screening to undergo a thorough full-text review (Supplementary Figure S1, available at https://weekly.chinacdc.cn/). From this process, we identified 10 relevant studies providing 81 data sets, sourced from eight nations: Qatar, Canada, China, Denmark, Japan, the Republic of Korea, Singapore, and Portugal. These studies encompassed a combined sample size of 17,214,915. For our meta-analysis and meta-regression, we included 12 data sets from 2 studies in the BA.1 to BA.2 group, 10 data sets from 3 studies in the BA.1 to BA.4/5 group, 12 data sets from 3 studies in the BA.2 to BA.4/5 group, and 15 data sets from 4 studies in the BA.1/2 to BA.4/5 group (Supplementary Table S2, available at https://weekly.chinacdc.cn/).

Compared to a non-infected cohort, individuals previously infected with the BA.1 variant showed 87.5% protection (47.9–97.0) against reinfection with the BA.2 variant (Supplementary Figure S2, available at https://weekly.chinacdc.cn/). This protection, however, waned from 89.8% at 1 month (64.6–97.1) to 81.1% at 5 months (31.9–94.8) (Tables 1–2). Between 30 and 60 days post-infection, an 82.0% protection rate (49.0–94.0) was observed amongst those unvaccinated, and a protection rate of 94.2% (89.2–96.9) amongst those vaccinated (Supplementary Table S2). In vaccinated individuals, the effectiveness of protection against reinfection with BA.4/5 variant after an initial BA.1 infection was 75.2% (42.1–89.4) (Supplementary Figure S2). Notably, this protection waned from 77.2% at 5 months post-infection (47.6–90.1) to 40.9% at 12 months (–32.8–73.7) (Tables 1–2).

Research conducted in Singapore (*4*) tracked the infection history of cohorts unexposed to COVID-19 who later contracted the BA.1 variant. Observations indicated that the protective effect of prior BA.1 infection against clinically attended symptomatic XBB variant reinfection diminished from a span of 40.0% (32.0–47.0) between 3–8 months post-infection to 27.0% (24.0–30.0) subsequent to 8 months (Table 1, Supplementary Table S2).

The protective effect of a BA.2 infection against subsequent reinfection with BA.4/5 variants was 88.9% (76.6–94.8) (Supplementary Figure S2), and this waned from 91.6% (80.9–96.3) at 4 months post-infection to 80.4% (56.7–91.1) at 8 months post-infection (Tables 1–2). Comparable findings were reported by a Singaporean cohort study (*4*), which demonstrated that the protective effect of a primary BA.2 infection against symptomatic reinfection by the XBB variant also declined over time, from 74.0% (72.0–75.0) during the 3–6 months post-infection period to 37.0% (32.0–43.0) after 8 months (Table 1, Supplementary Table S2). It is important to note that these studies were conducted exclusively among vaccinated populations due to a lack of data from unvaccinated groups.

An analysis of protection against reinfection with the

TABLE 1. Protection (%) against reinfection by different Omicron sub-lineages.

Type of variant for prior infection	Type of variant for reinfection				
	Time since primary infection	BA.2 (Meta-analysis)	BA.4/5 (Meta-analysis)	BA.2.75 (Systematic review)	XBB (Systematic review)
BA.1	5 months	81.1 (31.9–94.8)	77.2 (47.6–90.1)	NA	40.0 (32.0–47.0)[†]
	8 months	NA	65.7 (26.5–84.0)	NA	27.0 (24.0–30.0)[§]
	Total[*]	87.5 (47.9–97.0)	75.2 (42.1–89.4)	NA	NA
BA.2	5 months	NA	89.6 (76.9–95.4)	NA	74.0 (72.0 to 75.0)[¶]
	8 months	NA	80.4 (56.7–91.1)	NA	37.0 (32.0 to 43.0)[**]
	Total[*]	NA	88.9 (76.6–94.8)	NA	NA
BA.1/2	Total[*]	NA	86.2 (73.6–92.8)	49.9 (47.6 to 52.1)	NA
BA.4/5	Total[*]	NA	NA	80.6 (71.2 to 87.0)	NA

Note: NA means no data available.
[*] Total protection, regardless of time since primary infection.
[†] Time since primary infection: 3–8 months.
[§] Time since primary infection: ≥8 months.
[¶] Time since primary infection: 3–6 months.
[**] Time since primary infection: ≥8 months.

TABLE 2. Estimates of protection (%) against various Omicron variants based on the time elapsed since primary infection.

Time since primary infection (months)	BA.1 to BA.2	BA.1 to BA.4/5	BA.2 to BA.4/5
1	89.8 (64.6–97.1)	NA	NA
2	88.1 (60.6–96.4)	NA	NA
3	86.1 (54.5–95.8)	NA	NA
4	83.8 (45.3–95.2)	NA	91.6 (80.9–96.3)
5	81.1 (31.9–94.8)	77.2 (47.6–90.1)	89.6 (76.9–95.4)
6	NA	73.9 (41.9–88.3)	87.2 (71.8–94.2)
7	NA	70.1 (35.0–86.2)	84.1 (65.2–92.8)
8	NA	65.7 (26.5–84.0)	80.4 (56.7–91.1)
9	NA	60.1 (16.1–81.6)	NA
10	NA	55.0 (3.2–79.1)	NA
11	NA	48.5 (−12.8–76.4)	NA
12	NA	40.9 (−32.8–73.7)	NA

Note: NA means no data available.

