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SYSTEMATIC REVIEW

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Risk of reinfection and disease after SARS-CoV-2 primary infection: Meta-analysis

Maria Elena Flacco[1] | **Cecilia Acuti Martellucci**[1] | **Valentina Baccolini**[2] | **Corrado De Vito**[2] | **Erika Renzi**[2] | **Paolo Villari**[2] | **Lamberto Manzoli**[3]

[1]Department of Environmental and Preventive Sciences, University of Ferrara, Ferrara, Italy

[2]Department of Public Health and Infectious Diseases, Sapienza University, Rome, Italy

[3]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

Correspondence
Lamberto Manzoli, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy.
Email: lmanzoli@post.harvard.edu

Abstract

Introduction: A precise estimate of the frequency and severity of SARS-CoV-2 reinfections would be critical to optimize restriction and vaccination policies for the hundreds of millions previously infected subjects. We performed a meta-analysis to evaluate the risk of reinfection and COVID-19 following primary infection.

Methods: We searched MedLine, Scopus and preprint repositories for cohort studies evaluating the onset of new infections among baseline SARS-CoV-2-positive subjects. Random-effect meta-analyses of proportions were stratified by gender, exposure risk, vaccination status, viral strain, time between episodes, and reinfection definition.

Results: Ninety-one studies, enrolling 15,034,624 subjects, were included. Overall, 158,478 reinfections were recorded, corresponding to a pooled rate of 0.97% (95% CI: 0.71%–1.27%), with no substantial differences by definition criteria, exposure risk or gender. Reinfection rates were still 0.66% after ≥12 months from first infection, and the risk was substantially lower among vaccinated subjects (0.32% vs. 0.74% for unvaccinated individuals). During the first 3 months of Omicron wave, the reinfection rates reached 3.31%. Overall rates of severe/lethal COVID-19 were very low (2–7 per 10,000 subjects according to definition criteria) and were not affected by strain predominance.

Conclusions: A strong natural immunity follows the primary infection and may last for more than one year, suggesting that the risk and health care needs of recovered subjects might be limited. Although the reinfection rates considerably increased during the Omicron wave, the risk of a secondary severe or lethal disease remained very low. The risk–benefit profile of multiple vaccine doses for this subset of population needs to be carefully evaluated.

Maria Elena Flacco and Cecilia Acuti Martellucci contributed equally to the present work.

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KEYWORDS
COVID-19, meta-analysis, Omicron variant, reinfection, SARS-CoV-2

1 | INTRODUCTION

After the first documented case on August 2020 in Hong Kong,[1] an increasing number of field studies estimated the rate of SARS-CoV-2 reinfections after a primary episode.[2–27] Although the reported rates have been consistently low, the results differed according to the adopted definition of reinfection, setting, pandemic period, follow-up duration and uncertainties remain on the risk of developing a severe COVID-19 disease after a reinfection.[17,20,28] Moreover, the rapid spread of the SARS-CoV-2 Omicron variant (B.1.1.529)[29] has posed additional concerns on the degree of protection conferred by prior infections.[30,31]

As a precise estimate of the frequency and severity of reinfections would be critical to predict the course of the pandemic and optimize restriction and vaccination policies for the hundreds of millions of subjects who recovered from a SARS-CoV-2 infection,[32–34] we carried out a meta-analysis of the available prospective observational evidence to provide a pooled estimate of the risk of SARS-CoV-2 reinfection and severe and lethal COVID-19. Reinfection rates were also computed separately for each gender, exposure risk, vaccination coverage, definitions of reinfection and predominant viral strain.

2 | METHODS

The reporting of this meta-analysis was guided by the standards of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 Statement.[35] We extracted data from cohort studies evaluating the onset of a new SARS-CoV-2 infection (either asymptomatic or symptomatic) among subjects of all ages with a prior positive SARS-CoV-2 baseline status.

We searched MedLine and Scopus databases, up to 30 June 2022 using the following search strategy, without language restrictions: (coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or '2019-nCoV' or 2019nCoV or nCoV2019 or 'nCoV-2019' or 'COVID-19' or COVID19 or 'CORVID-19' or CORVID19 or 'WN-CoV' or WNCoV or 'HCoV-19' or HCoV19 or CoV or '2019 novel*' or Ncov or 'n-cov' or 'SARS-CoV-2' or 'SARSCoV-2' or 'SARSCoV2' or 'SARS-CoV2' or SARSCov19 or 'SARS-Cov19' or 'SARSCov-19' or 'SARS-Cov-19' or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*) AND (reinfection* or re-infection* or second episode or recurrence* or recrudescence* or relapse* or RCOVID19).[36] The references of the reviews and retrieved articles were also screened for additional pertinent papers. Given that several relevant clinical databases have been shared in public preprint repositories in the context of a public health emergency, we also searched for potential studies among those submitted in medRxiv.org.[37] In case of re-analyses published from the same cohort, we extracted the data of the publication with the longer follow-up or, if the length of follow-up was identical, with the largest sample size.

