**Title:**

The rate and influencing factors of SARS-CoV-2 Reinfection: systematic review and meta-analysis

**Short Running Title:**

The study of SARS-CoV-2 Reinfection Rate

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**Abstract**

**Background**: Understanding the SARS-COV-2 reinfection rate and its potential influencing factors is essential for further improvement and development of prevention and control strategies and measures to reduce the reinfection rate of SARS-CoV-2. This study aimed to quantitatively summarize the evidence of current reinfection studies.

**Methods**: We reviewed all English studies published up to Dec 4, 2022. Information extracted from each selected articles and quality assessment of these articles was used to evaluate the risk for bias in studies. The meta-analysis was performed to examine the rate and influencing factors of SARS-CoV-2 reinfection and protective effect of primary infection on reinfection in our study. Sources of heterogeneity were identified using a subgroup analysis defined by the minimum time interval of days to reinfection and variant strains.

**Results**: The weighted pooled rate of reinfection for SARS-CoV-2 was 1.08% ([95% CI, 0.77%-1.52%], *I*2 = 100%, *P* < 0.001). Subgroup-analysis of the minimum time interval definition for reinfection showed that rates of reinfection are 0.71%, 0.75%, 1.46% and 1.62% in less than 90 days, 90 days, greater than 90 days, unknown groups, respectively and 0.64%,1.8%,3.08%,0.95% in Alpha, Delta, Omicron, unknown groups. The weighted pooled RR value of the protective effect of primary infection on reinfection was 0.09 ([95% CI, 0.06-0.13], *I*2 = 92%, *P* < 0.01).

**Conclusions**: Overall, the reinfection rate of SARS-CoV-2 is relatively low and appears to be on the rise as duration from the first infection to the second infection and the novel coronavirus strain mutates.

**Keywords**: SARS-CoV-2; Reinfection Rate; Influencing factors

**Introduction**

The cumulative number of confirmed cases of COVID-19 has exceeded 700 million since the outbreak in 2019, with the emergence of Alpha, Beta, Lambda, Gamma, Delta, and Omicron variants [1-7]. In particular, the circulating Omicron variant has become the most infectious variant of COVID-19 so far because it has more mutation sites, greatly enhanced pathogenicity and infectivity, and has stronger immune escape ability[8]. Although, the World Health Organization (WHO) announced on 05 May 2023 that COVID-19 is no longer a public health emergency of international concern (PHEIC), it is important to prepare for and defend against emerging threats [9]. Because of the immune antibodies produced by the primary infection, their levels may drop sharply after a few weeks; In addition, the novel coronavirus is constantly mutating, and new strains may constantly emerge in the future. Antibodies or cells that specifically recognize previous antigens may not be able to effectively recognize new antigens, resulting in immune escape. Therefore, patients with primary COVID-19 infection are highly likely to be reinfected.

Suspected reinfections were first reported in South Korea back in April 2020; In August of that year, research at the University of Hong Kong confirmed the world's first case of reinfection in a person who had recovered from COVID-19[10]. A collaborative study by the University of Oxford, the University of Manchester and the UK's Health and Safety Authority (or according to the latest data from the Office for National Statistics) has revealed a significant increase in the rate of reinfection since 20 December 2021, and the risk of reinfection during the period when Omicron was the main circulating strain (2021.12.20-2022.01.09) was 16 times higher than that during the period when Delta was the main circulating strain (2021.05.17-2021.12.19). The latest official statistics for New York State, USA, showed that as of 15 May 2022, there were 243,020 cases of reinfection in New York State, accounting for 4.4% of all infections in New York State; and 212,463 of these reinfections occurred after 13 December 2021, accounting for 87.4% of reinfections in the state.

The high proportion of asymptomatic infections in the current outbreak dominated by the Omicron variant strain may also be a feature of future SARS-CoV-2 cases due to the generally reduced effectiveness of the currently administered vaccine to prevent infection, the fact that most of the infected adolescents and children present with asymptomatic infection, and the fact that cases identified in the major screening may be in latent phase. The risk of reinfection for the large number of recovered patients is of great concern, i.e., what are the chances of their reinfection with SARS-CoV-2? What are the characteristics of reinfected patients? These are questions that need to be answered urgently. However, the sample size of previous studies on the reinfection rate of COVID-19 ranged from dozens to 2 million, and the sample size was small in general, and the conclusions of these studies were quite different.