Omicron BA.4/5 variants following a BA.1/2 infection incorporated studies from four nations: Denmark, Japan, Portugal, and Qatar. Due to a gradual shift from the dominance of the Omicron BA.1 subvariant to the BA.2 subvariant in these countries, the two infection peaks of BA.1 and BA.2 combined, making it difficult to distinguish between their timelines. Our meta-analysis findings indicated that the conferred protection against reinfection with BA.4/5 after a BA.1/2 infection was 86.2% (73.6–92.8) in comparison to an uninfected population (Supplementary Figure S2). Notably, a test-negative design study conducted in Qatar (*5*) reported protection rates of 49.9% (47.6–52.1) against a BA.2.75 infection after a primary BA.1/2 infection; this protection rate decreased to 32.2% (25.5–38.3) for an unvaccinated population. The study also reported protection rates of 50.2% (43.1–56.4) against symptomatic infection. Furthermore, a primary BA.4/5 infection offered a protection rate of 80.6% (71.2–87.0) against a BA.2.75 variant infection; this dropped to 44.4% (-4.0–70.3), however, for the unvaccinated population. The reported protection against symptomatic infection was 91.4% (35.8–98.8) (Table 1, Supplementary Table S2).

According to meta-regression analyses of studies noting the duration since the initial infection, we discerned a decline in immunity against reinfection over time. However, due to limitations in available data, these estimated protection rates yielded wide confidence intervals (*CI*s), preventing any statistically significant differences from being determined within the meta-regression results. In spite of overlapping *CI*s within the meta-regression, at the same time since primary infection, BA.2 variant showed a higher protection estimate than BA.5 against BA.1 variant infection [at 5 months: 89.6% (76.9, 95.4) versus 77.2% (47.6, 90.1); at 8 months: 80.4% (56.7, 91.1) versus 65.7% (26.5, 84.0)]. A similar trend was observed when comparing immunity from BA.1 against BA.2, and BA.1 against BA.4/5 [at 5 months: 81.1% (31.9–94.8) versus 77.2% (47.6–90.1)] (Table 1-2, Figure 1, Supplementary Table S3).

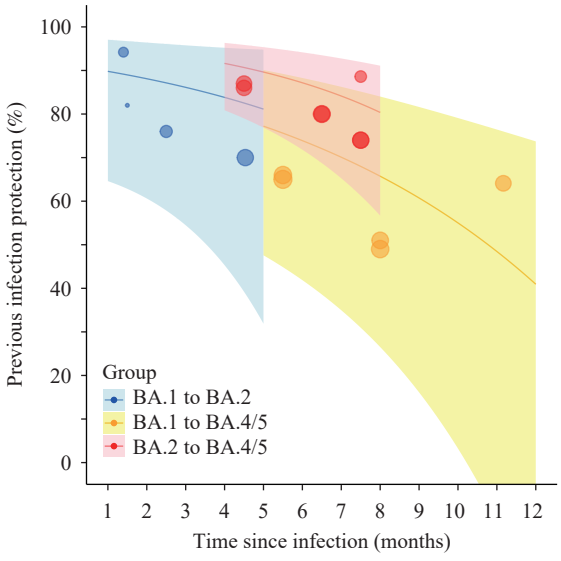

FIGURE 1. Estimated levels of protection against various Omicron variants based on the time elapsed since primary infection.
Note: The shaded areas represent the 95% confidence intervals (*CI*s). The size of each bubble is proportional to the reciprocal of the standard error (SE).

DISCUSSION

The likelihood of reinfection with the same Omicron variant is exceedingly low in instances where a previous infection has occurred. In two respective studies, there was an impressive 94%–97% immunity rate observed amongst individuals previously infected with the BA.4/5 strain, which remained effective for up to 100 days post primary infection (*6*–*7*). Our comprehensive review and meta-analysis revealed elevated protection rates against reinfection in individuals previously exposed to later, evolutionarily similar variants, as compared to those exposed to earlier strains. This was independent of the time elapsed since the initial infection. This conclusion is congruent with studies conducted in the Netherlands (*8*), Qatar (*5*), Singapore (*4*), and the United Kingdom (*9*). This could potentially elucidate the cyclical nature of the COVID-19 pandemic, characterized by repeated bouts of infections and reinfections, triggered by distinct variants in succession.

The variants BA.4 and BA.5 are derivatives of BA.2. In terms of antigenic distance, BA.4/5 shares a closer resemblance with BA.2 relative to BA.1. Serological research has revealed that after infection by the BA.2 variant, the convalescent sera possess a superior amount of neutralizing antibodies against BA.5 than the sera derived from BA.1 variant infection (*10*). This collective evidence suggests that the effectiveness of protection from prior COVID-19 infection against further infections is not solely dependent on declining immunity but is also influenced by viral evolution. Higher humoral immunity levels and closer antigenic distances contribute to enhanced protection provided by previous infections.

In assessing the future risks associated with COVID-19, it is crucial to consider not only the time elapsed since the peak of the previous wave but also the antigenic difference and evasion ability of humoral immunity between any potential new variant and the formerly dominant ones. Ensuring a timely update of the antigenic components within the COVID-19 vaccine, coupled with inoculating individuals not recently infected, stands as a vital strategy in combating this disease. While this approach may not fully synchronize with the evolution of SARS-CoV-2, potentially leading to a mismatch between subsequent infection strains and the vaccine strain, a narrower antigenic distance can ostensibly offer improved protection over a match with a more antigenically distant strain. Given that both infection- and vaccine-induced protection diminish over time, the duration since either the infection or vaccination must be factored into vaccination policy considerations.

This study was subject to at least two limitations. One limitation of our research is that the time since primary infection provided by some studies is a time range. In order to conduct meta-regression, we used the median of this range. Another limitation lies in the limited number of studies incorporated. Upon retrieval and examination, only ten studies pertaining to the protection against Omicron variant infection satisfied the inclusion criteria. To offset potential overemphasis arising from the inclusion of numerous data points from a single study, we employed a three-tier meta-analysis approach. Nonetheless, as the available data pool was relatively insufficient, stratified analyses could not be conducted. Some specialists assert that a minimum of ten studies is required to facilitate valid meta-regression, which is greater than what we currently have. The scarcity of data broadens *CI*s, hampers the extraction of useful statistical inferences, and adds uncertainty to the stability of our final findings.