Each included article was independently evaluated by three reviewers (CAM, VB and ER), who extracted the main study characteristics (first author, publication year, study design, population, overall sample, mean age and gender distribution of the participants, length of follow-up, dominant variant, vaccination coverage (if underway), protocol of evaluation of SARS-CoV-2 (re)infection, minimum time lag between primary and secondary positive episodes) and the raw numbers of: (a) SARS-CoV-2 reinfections (asymptomatic infections or mild diseases, with fever or malaise plus at least one of the followings: sore throat, muscle pain, shortness of breath, dry cough, headache, conjunctivitis and diarrhoea with no hospital admission); (b) severe COVID-19 diseases (requiring hospital admission with no use of an intensive care unit); (c) subjects with very severe/lethal COVID-19 disease (requiring admission in an intensive care unit and/or causing death).[11] In case of discrepancies in data extraction, a fourth author was contacted (MEF), and consensus achieved through discussion.

The first infection was defined by the presence of: (a) a positive reverse-transcriptase polymerase chain reaction (RT-PCR) test; and/or (b) a baseline positive serology, investigated with the use of an anti-trimeric spike IgG enzyme-linked immunosorbent assay (ELISA).[38]

In accordance with the CDC criteria,[39] a reinfection was defined by the presence of:

a. two positive PCR samples detected ≥45 days apart with ≥1 negative RT-PCR test collected between the first and second episode[40] and/or confirmation of infection with two different phylogenetic strains by viral genomic sequencing[28];
b. two positive PCR samples detected ≥45 days apart in subjects with a symptomatic second episode or in close contact with a laboratory-confirmed COVID-19 case[39];

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c. a positive PCR test ≥45 days after the first positive serology (detection of anti-S1 domain of spike protein IgG antibodies using an enzyme-linked immunosorbent assay—ELISA).[38,39]

When a study adopted a time lag between two positive episodes <45 days, we conservatively extracted and included only the cases with a new positive RT-PCR occurring ≥45 days after the first episode, unless other evidences of reinfection (negative PCR or different genome sequence) were available.

We used random-effect meta-analyses of proportions to combine data and obtain summary estimates of the incidence of (a) SARS-CoV-2 re-infection, (b) severe COVID-19 and (c) very severe/lethal COVID-19. We computed the pooled rate of each outcome twice: (1) using ≥45 days as the minimum time lag between two positive episodes; (2) adopting a more stringent time lag of ≥90 days.[39] Additionally, when data were available, we performed several stratified analyses and computed separate estimates by (a) gender; (b) exposure risk (health care workers vs. the general population); (c) vaccination status (unvaccinated; coverage of 25–50% of the sample; coverage of 100%); (d) dominant viral strain (Alpha or Beta; Delta; Omicron); (e) months between first episode and reinfection (<6; 6–11; ≥12); (f) risk of reinfection misclassification. As the definition of reinfection has evolved over time,[28] some studies did not verify the presence of an intermediate negative RT-PCR sample or viral genomic sequencing data during the ≥45 days between the positive swabs. Since a new positive RT-PCR in a subject with a previously documented infection may indicate reinfection, but also persistence of nonviable RNA after the first episode—documented up to 104 days after the initial infection—or relapse,[41] these studies were considered at risk of misclassification bias. All analyses were carried out using Stata, version 13.1 (Stata Corp., College Station, TX, 2013).

3 | RESULTS

Of the 3282 papers initially retrieved, we included 91 cohort studies evaluating the onset of reinfection, severe and very severe/lethal COVID-19 among 15,034,624 previously infected subjects (Figure 1), either among health care workers (27 publications; n = 37,598[2,8,9,15,17,24,36,38,42–59]) or in the general population (67 publications; n = 14,997,026[3–7,10,12,16–23,25–27,43,49,60–106]).

Four studies contributed with more than one dataset,[4,17,49,71] as the same publication provided separate data for both staff and residents of long-term care facilities,[17,49] or adopted different approaches to evaluate the baseline positivity in two separate groups of subjects,[4] finally provided individual participants data.[71] This led to a total of 94 datasets included in the analyses.