In order to clarify the risk of reinfection and to provide more reliable results, this study is intended to quantitatively summarize the evidence of current reinfection studies through a systematic literature review using meta-analysis to reveal the reinfection rate and its influencing factors, and to provide evidence-based support for further improvement and development of prevention and control strategies and measures to reduce the reinfection rate of SARS-CoV-2.

**Methods**

**Search strategy**

Through the development of a literature search strategy and selection criteria, our literature search identified relevant articles on SARS-CoV-2 reinfection and influencing factors of reinfection. The study protocol was pre-registered on Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) with the registration number CRD42022358817. The literature was searched for studies published up to December 4, 2022, using three English language databases: PubMed, Elsevier ScienceDirect, and Web of Science. The search keywords search formula can be found in Table A1. We used Endnote version X 9.2 to remove duplicate records. The screening of titles, abstracts, and full text was done independently by two people. Differences in the screening process were resolved by consensus or referred to a third person.

Articles included in our study had relevant estimates of reinfection rates (mainly means, median values, standard deviations, confidence interval ranges, etc.) obtained by calculation and studies that addressed influencing factors of reinfection rates. Most of the included studies were designed as cohort studies and were either research articles estimating reinfection rate values or articles on influencing factors of reinfection rates, while fewer studies were a combination of both. For non-research articles (e.g., reviews, comments, and letters) in which data on reinfection rates or impact factors were addressed in the article, we located and evaluated relevant primary studies for inclusion instead. The specific literature screening process is shown in Figure 1.

(Table A1 & Figure 1 are here.)

**Data extraction**

Information extracted from each selected article included: article name, first author, journal of publication, year of publication, study site, study time, study design, definition of reinfection, minimum days after initial infection of the definition of reinfection, median duration from the first infection to the second infection, variant strains, study sample size, influencing factors of reinfection rates, and relevant findings on reinfection rates (e.g., mainly mean, median, standard deviation, confidence interval range). Fields extracted for each article were completed by a total of two individuals. The quality and accuracy of the extracted samples were checked by a third person.

**Quality assessment**

The Newcastle–Ottawa Scale (NOS) for cohort study was used to evaluate the risk for bias in cohort studies, and the Joanna Briggs Institute critical appraisal tool (JBI) was used to evaluate the risk for bias for cross-sectional and ecological studies. The evaluation of literature quality was done independently by two evaluators (H-J and Z-Z), and a third person (W-ZL) intervened to discuss controversial ones. Evaluation items included (i) study population selection: representativeness of the exposed cohort, selection of the non-exposed cohort, determination of exposure, and whether any of the study subjects had an outcome event before the start of the study; (ii) intergroup comparability: comparability of the cohort based on the design or analysis obtained; and (iii) outcome: assessment of the outcome event, adequacy of follow-up for the observed occurrence of the outcome, and completeness of follow-up.

**Statistical analyses**

A meta-analysis of reinfection rates in SARS-CoV-2 patients was performed to determine heterogeneity between all studies based on the Cochran Q test and *I2*. If *P* > 0.1 for the Q test and *I2* ≤ 50%, a fixed-effects model was used for the combined analysis, otherwise a random-effects model was used for the combined analysis. Sensitivity analysis was performed by examining the change in combined effect values before and after exclusion from the literature with a test level of α= 0.01. Sources of heterogeneity were identified using a subgroup analysis defined by the minimum days after initial infection of the definition of reinfection (<90, 90, >90, unknown) and variant strains (Alpha, Delta, Gamma, Omicron, unknown). Simple linear regression was used to analyse the effect of median duration from the first infection to the second infection on reinfection rate. Meta-analysis was performed to examine the protective effect of primary infection on reinfection, applying Egger linear regression for potential publication bias, and performing sensitivity analyses for the 12 studies that included (or could calculate) RR values for the protective effect of primary infection with SARS-CoV-2 on reinfection. All statistical analyses were conducted in the "meta" package of R software (version 4.1.2).

**Results**

Based on our search strategy, a total of 5216 studies were retrieved and 92 studies were finally selected for systematic review. Of these, 26 studies in 2021 and 66 in 2022.The type of study include cohort study, cross-sectional study and ecological study. Scores of quality assessmentrange from 4-8, which is at a moderate and high quality.

**1.Reinfection rate of SARS-CoV-2**

The original literature reported the reinfection rates of SARS-CoV-2 ranging from 0.00 % to 36.83%. Heterogeneity tests showed a high degree of heterogeneity among studies (*I2* = 100%, *P* < 0.001), so a random-effects model was used to pool the reinfection rates. The weighted pooled rate of reinfection for SARS-CoV-2 was 1.08% (95% CI, 0.77%-1.52%) (Figure 2). Sensitivity analysis showed that the results of the reinfection rate study were reliable (Figure A1).