The global population has previously encountered pandemics involving the BA.1, BA.2, and BA.4/5 variants, with the infectious strain now transitioning to the XBB sub-lineage. While these past variant pandemics have subsided, further exploration of existing literature can deepen our understanding of the immune mechanisms underlying COVID-19. This will assist in securing epidemiological parameters of the disease, comprehending the mechanisms behind COVID-19 outbreaks, and providing essential evidence for infectious disease model research and assessments of reinfection risk.

Our comprehension of COVID-19 continues to evolve, highlighting the need for critical research into topics such as antigenic separation, immune evasion, and the extent of cross-protection. While predicting the trajectory of SARS-CoV-2 mutation remains a formidable challenge, establishing a link between pathogenesis and immunology through empirical research might expedite and enhance the precision of risk assessments for new variants. Understanding the degree of protection provided by previous COVID-19 infections against new variants can further inform and guide national response strategies.

Conflicts of interest: No conflicts of interest.

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SUPPLEMENTARY MATERIAL

METHODS

Search Strategy and Selection Criteria

We conducted a thorough search of databases, including PubMed, WHO COVID-19, SSRN, MedRxiv, Embase, and WanFang Database. The search, undertaken prior to October 24, 2023, focused on cohort studies, test-negative designs, and case-control studies with keywords related to reinfection, prior infection, and Omicron. This study adheres to the PRISMA guidelines and is officially registered with PROSPERO (CRD42023466200).

Inclusion and Exclusion Criteria

To remove the potential bias introduced by vaccination status, we included studies examining the protection conferred by a prior Omicron infection in individuals who had been infected once, compared to infection-naive individuals with a similar vaccination status. We excluded studies that failed to differentiate between an initial infection and a reinfection with a variant strain.

Outcomes

Reinfection was characterized as two separate outbreaks caused by two distinct predominant strains, confirmed through either two positive results from polymerase-chain-reaction (PCR), rapid antigen test, or self-reported infections. The studies included did not need to differentiate between symptomatic and asymptomatic infections.

Study Selection and Data Extraction

Upon reviewing titles and abstracts, we pinpointed studies and reports pertaining to immunity from COVID-19 infection. Relevant studies and reports had their main texts and supplementary materials scrutinized by two independent reviewers to ascertain if they met the inclusion criteria. One reviewer manually undertook the extraction process, which a second reviewer independently confirmed. In cases of disagreement, the input of a third reviewer was sought.

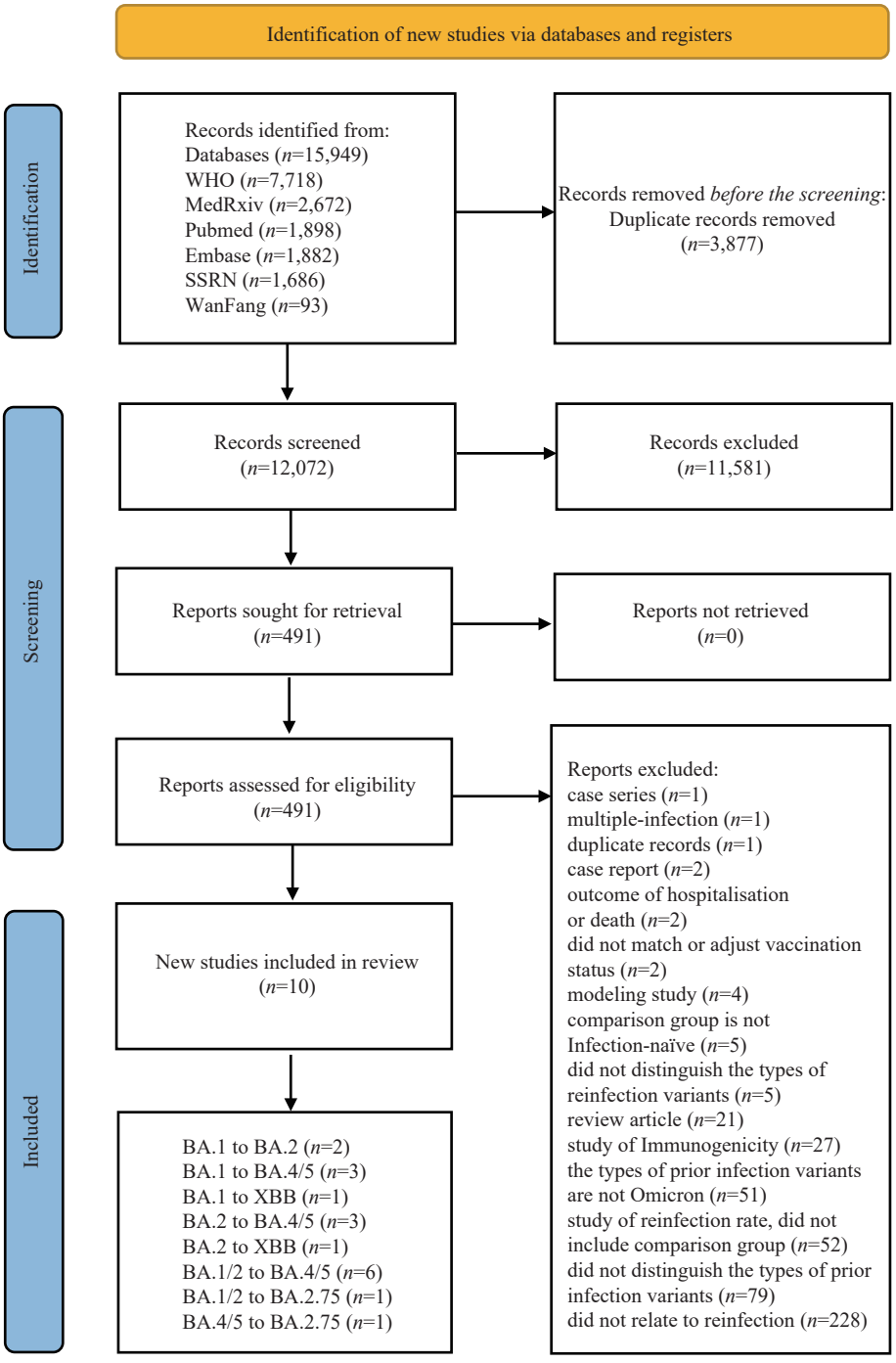
The data extracted encompassed the author's name, country of research, study design, COVID-19 vaccination status, reinfection outcome, variant type during initial infection and reinfection, time elapsed since primary infection, sample size, and the effectiveness of protection (expressed as 1-OR/HR/RRHR) along with its 95% confidence interval (*CI*). The effect value was adjusted for covariates in a multivariate analysis, and this adjusted value was favored and utilized when available.