As shown in Table S1, most of the included studies (n = 43) were carried out in Europe,[2,4–10,12,15,17,18,21,24,26,36,38,44,46–51,58,66,69,71,72,75,81,85–88,91–93,95,99,102] 24 in the USA,[20,22,23,25,42,43,57,59,63,67,77,79,82–84,89,90,97,98,103,105–107] 18 in Asia[3,16,19,27,45,52–54,56,60,62,64,65,70,73,74,100,101] and the remaining six in South America or South Africa.[61,68,80,94,96,104] The mean age of the participants ranged from 15 to 87 years, and the average follow-up ranged from 29 to 371 days. Overall, 38 publications strictly followed the CDC criteria to identify the reinfections and were classified at low risk of misclassification bias.[10,16,19,20,22–24,26,36,44,45,48–50,54,56,58,59,68,71,72,75,84,86,89–91,94,99,100,102] All but five studies (n = 3,854,961)[66,71,88,91,96] were completed before the emergence of BA.1/B.1.1.529 (Omicron) variant. A total of 52 out of the 91 included studies reported an incidence of reinfections below 1%, and 47 an absolute risk of severe or lethal COVID-19 below 0.1%.

Overall, a total of 158,478 reinfections were recorded among the 15,034,624 subjects with a previous infection,[2–10,12,13,15–27,36,38,42–107] corresponding to a pooled rate of 0.97% (95% CI: 0.71%–1.27%—Table 1; Figure 2). The summary rate of reinfection rose to 1.07% (95% CI: 0.73%–1.46%) when only the 69 datasets with a more conservative time lag of ≥90 days between the two episodes were considered[3–6,8–10,12,18–23,25,26,36,42–44,46–50,52–56,59,61–65,67–69,72–84,86,87,89,91–96,98,101,103,105–107] and it slightly varied by reinfection definition criteria (0.93% vs 1.01% when considering studies with high vs low risk of misclassification). The risk of reinfection was higher among health care workers as compared to the general population (1.20% vs 0.90), and among females (0.79% vs 0.55% among males), although these estimates showed largely overlapping confidence intervals. Conversely, the reinfection rate varied widely by vaccination status: a lower likelihood of reinfection was observed in the studies where 100% of the subjects received at least one vaccine dose (0.32% vs. 0.77% among the unvaccinated—Table 1). Overall, the pooled rates of reinfection were higher in US-based studies (1.08%; 95% CI: 0.93%–1.25%) than in studies performed in Europe (0.63%; 95% CI: 0.44%–0.84%), or in Asia (0.77%; 95% CI: 0.50%–1.10%).

When the analyses were stratified by time from the primary infection, the highest reinfection rates were observed after 6–11 months from the first episode, reaching 1.12% (95% CI: 0.57%–1.82%); the pooled rates then substantially decreased to 0.66% after ≥12 months from the first infection.

Finally, when the analyses were stratified by predominant strain, a sharply rising trend was observed with the emergence of new variants: the pooled reinfection rates were 0.57% (95% CI: 0.28%–0.94%) in the studies providing specific data on the Alpha wave; the rates rose to 1.25%

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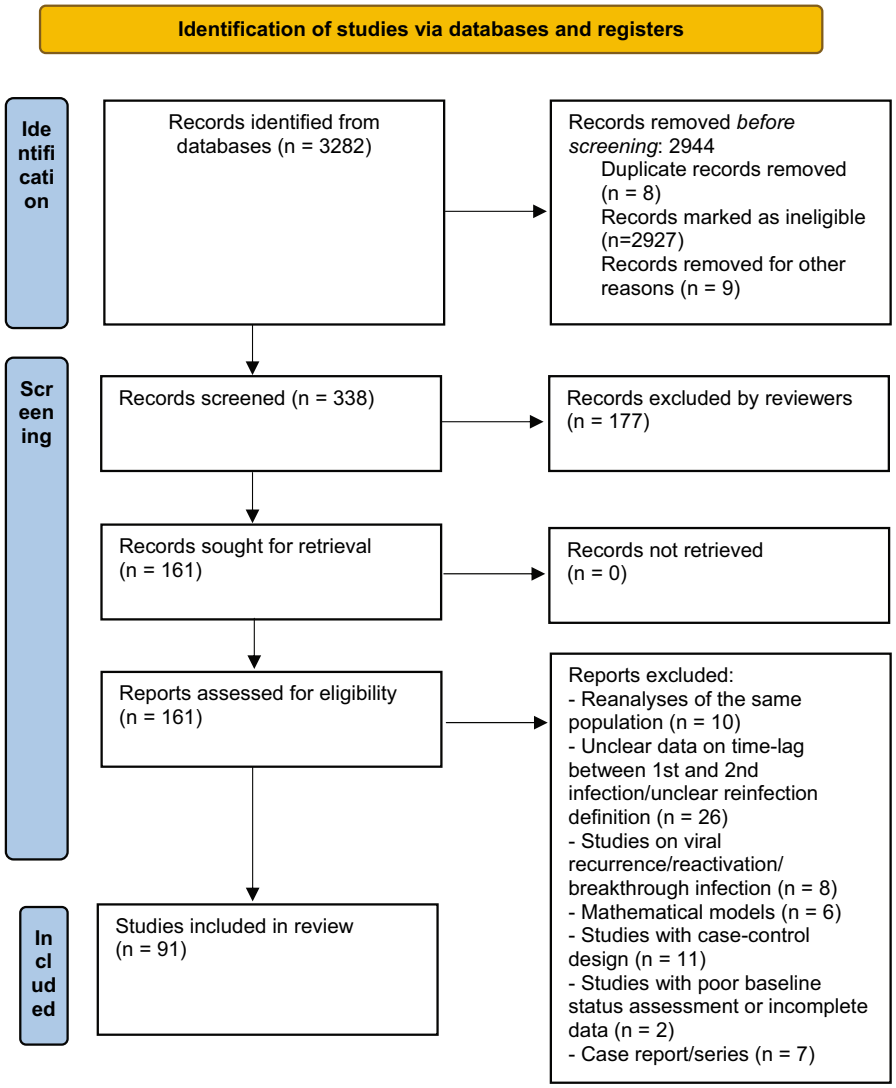