(Figure 2& Figure A1 are here.)

**2.Subgroup analysis**

The results of the subgroup analysis of the minimum time interval definition for reinfection and variant strains showed that there was also heterogeneity in the rate of SARS-CoV-2 reinfection among subgroups (Figure 3-4). The longer the minimum time interval definition for reinfection, the higher the reinfection rate. There is a linear relationship between the median duration from the first infection to the second infection and the reinfection rate (the estimate of regression coefficient was 1.57\*10-4, *p=0.005*).

(Figure 3& Figure 4 are here.)

**3. Influencing factors of SARS-CoV-2 reinfection**

**3.1 Primary infection with SARS-CoV-2**

Twelve prospective, retrospective cohort-based studies included SARS-CoV-2 infected and uninfected individuals during the first wave of the epidemic and compared the infection rates of both groups of primary infected and uninfected individuals during the second wave of the epidemic to assess the protective effect of primary infection with SARS-CoV-2 on reinfection (Table A2).

The results showed a more significant heterogeneity between the results of studies in the literature for the protective effect provided by primary infection (*I2* = 92%*, P* < 0.01), and the rates were pooled using a random effects model. The weighted pooled RR value was 0.09 (95% CI, 0.076-0.13) (Figure 5). Egger test results showed no publication bias (*t*=-0.22*, P*=0.83) (Figure A2). The results of sensitivity analysis showed reliable results of the primary infection protection study (Figure A3).

(Table A2, Figure 5 & Figure A2-A3 are here.)

**3.2 Other influencing factors**

By comparing the reinfection rate of SARS-CoV-2 in primary infected individuals who received a single dose of BNT162b2 vaccine with primary infected individuals who did not receive the vaccine, Gazit et al. found a significantly lower risk of SARS-CoV-2 reinfection in primary infected individuals who had received the vaccine compared with primary infected individuals who did not receive the vaccine (HR=0.18 [95% CI, 0.15-0.20]), where there was also a reduced risk of symptomatic SARS-CoV-2 reinfection (HR=0.24 [95% CI, 0.20-0.29]) [11]. Malhotra et al. found that two doses of BBV152 vaccine were 86% effective in protecting patients from reinfection (95% CI, 77%-92%). The protection rate was 87% (95% CI, 76% to 93%) for symptomatic reinfection and 84% (95% CI, 47% to 95%) for asymptomatic reinfection[12].

Based on a case-control study design, Chen et al. found that alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations were significantly higher in the SARS-CoV-2 reinfection case group compared to controls without reinfection (*P* = 0.020*, P* = 0.007) [13]. In addition, asthma (OR = 1.9 [95% CI, 1.1 -3.2]), smoking (OR=1.9 [95% CI, 1.1-3.2])[14], unstable living environment (HR=2.7 [95% CI, 1.7-4.4])[15] and gender as female (HR=1.6 [95% CI, 1.3 -1.9])[16] were considered risk factors for SARS-CoV-2 reinfection, and the use of therapeutic medication during primary infection was protective against reinfection (HR=0.3 [95% CI, 0.1-0.8])[15].

**Discussion**

The weighted combined meta-analysis of this study yielded a reinfection rate of 1.08% (95% CI, 0.77%-1.52%) for SARS-CoV-2. Possible reasons for reinfection in patients include (1) duration in immune antibody levels from vaccination and primary infection, and (2) immune escape due to continuous mutation of the virus.

The increase in breakthrough infections following full-dose vaccination and secondary infections following recovery from infection in the last two years has renewed widespread community concern. Typically, after a first infection with a new coronavirus (or after vaccination), the body improves T-cell immunity and antibody-secreting memory B cells enhance the response to spike-in proteins and the effectiveness of neutralizing antibodies, thus providing some protection to the body. At the same time, our results indicated that the studies in the literature on the protection provided by primary infection are more heterogeneous, and the results of sensitivity analysis indicate that the primary infection protection studies are reliable. Twelve of the papers reviewed in this paper showed that primary infection provides some protection from reinfection in recovered patients. However, because the immune antibodies produced by primary infection with SARS-CoV-2 may drop dramatically after only a few weeks, unlike SARS and MERS which persist in the body for a year or even years, patients may not be able to establish long-term immunity to the SARS-CoV-2. One study looked at the follow-up of patients with primary SARS-CoV-2 infection and found that antibodies were reduced in 81% of asymptomatic infected individuals within 8 weeks and 62% of those with symptoms[17].