Risk-of-bias Assessment

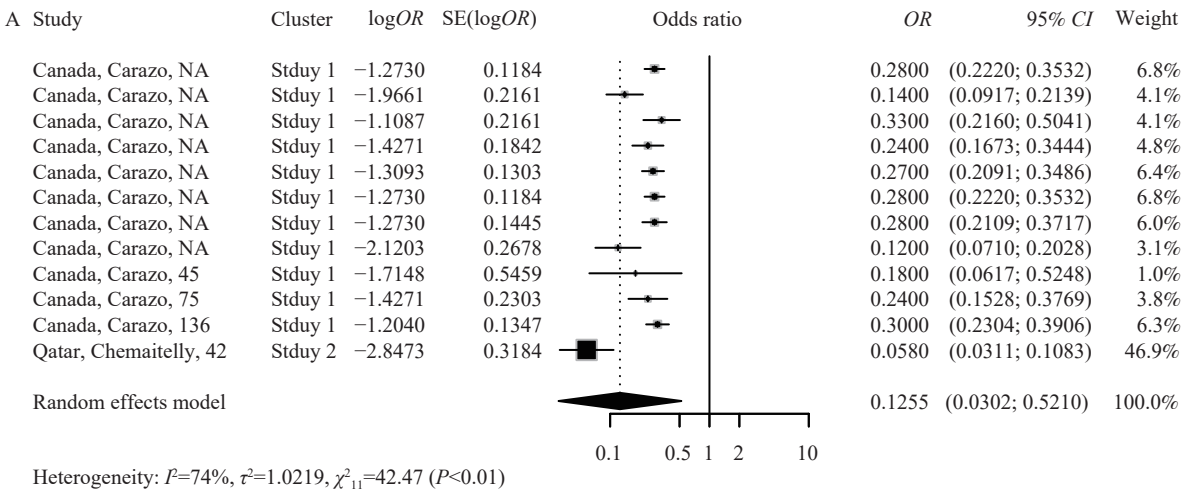
The risk of bias in the studies was evaluated using the ROBINS-I tool. This assessment was independently carried out by two reviewers for each documented outcome. Any discrepancies between the reviewers were reconciled by a third party. All studies received equal treatment in the primary analysis, irrespective of their quality rating.

Data Analysis

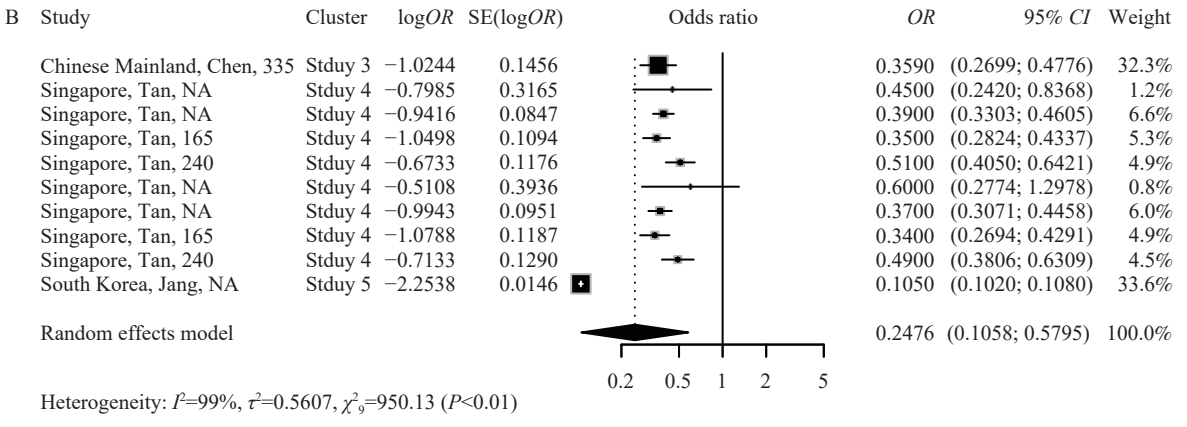
We employed three-level meta-analytic models using the 'metagen' function of the 'meta' package (version 6.3) in R (version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria) for consolidating protection data. The restricted maximum likelihood estimator was leveraged for determining within-study and between-study heterogeneity variance, denoted by τ^2. In cases where data incorporated time since primary infection, we implemented a meta-regression of log odds to estimate the attenuation of protection over time, evaluated in one-month increments. For studies that did not provide time since primary infection, we estimated this parameter employing GISAID data, which was then incorporated into our meta-regression analyses. Both meta-analysis and meta-regression were restricted to groups containing more than two articles with valid, extracted data.