FIGURE 1 PRISMA 2020 flow diagram. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

(95% CI: 0.97%–1.55%) with the Delta strain and peaked to 3.31% (95% CI: 1.15%–6.53%) during the first three months of the Omicron wave.

In the 59 available datasets,[2,3,5,6,10,16–22,25–27,36,44,46–59,63–67,69,71–74,79,82,84–87,90,93–95,99–104] a total of 1380 severe COVID-19 diseases were diagnosed among 5,006,604 subjects with a previous infection, corresponding to a pooled rate of 0.02% (95% CI: 0.00%–0.04%—Table 1). This rate did not substantially vary when only the studies with longer time lag were considered, while it increased—still, however, remaining below 0.1%—when only the studies that used CDC criteria to define reinfections were included (summary rate 0.07%; 0.04%–0.10%). The risk of severe COVID-19 was always below 0.1% with any predominant strain and in the studies where 100% of the subjects received at least one vaccine dose (0.01% vs 0.10% among the unvaccinated—Table 1).

Finally, in the 54 datasets that provided data for the analysis of very severe/lethal COVID-19,[2,3,5,6,10,16–22,25–27,44,47–59,64–66,69,71–73,79,81,82,84–87,92,94,95,99–104] a total of 199 events were recorded among 3,574,793 previously infected individuals, corresponding to a pooled rate of 0.02% (0.01%–0.03%), which did not differ by time lag or definition criteria.

4 | DISCUSSION

The main findings of this meta-analysis, based upon the pooled results of 91 cohort studies, including more than 15 million individuals who were previously infected with SARS-CoV-2 provide some solid confirmations, and a few updates: (a) after an average of twelve months of follow-up, the overall risk of reinfection approaches 1%, with no substantial differences across genders, exposure risk and definition criteria; (b) the likelihood of reinfection increased considerably over time, particularly with the spread of new highly transmissible variants, peaking during the first three months of the Omicron wave; (c) the summary rates of severe or lethal COVID-19 were still very

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TABLE 1 Pooled rates of reinfection[a], severe COVID-19 disease[b] and very severe/lethal COVID-19[c] among subjects with a previous SARS-CoV-2 infection, overall and according to re-infection definition criteria, gender, exposure risk (type of population), time lag between first infection and second episode, vaccination status and predominant strain