At the same time, the emergence of mutant strains of the virus leads to immune escape as antibodies or cells that specifically recognize the previous antigen fail to do so effectively. First-time infections with SARS-CoV-2 strains induce antibodies that do not cross-recognize (or neutralize) a different strain for reinfection, leading to secondary infections. Although mRNA vaccine-elicited antibodies cross-neutralize the Alpha and Beta variants, evidence from molecular biology suggests that genetically distinct viral strains (e.g. Delta vs. Omicron) or new variants (e.g. BA.1, BA.2), whether by natural infection or vaccination, have the potential to evade the immune system[18].

The diversity of study participants included in this study was significant, with large differences in sample size, study years, study geography, criteria for determining secondary infection cases and other indicators, thus revealing a large heterogeneity in the results of the current studies. Our Meta-analysis results for both SARS-CoV-2 reinfection rates (and the protective effect of primary infection) showed more significant heterogeneity between the results of the studies, possibly due to differences in the main prevalent variants during the study period. According to the WHO weekly epidemiological update, the Omicron variant has now spread to more than 150 countries and territories worldwide. The transmissibility of the virus varies by strain. The Alpha, Beta and Delta variants are 1.7, 1.5 and 2 times more transmissible, respectively, than the original strain[19-22]; while Omicron has 50 mutations[22], of which are concentrated in the echinoderm protein, making the strain more pathogenic and infectious, with greater immune escape[23]. Studies have shown that the Omicron variants is 13 times more infectious than the original strain[24] and infects and replicates 70 times faster in the human bronchus than the Delta mutant. Our study found that the reinfection rate of the novel coronavirus is relatively low, but with the mutation of the strain, the reinfection rate has an increasing trend, which may be explained by the transmissibility, pathogenicity and infectivity of SARS-CoV-2. Therefore, in the future, we should focus on intensive monitoring.

In addition, differences in the minimum time interval between positive tests used to define SARS-CoV-2 reinfection have a direct impact on the reinfection rate. Euser et al. analyzed the reinfection rate of SARS-CoV-2 infected cases during the study period using four different time intervals of 2, 4, 8 and 16 weeks and showed that the number of reinfection cases was 260 when the interval between positive tests was at least 2 weeks and 89 when the interval was at least 4 weeks. 260 cases, decreasing to 89 cases (0.19%) at an interval of at least 4 weeks, and decreasing to 52 and 37 cases between 8 and 16 weeks respectively[25]. Eighteen of the studies included in this study used 4 weeks[26], 45 days[27], 50 days[28], 8 weeks[7], 60 days[29], 90 days[4, 5, 14, 15, 30-34] as the minimum time interval between positive tests, respectively. This could also explain to some extent the heterogeneity of SARS-CoV-2 reinfection rates across studies.

In conclusion, due to the limitations of the study area, the different study time periods, and the inconsistent criteria for determining SARS-CoV-2 infection, the current study results may not fully reflect the current situation of SARS-CoV-2 reinfection rate, and the research on this issue is still at the stage of describing the phenomenon of individual cases. At the same time there are numerous variants of SARS-CoV-2, and reinfection and the factors affecting it can be analyzed according to the different variants Therefore, there is a need to further standardize and unify the criteria for determining cases of reinfection of new crowns, increase laboratory testing, and strengthen research on the etiology of reinfection cases. The present study found a high degree of heterogeneity in the current studies, and regression models may be needed to control for confounding factors in order to eliminate heterogeneity in future.

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**Figure legends**

Figure 1. Flow chart illustrating study selection process

Figure 2. Forest plot of SARS-CoV-2 reinfection rate

Figure 3. Forest plot of subgroup analysis of SARS-CoV-2 reinfection rate with different minimum time intervals

Figure 4. Forest plot of subgroup analysis of SARS-CoV-2 reinfection rate with different variant strains

Figure 5. Meta-analysis forest plot of RR values of the protective effect of primary infection with SARS-CoV-2 against reinfection

**Author Contributions**

JH and ZLW designed the study and wrote the manuscript. ZLW analyzed the data. ZZ, YY and YHL helped with research design, data collection. KL, JS, JQH and XC helped with data processing. MPW, and ZJZ helped with critical revision of manuscript. ZJZ supervised all aspects of this study. All authors contributed to and approved the final version for submission.

**Conflict of Interest Statement**

The authors have no relevant financial or non-financial interests to disclose.