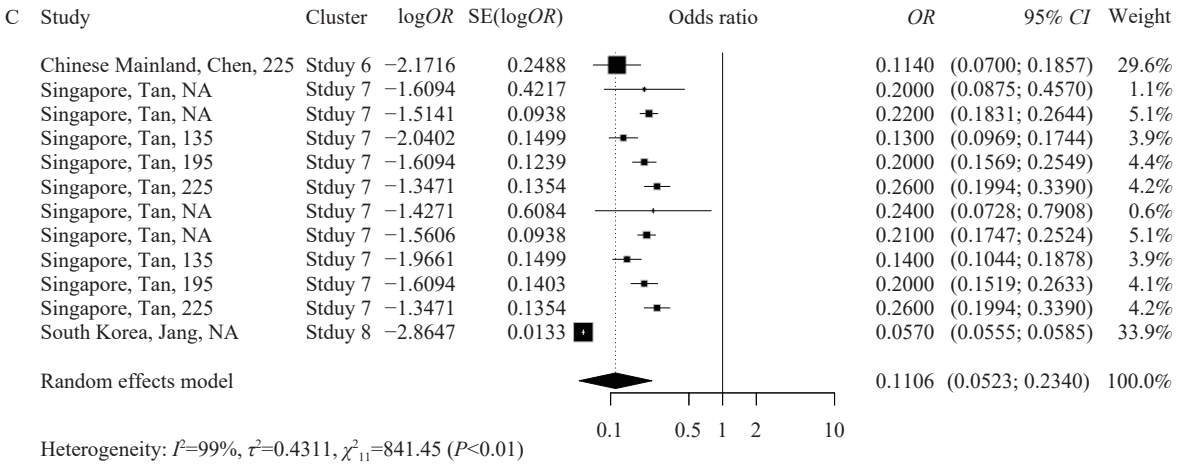
SUPPLEMENTARY FIGURE S1. Study selection.
Abbreviation: WHO=World Health Organization; COVID-19=coronavirus disease 2019; SSRN=social science research network.



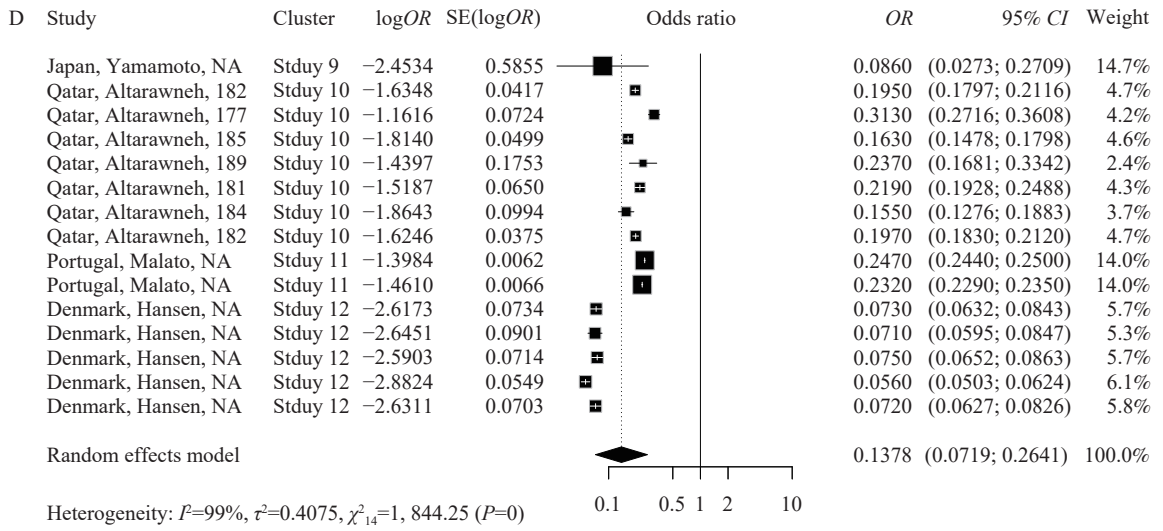
Heterogeneity: I^2=74%, τ^2=1.0219, χ^2_{11}=42.47 (P<0.01)



Heterogeneity: I^2=99%, τ^2=0.5607, χ^2_9=950.13 (P<0.01)



Heterogeneity: I^2=99%, τ^2=0.4311, χ^2_{11}=841.45 (P<0.01)



SUPPLEMENTARY FIGURE S2. Forest plots of protection against reinfection by different Omicron sub-lineages. (A) Protection of BA.1 infection against reinfection with BA.2. (B) Protection of BA.1 infection against reinfection with BA.4/5. (C) Protection of BA.2 infection against reinfection with BA.4/5. (D) Protection of BA.1/2 infection against reinfection with BA.4/5. Abbreviation: *OR*=odds ratio; SE=standard error; *CI*=confidence interval.

SUPPLEMENTARY TABLE S1. Search strategy.

Keyword	Platform	Search Results
(re-infection) OR (reinfection) OR (repeated infection) OR (recurrent Infection) OR (previously infected) OR (previous infection) OR (prior infection) AND ("Omicron" OR "B.1.1.529") AND ("2020/1/1"[Date - Publication] : "2023/10/24"[Date - Publication])	Pubmed	1,898
(Reinfection OR repeated infection OR recurrent infection OR previously infected OR previous infection OR prior infection) AND ("Omicron" OR "B.1.1.529")	WHO COVID-19 database	7,718
Omicron	SSRN	1,686
(Reinfection OR repeated infection OR recurrent infection OR previous infection OR prior infection) AND (Omicron OR B.1.1.529)" and posted between "01 Jan, 2020 and 24 Oct, 2023"	MedRxiv	2,672
('re infection' OR reinfection OR (repeated AND infection) OR (recurrent AND infection) OR (previously AND infected) OR (previous AND infection) OR (prior AND infection)) AND ('omicron' OR 'b.1.1.529') AND [01-01-2020]/sd NOT [24-10-2023]/sd	Embase	1,882
(再感染 OR 既往感染 OR 重复感染) AND ("奥密克戎" OR "Omicron")	WanFang Database	93

SUPPLEMENTARY TABLE S2. Characteristics of the included studies.