Outcomes	Study ref.[g]	N. datasets[g] (raw data)	Pooled rates, % (95% CI)	I, %
Reinfection[a]				
Estimated pooled rate	2–10,12,13,15–27,36,38,42–107	94 (158,478/15,034,624)	0.97 (0.71–1.27)	99
Including only studies with time lag ≥90 days[h]	3–6,8–10,12,18–23,25,26,36,42–44,46–50,52–56,59,61–65,67–69,72–84,86,87,89,91–96,98,101,103,105–107	69 (142,596/11,895,618)	1.07 (0.73–1.46)	99
Stratified analyses				
1. By reinfection definition criteria				
Probable reinfection (high risk of misclassification)[d]	2,4,5,7–9,12,15,17,18,21,25,27,38,42,46,47,51–53,55,57,60,62,64–66,69,70,73,74,76–83,85,87,88,92,93,95–98,101,103–107	56 (155,051/12,868,418)	0.93 (0.64–1.28)	99
Confirmed reinfection (low risk of misclassification)[e]	10,16,19,20,22–24,26,36,44,45,48–50,54,56,58,59,68,71,72,75,84,86,89–91,94,99,100,102	38 (3427/2,166,206)	1.01 (0.61–1.49)	99
2. By gender				
Males	5,9,18,22,36,42,47,49–51,55–57,59,65,69–72,74,82,86,87,93,95,96,102,103,105,107	32 (47,969/2,634,694)	0.55 (0.14–1.16)	99
Females	5,9,18,22,36,42,47,49–51,55–57,59,65,69–72,74,82,86,87,93,95,96,102,103,105,108	32 (70,099/7,695,452)	0.79 (0.18–1.69)	99
3. By exposure risk				
General population	3–7,10,12,13,16–23,25–27,49,60,62–64,67,69,72,75–77,86,95,99,100,103,105	67 (157,806 /14,997,026)	0.90 (0.61–1.24)	99
Health care workers	2,8,9,15,17,24,36,38,42–59	27 (672/37,598)	1.20 (0.59–1.98)	92
4. By length of follow-up (time between first infection and reinfection)				
Less than 6 months (<183 days)	3,6,7,15–17,19,20,22–25,27,38,46,49,57,63,67,70,71,73,75–77,83,84,88,93,97,98,107	34 (35,487/8,123,293)	0.58 (0.50–0.68)	99
6-11 months (183–364 days)	2,9,10,18,21,26,36,42,44,45,50–52,54,59,61,65,71,79,86,90,91,94,95,102,103,106	27 (3146/1,987,532)	1.12 (0.57–1.82)	99
12 or more months (≥365 days)	8,55,71	4 (362/48,384)	0.66 (0.50–0.84)	24
5. By vaccination status				
Unvaccinated	49–51,55,57,63,68,71,93,97,98,102,104	14 (12,408/3,116,047)	0.74 (0.57–0.93)	99
Vaccination campaign covering 25–50% of the sample	36,47,54,56,74,79,83,94,105	9 (21,800/5,727,836)	0.95 (0.45–1.64)	99
Vaccination campaign covering 100% of the sample	3,71	3 (588/248,049)	0.32 (0.11–0.64)	99
6. By predominant viral strain[f]				
Alpha (B.1.1.7)	3,8,17,47,49,71,81,87,90,104	11 (5566/1,209,861)	0.57 (0.28–0.94)	99
Delta (B.1.617.2)	30,45,52,53,56,65,70,73,74,79,80,83,89,93,106	15 (26,583/5,225,116)	1.25 (0.97–1.55)	100
Omicron (B.1.1.529)	66,71,88,91,96	5 (112,928/3,854,961)	3.31 (1.15–6.53)	99

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TABLE 1 (Continued)

Outcomes	Study ref.[g]	N. datasets[g] (raw data)	Pooled rates, % (95% CI)	I, %
7. By geographic area				
Europe	2,4–10,12,15,17,18,21,24,26,36,38,44,46–51,58,66,69,71,72,75,81,85–88,91–93,95,99,102	46 (17,186/3,263,398)	0.63 (0.44–0.84)	100
US	20,22,23,25,42,43,57,59,63,67,77,79,82–84,89,90,97,98,103,105–108	24 (28,136/6,119,540)	1.08 (0.93–1.25)	99
Asia	3,16,19,27,45,52–54,56,60,62,64,65,70,73,74,100,101	18 (8161/1,063,517)	0.77 (0.50–1.10)	99
Severe COVID-19 disease[b]				
Estimated pooled rate	2,3,5,6,10,16–22,25–27,36,44,46–59,63–67,69,71–74,79,82,84–87,90,93–95,99–104	59 (1380/5,006,604)	0.02 (0.00–0.04)	98
Including only studies with time lag ≥90 days[h]	3,5,6,10,18–22,25,26,36,44,46–50,52–56,59,63–65,67,69,72–74,79,82,84,86,87,90,93–95,103	44 (1322/4,785,454)	0.02 (0.00–0.06)	99
Stratified analyses				
1. By reinfection definition criteria				
Probable reinfection (high risk of misclassification)[d]	2,5,17,18,21,25,27,46,47,51–53,55,57,64–66,69,73,74,79,82,85,87,93,95,101,103,104	30 (1282/2,907,510)	0.05 (0.01–0.10)	99
Confirmed reinfection (low risk of misclassification)[e]	3,6,10,16,19,20,22,26,36,44,48–50,54,56,58,59,63,67,71,72,84,86,90,94,99,100,102	29 (98/2,099,094)	0.07 (0.04–0.10)	93
2. By vaccination status				
Unvaccinated	49–51,55,57,63,71,93,102,104	11 (164/1,066,987)	0.10 (0.04–0.19)	86
Vaccination campaign covering 25–50% of the sample	36,47,54,56,74,79,94	7 (43/2,371,936	0.00 (0.00–0.01)	95
Vaccination campaign covering 100% of the sample	3,48,71	3 (17/248,049)	0.01 (0.00–0.03)	93
3. By predominant viral strain[f]				
Alpha (B.1.1.7)	3,17,47,49,71,87,90,104	9 (88/950,690)	0.03 (0.01–0.06)	92
Delta (B.1.617.2)	52,53,56,65,73,74,79,93	8 (1087/1,862,216)	0.07 (0.00–0.20)	100
Omicron (B.1.1.529)	66,71	2 (19/64,522)	0.03 (0.02–0.04)	–
Very severe/lethal COVID-19[c]				
Estimated pooled rate	2,3,5,6,10,16–22,25–27,44,47–59,64–66,69,71–73,79,81,82,84–87,92,94,95,99–104	54 (199/3,574,793)	0.02 (0.00–0.03)	91
Including only studies with time lag ≥90 days[h]	3,5,6,10,18–22,25,26,44,47–50,52–56,59,64,65,67,69,72,73,79,81,82,84,86,87,94,95,101,103	39 (183/3,392,229)	0.02 (0.01–0.03)	93

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TABLE 1 (Continued)

Outcomes	Study ref.[g]	N. datasets[g] (raw data)	Pooled rates, % (95% CI)	I, %
Stratified analyses				
1. By reinfection definition criteria				
Probable reinfection (high risk of misclassification)[d]	2,5,17,18,21,25,27,47,51–53,55,57,64,65,69,73,79,81,82,85,87,92,95,101,103,104	28 (171/1,490,266)	0.02 (0.01–0.03)	92
Confirmed reinfection (low risk of misclassification)[e]	3,6,10,16,19,20,22,26,44,48–50,54,56,58,59,67,71,72,84,86,94,99,100,102	26 (28/2,084,527)	0.02 (0.01–0.03)	92

Notes: Raw data show the number of subjects with each outcome upon the total number of included subjects. Data from single studies have been combined using proportion meta-analysis (random-effect model).

Abbreviations: CI, confidence interval; SARS-CoV-2, severe acute respiratory syndrome coronavirus.

[a]Asymptomatic infection or mild disease, defined as fever or malaise plus at least one of the followings: sore throat, muscle pain, shortness of breath, dry cough, headache, conjunctivitis and diarrhoea with no hospital admission.

[b]Severe disease, requiring hospital admission, not in an intensive care unit.

[c]Very severe or lethal disease, requiring admission in an intensive care unit and/or causing death.

[d]A probable reinfection was defined as a new positive RT-PCR sample ≥45 days after a proven baseline SARS-CoV-2 infection (either assessed through a first positive nasopharyngeal swab or a positive serology—detection of anti-S1 domain of spike protein IgG antibodies using an enzyme-linked immunosorbent assay—ELISA), with no intermediate negative RT-PCR sample or viral genomic sequencing.

[e]A confirmed reinfection was defined as a new positive RT-PCR sample ≥45 days after a proven baseline SARS-CoV-2 infection (either assessed through a first positive nasopharyngeal swab or a positive serology—detection of anti-S1 domain of spike protein IgG antibodies using an enzyme-linked immunosorbent assay—ELISA), with ≥1 intermediate negative RT-PCR sample and/or a confirmation of infection with two different phylogenetic strains, obtained through viral genomic sequencing.

[f]Alpha wave: from September 2020 (first detection: UK; worldwide geographic distribution); Delta wave: from December 2020 (first detection: India; worldwide geographic distribution); Omicron wave: from December 2021 (first detection: South Africa; worldwide geographic distribution; Available in: https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html). For Italy: Omicron wave started from 28 December 2021 when the proportion of Omicron variant in the available positive swabs was higher than 50%. Available in: Italian National Institute of Health (2021) Stima della prevalenza delle varianti VOC (Variants of Concern) in Italia: beta, gamma, delta, omicron e altre varianti di SARS-CoV-2. (https://www.iss.it/documents/20126/0/Report_flashVarianti_14gennaio22.pdf/b44b1a7d-a0c1-67fd-44b7-34c8b775c088?t=1642162662435).

[g]Four studies[4,17,49,71] contributed with more than one dataset; thus, the number of references does not always match the number of datasets included in each analysis (see methods for further details).

[h]Excluding studies with a time lag <90 days between two positive RT-PCR tests, with or without an intermediate negative PCR/viral genomic confirmation between the first and second episode.