Group	Country	Study Design	Vaccination Status	Outcome of reinfection	Protection (95% *CI*)	Time since primary infection (reported)	Time since primary infection (predicted)*	sample size
BA.1 to BA.2								
Chemaitelly et al. (2022) (*1*)	Qatar	TND	Vaccinated (adjusted)	Infection	94.2 (89.2 to 96.9)	39 to 45 days	NA	41,988
Carazo et al. (2023) (*2*)	Canada	Cohort	Unvaccinated	Infection	82.0 (49.0 to 94.0)	30 to 59 days	NA	2,567
Carazo et al. (2023) (*2*)	Canada	Cohort	Unvaccinated	Infection	76.0 (63.0 to 85.0)	60 to 89 days	NA	2,567
Carazo et al. (2023) (*2*)	Canada	Cohort	Unvaccinated	Infection	70.0 (61.0 to 77.0)	90 to 182 days	NA	2,567
Carazo et al. (2023) (*2*)	Canada	Cohort	Unvaccinated	Infection	72.0 (65.0 to 78.0)§	NA	81	2,567
Carazo et al. (2023) (*2*)	Canada	Cohort	Unvaccinated	Symptomatic infection	86.0 (79.0 to 91.0)§	NA	81	630
Carazo et al. (2023) (*2*)	Canada	Cohort	Unvaccinated	Infection	67.0 (79.0 to 91.0)§	NA	81	1,167
Carazo et al. (2023) (*2*)	Canada	Cohort	Unvaccinated	Infection	76.0 (65.0 to 83.0)§	NA	81	1,258
Carazo et al. (2023) (*2*)	Canada	Cohort	Unvaccinated	Infection	73.0 (65.0 to 79.0)§	NA	81	2,416
Carazo et al. (2023) (*2*)	Canada	Cohort	Unvaccinated	Infection	72.0 (65.0 to 78.0)§	NA	81	2,567
Carazo et al. (2023) (*2*)	Canada	Cohort	Unvaccinated	Infection	72.0 (63.0 to 79.0)§	NA	81	2,040
Carazo et al. (2023) (*2*)	Canada	Cohort	Unvaccinated	Symptomatic infection	88.0 (80.0 to 93.0)§	NA	81	433
BA.1 to BA.4/5								
Chen et al. (2023) (*3*)	China	Cohort	Vaccinated (matched)	Symptomatic infection	64.1 (52.4 to 73.1)	329 to 341 days	NA	386
Tan et al. (2023) (*4*)	Singapore	Cohort	Completed primary series	Medically attended symptomatic infection	55.0 (17.0 to 76.0)	NA	265	1,733,535
Tan et al. (2023) (*4*)	Singapore	Cohort	Boosted	Medically attended symptomatic infection	61.0 (54.0 to 67.0)	NA	265	1,902,581
Tan et al. (2023) (*4*)	Singapore	Cohort	Vaccinated (adjusted)	Medically attended symptomatic infection	65.0 (57.0 to 72.0)	3 to <8 months	NA	1,779,968
Tan et al. (2023) (*4*)	Singapore	Cohort	Vaccinated (adjusted)	Medically attended symptomatic infection	49.0 (35.0 to 59.0)	≥8 months	NA	1,858,209
Tan et al. (2023) (*4*)	Singapore	Cohort	Completed primary series	Medically attended symptomatic infection	40.0 (-31.0 to 72.0)§	NA	265	1,351,636
Tan et al. (2023) (*4*)	Singapore	Cohort	Boosted	Medically attended symptomatic infection	63.0 (55.0 to 69.0)§	NA	265	1,514,582
Tan et al. (2023) (*4*)	Singapore	Cohort	Vaccinated (adjusted)	Medically attended symptomatic infection	66.0 (57.0 to 73.0)§	3 to <8 months	NA	1,402,809
Tan et al. (2023) (*4*)	Singapore	Cohort	Vaccinated (adjusted)	Medically attended symptomatic infection	51.0 (37.0 to 62.0)§	≥8 months	NA	1,465,449
Jang et al. (2023) (*5*)	South Korea	Case-control	Vaccinated (adjusted)	Infection	89.5 (89.2 to 89.8)	NA	190	5,085,535
BA.1 to XBB								
Tan et al. (2023) (*4*)	Singapore	Cohort	Completed primary series	Medically attended symptomatic infection	3.00 (−13.0 to 16.0)	NA	NA	800,221
Tan et al. (2023) (*4*)	Singapore	Cohort	Boosted	Medically attended symptomatic infection	30.0 (27.0 to 32.0)	NA	NA	878,615
Tan et al. (2023) (*4*)	Singapore	Cohort	Vaccinated (adjusted)	Medically attended symptomatic infection	40.0 (32.0 to 47.0)	3 to <8 months	NA	796,534
Tan et al. (2023) (*4*)	Singapore	Cohort	Vaccinated (adjusted)	Medically attended symptomatic infection	27.0 (24.0 to 30.0)	≥8 months	NA	883,260
Tan et al. (2023) (*4*)	Singapore	Cohort	Completed primary series	Medically attended symptomatic infection	16.0 (−6.0 to 33.0)§	NA	NA	630,473
Tan et al. (2023) (*4*)	Singapore	Cohort	Boosted	Medically attended symptomatic infection	30.0 (27.0 to 33.0)§	NA	NA	706,028
Tan et al. (2023) (*4*)	Singapore	Cohort	Vaccinated (adjusted)	Medically attended symptomatic infection	41.0 (32.0 to 49.0)§	3 to <8 months	NA	631,880
Tan et al. (2023) (*4*)	Singapore	Cohort	Vaccinated (adjusted)	Medically attended symptomatic infection	28.0 (25.0 to 31.0)§	≥8 months	NA	705,569