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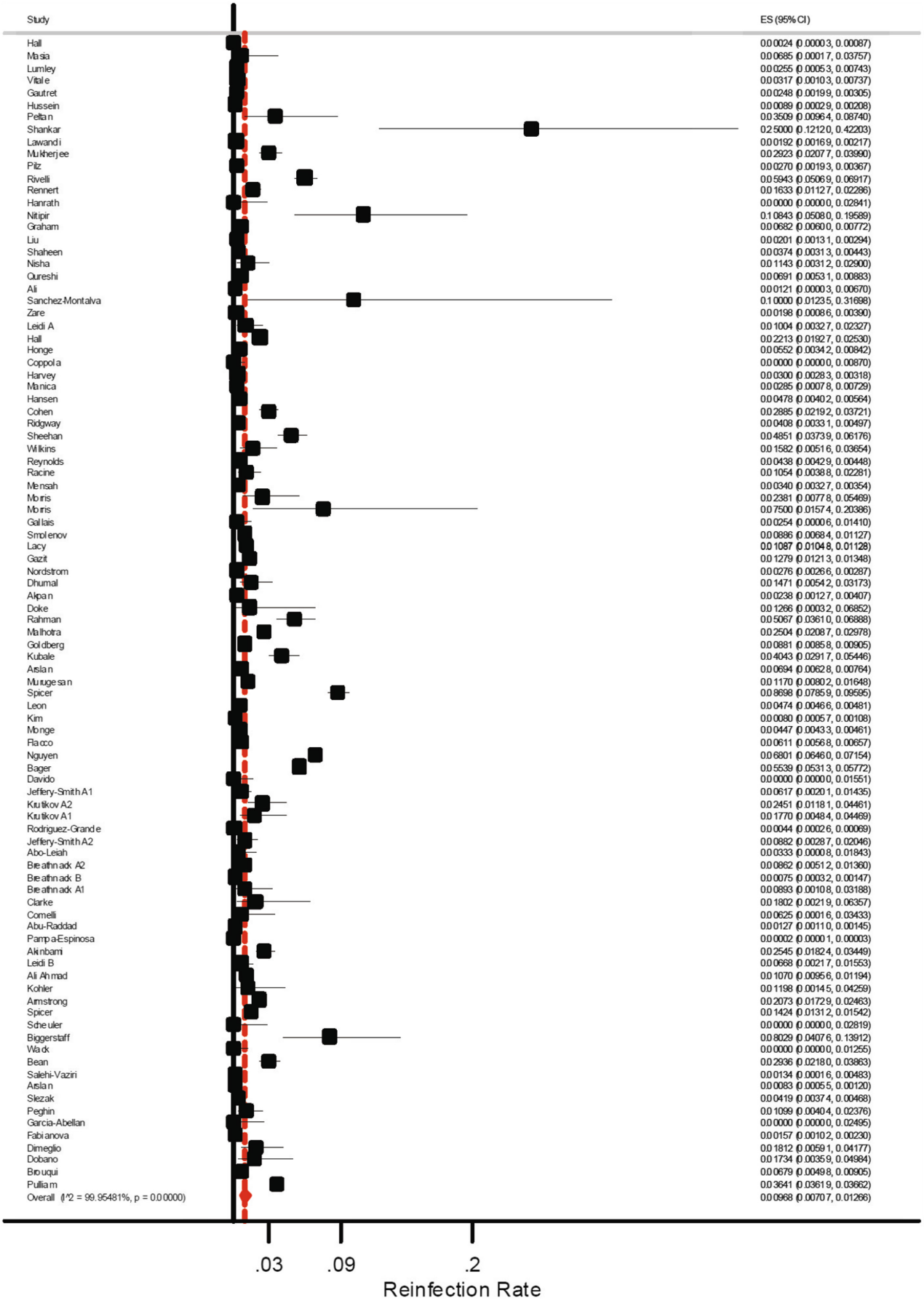

FIGURE 2 Proportion meta-analysis of the risk of SARS-CoV-2 reinfection among previously infected subjects

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low, ranging from 2 to 7 out of 10,000 subjects according to the adopted definition criteria, and were not affected by strain predominance; (d) the pooled risk of reinfection was significantly lower among the subjects that received one or more vaccine doses, versus the unvaccinated.

A low risk of reinfection and a very low risk of severe or lethal COVID-19 for those who recovered from a primary infection were reported in the vast majority of the published studies, as well in the available systematic reviews.[108–111] Most of the available information, however, included data preceding the emergence of the Omicron wave,[110] or relied upon very preliminary data.[108] Importantly, we expanded the existing evidence with the analysis of a very large database across different geographic areas, including reinfections up to the first three months of the Omicron wave, and providing confirmation[96] of a substantially increased risk of reinfection, temporally linked with the emergence of this variant.