Continued

Group	Country	Study Design	Vaccination Status	Outcome of reinfection	Protection (95% *CI*)	Time since primary infection (reported)	Time since primary infection (predicted)*	sample size
BA.2 to BA.4/5								
Chen et al. (2023) (*3*)	China	Cohort	Vaccinated (matched)	Symptomatic infection	88.6 (81.7 to 93.1)	210 to 231 days	NA	346
Tan et al. (2023) (*4*)	Singapore	Cohort	Completed primary series	Medically attended symptomatic infection	80.0 (53.0 to 91.0)	NA	181	1,737,378
Tan et al. (2023) (*4*)	Singapore	Cohort	Boosted	Medically attended symptomatic infection	78.0 (74.0 to 82.0)	NA	181	2,124,162
Tan et al. (2023) (*4*)	Singapore	Cohort	Vaccinated (adjusted)	Medically attended symptomatic infection	87.0 (82.0 to 90.0)	3 to <6 months	NA	1,866,720
Tan et al. (2023) (*4*)	Singapore	Cohort	Vaccinated (adjusted)	Medically attended symptomatic infection	80.0 (74.0 to 84.0)	6 to <7 months	NA	1,805,491
Tan et al. (2023) (*4*)	Singapore	Cohort	Vaccinated (adjusted)	Medically attended symptomatic infection	74.0 (66.0 to 80.0)	7 to <8 months	NA	1,885,447
Tan et al. (2023) (*4*)	Singapore	Cohort	Completed primary series	Medically attended symptomatic infection	76.0 (24.0 to 93.0)§	NA	181	1,352,984
Tan et al. (2023) (*4*)	Singapore	Cohort	Boosted	Medically attended symptomatic infection	79.0 (74.0 to 82.0)§	NA	181	1,743,385
Tan et al. (2023) (*4*)	Singapore	Cohort	Vaccinated (adjusted)	Medically attended symptomatic infection	86.0 (82.0 to 90.0)§	3 to <6 months	NA	1,492,493
Tan et al. (2023) (*4*)	Singapore	Cohort	Vaccinated (adjusted)	Medically attended symptomatic infection	80.0 (74.0 to 85.0)§	6 to <7 months	NA	1,430,362
Tan et al. (2023) (*4*)	Singapore	Cohort	Vaccinated (adjusted)	Medically attended symptomatic infection	74.0 (66.0 to 80.0)§	7 to <8 months	NA	1,501,919
Jang et al. (2023) (*5*)	South Korea	Case-control	Vaccinated (adjusted)	Infection	94.3 (94.1 to 94.4)	NA	106	5,002,210
BA.2 to XBB								
Tan et al. (2023) (*4*)	Singapore	Cohort	Completed primary series	Medically attended symptomatic infection	22.0 (9.0 to 33.0)	NA	NA	802,046
Tan et al. (2023) (*4*)	Singapore	Cohort	Boosted	Medically attended symptomatic infection	51.0 (49.0 to 53.0)	NA	NA	982,831
Tan et al. (2023) (*4*)	Singapore	Cohort	Vaccinated (adjusted)	Medically attended symptomatic infection	74.0 (72.0 to 75.0)	3 to <6 months	NA	855,858
Tan et al. (2023) (*4*)	Singapore	Cohort	Vaccinated (adjusted)	Medically attended symptomatic infection	58.0 (55.0 to 61.0)	6 to <7 months	NA	820,235
Tan et al. (2023) (*4*)	Singapore	Cohort	Vaccinated (adjusted)	Medically attended symptomatic infection	49.0 (47.0 to 52.0)	7 to <8 months	NA	881,230
Tan et al. (2023) (*4*)	Singapore	Cohort	Vaccinated (adjusted)	Medically attended symptomatic infection	37.0 (32.0 to 43.0)	≥8 months	NA	809,865
Tan et al. (2023) (*4*)	Singapore	Cohort	Completed primary series	Medically attended symptomatic infection	22.0 (−10.0 to 39.0) §	NA	NA	631,104
Tan et al. (2023) (*4*)	Singapore	Cohort	Boosted	Medically attended symptomatic infection	51.0 (49.0 to 53.0) §	NA	NA	810,325
Tan et al. (2023) (*4*)	Singapore	Cohort	Vaccinated (adjusted)	Medically attended symptomatic infection	74.0 (72.0 to 76.0) §	3 to <6 months	NA	689,979
Tan et al. (2023) (*4*)	Singapore	Cohort	Vaccinated (adjusted)	Medically attended symptomatic infection	59.0 (55.0 to 62.0) §	6 to <7 months	NA	654,656
Tan et al. (2023) (*4*)	Singapore	Cohort	Vaccinated (adjusted)	Medically attended symptomatic infection	50.0 (47.0 to 52.0) §	7 to <8 months	NA	710,310
Tan et al. (2023) (*4*)	Singapore	Cohort	Vaccinated (adjusted)	Medically attended symptomatic infection	37.0 (31.0 to 43.0) §	≥8 months	NA	643,953
BA.1/2 to BA.4/5								
Yamamoto et al. (2023) (*6*)	Japan	Cohort	All vaccinated (92% 3 doses)	Infection	91.4 (73.2 to 97.3)	NA	NA	2,368
Altarawneh et al. (2022) (*7*)†	Qatar	TND	Vaccinated (matched)	Infection	80.5 (78.8 to82.0)§	168 to 193 days	NA	65,853
Altarawneh et al. (2022) (*7*)†	Qatar	TND	Unvaccinated	Infection	68.7 (64.0 to 72.9)§	167 to 190 days	NA	22,850
Altarawneh et al. (2022) (*7*)†	Qatar	TND	All vaccinated	Infection	83.7 (82.0 to 85.2)§	170 to 194 days	NA	43,003
Altarawneh et al. (2022) (*7*)†	Qatar	TND	Vaccinated (adjusted)	Symptomatic infection	76.3 (66.6 to 83.2)§	175 to 196 days	NA	2,838
Altarawneh et al. (2022) (*7*)†	Qatar	TND	Vaccinated (adjusted)	Infection	78.1 (75.1 to 80.7)§	169 to 193 days	NA	23,125