In the context of the pandemic, there has been debate on the health policies to adopt for the population of previously infected subjects.[40,112] On one side, the restriction policies and vaccination requirements have been less strict in several countries, in consideration of their low/very low-risk profile.[113–115] On the other side, concerns on the appropriateness of such policies remained, because the duration of the natural immunity was unknown and, more recently, because of the spread of the Omicron variant, which showed a marked increase in the number of infections and hospitalizations as a result of a very high level of community transmission.[116–118] This led some countries to establish a time limit from the first infection, after which one or two doses of vaccine were requested.[119] However, data are strongly needed to support such policies, since no study evaluated the risk of reinfection after 12 months of follow-up, during the Omicron wave, and no information was available on the potential impact of vaccination after the first infection.

Some of the findings of our analysis are reassuring, supporting less strict, targeted policies for the subjects who recovered from a previous infection: the rates of severe or lethal COVID-19 were extremely low, suggesting that the health risk and impact on the health services of these subjects, during the next phases of the SARS-CoV-2 pandemic, might be very limited. On the other side, however, we observed a concerning, marked increase in the reinfection rates during the Omicron wave, and a significantly lower risk of reinfection among the vaccinated subjects, thus vaccinating also this population may definitely play an important role to control the pandemic. It remains to be considered that, if during the Omicron wave the risk of a secondary severe disease or death will remain close to zero despite the large increase of reinfections, the risk–benefit profile of multiple vaccine doses for this population will have to be carefully evaluated. Unfortunately, of the five studies providing data on the Omicron wave, only two (although based upon a very large sample) specifically assessed the number of severe COVID-19.[66,71] On one side, the very low pooled rates of hospitalization recorded even after Omicron surge are reassuring. On the other side, however, such findings require confirmation, and the large increase in reinfections during the first months of Omicron predominance is a matter of serious concern.

Interestingly, and in line with previous studies,[71,96] we found some degree of variation in reinfection rates across geographical areas. Besides the genetic pattern, the main potential explanations include differences in the detection process caused by the adoption of diverse testing policies, diagnostic methods and health-seeking behaviours,[65,96] and the fact that countries have been sequentially hit by different variants of SARS-CoV-2.[120] Indeed, the mutual combination of these factors may explain, at least in part, the spatial unevenness of SARS-CoV-2 spread, which has been observed even at a sub-national level.[96,121]

The study has some limitations that should be considered when interpreting the results. On one side, the incidence of reinfection could have been overestimated in several of the included studies, which confirmed the reinfection status adopting less stringent definition criteria.[39] On the other side, the rate of reinfection may have been underestimated in most studies, as the existing monitoring systems could not detect all of the asymptomatic reinfections. Indeed, many subjects might not have seeked medical attention because of mild or even sub-clinical disease. To address this potential detection bias, a sensitivity analysis based upon the average number of PCR tests performed, taken as a proxy of health-seeking behaviour, may have increased the precision of our estimates.[73] Unfortunately, these data were not available. Notably, however, the pooled estimates of reinfection incidence were comparable in the general population and health care workers, who have often been subjects to continuous testing.[38] Second, individual-participant data were available for one study only[71]; thus, we could not perform stratified analyses based upon age, concomitant immunological conditions potentially affecting the risk of reinfection or, as above said, health-seeking behaviours.[11,76]

Acknowledging these caveats, the present meta-analysis showed that, among more than 15 million previously infected individuals, the overall rates of reinfection showed an increasing trend along with the emergence of Omicron variant, although the risk of severe or lethal COVID-19 was still very low, and vaccination may be effective in reducing the risk of reinfection. Further data from studies with even longer follow-up, carried out after the first months of the Omicron wave, and assessing whether the risk of severe or lethal COVID-19 will vary

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with the spread of new variants,[122] are inevitably needed to guide the future public health policies targeted to the large population of subjects who recovered from a SARS-CoV-2 infection.

AUTHOR CONTRIBUTIONS

All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission. MEF and LM conceived and designed the systematic review and were involved in all phases of the study. MEF, CAM and VB wrote the protocol. MEF and CAM designed and implemented the search strategy. CAM, VB and ER extracted the data. MEF and CAM performed the data analysis. MEF and LM wrote the manuscript, which was revised by CDV and PV. All authors were involved in the critical revision of the intellectual content of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

The data presented in this study are available upon reasonable request from the corresponding author.

ORCID

Cecilia Acuti Martellucci https://orcid.org/0000-0002-4308-2144
Valentina Baccolini https://orcid.org/0000-0002-7873-7817
Lamberto Manzoli https://orcid.org/0000-0002-8129-9344

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