Continued

Group	Country	Study Design	Vaccination Status	Outcome of reinfection	Protection (95% *CI*)	Time since primary infection (reported)	Time since primary infection (predicted)*	sample size
Altarawneh et al. (2022) (*7*)†	Qatar	TND	Vaccinated (adjusted)	Symptomatic infection	84.5 (81.1 to 87.2)§	168 to 195 days	NA	12,363
Altarawneh et al. (2022) (*7*)†	Qatar	TND	Vaccinated (adjusted)	Infection	80.3 (78.8 to 81.7)§	168 to 193 days	NA	77,399
Malato et al. (2022) (*8*)	Portugal	Cohort	All vaccinated (98% 2 doses)	Infection	75.3 (75.0 to 75.6)	NA	NA	6,885,922
Malato et al. (2022) (*8*)	Portugal	Cohort	All vaccinated (98% 2 doses)	Infection	76.8 (76.5 to 77.1)§	NA	NA	6,279,978
Hansen et al. (2023) (*9*)	Denmark	Case-control	Three mRNA doses	Infection	92.7 (91.6 to 93.7)	NA	NA	187,347
Hansen et al. (2023) (*9*)	Denmark	Case-control	Three mRNA doses	Infection	92.9 (91.6 to 93.7)§	NA	NA	17,238
Hansen et al. (2023) (*9*)	Denmark	Case-control	Three mRNA doses	Infection	92.5 (91.4 to 93.5)§	NA	NA	104,339
Hansen et al. (2023) (*9*)	Denmark	Case-control	Three mRNA doses	Infection	94.4 (93.8 to 95.0)§	NA	NA	219,643
Hansen et al. (2023) (*9*)	Denmark	Case-control	Three mRNA doses	Infection	92.8 (91.7 to 93.7)§	NA	NA	187,347
BA.1/2 to BA.2.75								
Chemaitelly et al. (2023) (*10*)	Qatar	TND	Vaccinated (matched)	Infection	49.9 (47.6 to 52.1)	NA	NA	105,431
Chemaitelly et al. (2023) (*10*)	Qatar	TND	Vaccinated (matched)	Symptomatic infection	50.2 (43.1 to 56.4)	NA	NA	13,099
Chemaitelly et al. (2023) (*10*)	Qatar	TND	Vaccinated (matched)	Infection	47.4 (44.8 to 49.8)§	NA	NA	105,431
Chemaitelly et al. (2023) (*10*)	Qatar	TND	Vaccinated (matched)	Symptomatic infection	49.7 (42.3 to 56.1)§	NA	NA	13,099
Chemaitelly et al. (2023) (*10*)	Qatar	TND	Unvaccinated	Infection	32.2 (25.5 to 38.3)§	NA	NA	35,577
Chemaitelly et al. (2023) (*10*)	Qatar	TND	All vaccinated	Infection	53.9 (51.5 to 56.3)§	NA	NA	69,854
BA.4/5 to BA.2.75								
Chemaitelly et al. (2023) (*10*)	Qatar	TND	Vaccinated (matched)	Infection	80.6 (71.2 to 87.0)	NA	NA	102,271
Chemaitelly et al. (2023) (*10*)	Qatar	TND	Vaccinated (matched)	Symptomatic infection	91.4 (35.8 to 98.8)	NA	NA	12,680
Chemaitelly et al. (2023) (*10*)	Qatar	TND	Vaccinated (matched)	Infection	79.4 (69.4 to 86.2)§	NA	NA	102,271
Chemaitelly et al. (2023) (*10*)	Qatar	TND	Vaccinated (matched)	Symptomatic infection	91.3 (35.0 to 98.8)§	NA	NA	12,680
Chemaitelly et al. (2023) (*10*)	Qatar	TND	Unvaccinated	Infection	44.4 (−4.0 to 70.3)§	NA	NA	34,862
Chemaitelly et al. (2023) (*10*)	Qatar	TND	All vaccinated	Infection	87.4 (78.7 to 92.5)§	NA	NA	67,409

Note: "NA" means not applicable.

Abbreviation: TND=Test-negative design.

* Time since primary infection was determined based on GISAID data, with 50% serving as the judgment standard for epidemic strain. A variant was considered dominant if it exceeds 50%.

† Based on the research start date and the definition of interval of reinfection, if the most recent infection occurred during the BA.1/2 dominant period, the variant for prior infection was considered to belong to BA.1/2.

§ Sensitivity analysis results of the original literature.

SUPPLEMENTARY TABLE S3. Results of meta-regression.

Group	Estimate	Se	*P*
Result of meta-regression (BA.1 to BA.2):			
Intercept	−2.4363	0.6758	0.0003
Time since infection(days)	0.0051	0.0037	0.1622*
Result of meta-regression (BA.1 to BA.4/5):			
Intercept	−2.1593	0.5595	0.0001
Time since infection(days)	0.0045	0.0015	0.0029*
Result of meta-regression (BA.2 to BA.4/5):			
Intercept	−3.3310	0.5131	<0.0001
Time since infection(days)	0.0071	0.0016	<0.0001*

Note: Even though the *P* value for the BA.1 to BA.2 group surpassed 0.05, meta-regression was conducted due to the substantial impact of time on the analysis.
Abbreviation: SE=Standard error.
* *P* values represent results of test of moderators.

SUPPLEMENTARY TABLE S4. Results of the bias assessment (ROBINS-I).

First author (Year)	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Chemaitelly et al. (2022) (*1*)	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Carazo et al. (2023) (*2*)	Moderate	Serious	Low	Low	Serious	Low	Low	Serious
Chen et al. (2023) (*3*)	Serious	Serious	Low	Low	Moderate	Serious	Moderate	Serious
Tan et al. (2023) (*4*)	Moderate	Low	Low	Low	Serious	Low	Low	Serious
Jang et al. (2023) (*5*)	Moderate	Serious	Low	Low	Low	Low	Moderate	Moderate
Yamamoto et al. (2023) (*6*)	Moderate	Low	Low	Low	Moderate	Moderate	Low	Moderate
Altarawneh et al. (2022) (*7*)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Malato et al. (2022) (*8*)	Serious	Low	Low	Low	Serious	Low	Moderate	Serious
Hansen et al. (2023) (*9*)	Moderate	Serious	Low	Low	Moderate	Low	Low	Serious
Chemaitelly et al. (2023) (*10*)	Moderate	Low	Low	Low	Low	Low	Low	Moderate

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