Annals of Internal Medicine REVIEW

Risk for Reinfection After SARS-CoV-2: A Living, Rapid Review for American College of Physicians Practice Points on the Role of the Antibody Response in Conferring Immunity Following SARS-CoV-2 Infection

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Background: The strength and duration of immunity from infection with SARS-CoV-2 are important for public health planning and clinical practice.

Purpose: To synthesize evidence on protection against reinfection after SARS-CoV-2 infection.

Data Sources: MEDLINE (Ovid), the World Health Organization global literature database, ClinicalTrials.gov, COVID19reviews.org, and reference lists.

Study Selection: Longitudinal studies that compared the risk for reinfection after SARS-CoV-2 infection versus infection risk in individuals with no prior infection.

Data Extraction: Two investigators sequentially extracted study data and rated quality.

Data Synthesis: Across 18 eligible studies, reinfection risk ranged from 0% to 2.2%. In persons with recent SARS-CoV-2 infection compared with unvaccinated, previously uninfected individuals, 80% to 98% of symptomatic infections with wild-type or Alpha variants were prevented (high strength of evidence). In the meta-analysis, previous infection reduced risk for reinfection by 87% (95% CI, 84% to 90%), equaling 4.3 fewer infections per 100 persons in both the general population (risk difference, −0.043 [CI, −0.071 to −0.015]) and health care workers (risk difference, −0.043 [CI, −0.069 to −0.016]), and 26.6 fewer infections per 100 persons in care facilities (risk difference, −0.266 [CI, −0.449 to −0.083]). Protection remained above 80% for at least 7 months, but no study followed patients after the emergence of the Delta or Omicron variant. Results for the elderly were conflicting.

Limitation: Methods to ascertain and diagnose infections varied.

Conclusion: Before the emergence of the Delta and Omicron variants, persons with recent infection had strong protection against symptomatic reinfections for 7 months compared with unvaccinated, previously uninfected individuals. Protection in immunocompromised persons, racial and ethnic subgroups, and asymptomatic index case patients is unclear. The durability of protection in the setting of the Delta and Omicron variants is unknown.

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Despite progress in understanding the immunology of SARS-CoV-2, uncertainty remains about who is protected (1). Expert consensus has coalesced around the need for a "protective correlate"—a marker that could be used clinically and in public health settings to gauge an individual's protection against infection, either from vaccination or from immunity acquired by infection (2). Serum antibodies are the presumptive candidate for such a marker, but, at present, the link between antibody levels and protection is not well established.

Our living review aims to assess the potential value of antibody testing as a correlate of protection against infection. In our original review, we found that, in immunocompetent patients, seroconversion is an almost universal consequence of recent infection (1). For this reason, we expanded the scope of this update to include all studies that compare the risk for reinfection in adults with SARS-CoV-2 infection versus the risk for infection in adults without a prior infection, whether cohorts were assigned using a polymerase chain reaction (PCR) test, an antibody test, or a combination of both. We conducted meta-analyses to estimate protection from prior infection and to evaluate factors that may affect protection.

METHODS

Data Sources, Searches, and Study Selection

This update focuses on 2 of the key questions addressed in our living review (as modified to reflect the inclusion decision described in the previous paragraph). This review used rapid methods, primarily in the screening stages of the review. Details of the plan for updating each question and a summary of our methods are described in our protocol (3). A final update of all key questions in this review will be produced in early 2022. The PROSPERO record for our original review is CRD42020207098.

For this update, our search strategies focused on identifying longitudinal controlled studies of risk for reinfection published before 22 September 2021. We searched Ovid

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MEDLINE ALL, the World Health Organization global literature database, ClinicalTrials.gov, COVID19reviews.org, and reference lists of reviews (**Supplement** Item 1, available at Annals.org).

We included longitudinal studies that compared the risk for reinfection for individuals who had a documented infection with SARS-CoV-2 (the "positive" cohort) with the risk for new infection in those with no prior infection (the "negative" cohort) (4). Studies in the general population, health care workers, college students, and long-term care facilities were eligible, as were registry-based studies of patients with a specific condition. Studies without an uninfected comparison cohort were ineligible.

We used the Joanna Briggs Institute cohort study checklist (5) to screen for methodological limitations that would almost certainly invalidate the study findings (**Supplement Table 1**, available at Annals.org). Using this tool, we excluded 2 studies (6, 7) that used invalid criteria to allocate participants to the positive and negative cohorts or did not follow participants for an adequate length of time for potential reinfection.

Data Extraction and Quality Assessment

We extracted the following information by study: study design, population, data sources, study inclusion and exclusion criteria, age, race, gender, comorbid conditions, immunoassay type and brand (when applicable), definition of reinfection, follow-up test type and frequency of follow-up testing, primary infection symptom status, waiting period (if applicable), counts for all infection events and nonevents, and main findings.

For included studies, we identified potential biases in the following 4 areas: sampling, cohort assignment, case definition, and ascertainment of cases during follow-up. We abstracted information relevant to these methodological features from each study, recording variations in methods that could affect the observed effect. Considerations include the following.

Sampling. We assessed whether selection bias could arise from the data sources used to identify eligible persons. Selection bias could spuriously influence effect size if some groups were less likely to be recruited, if the cohorts were differentially enriched with persons who had unusual risk profiles, or if cohort inception was poorly delineated.

Cohort assignment. Within a given sample, the "positive" (infected) and "negative" (not infected) cohorts form the denominators for follow-up and analyses. To assess misclassification, we considered which tests were used (serologic, virologic, and clinical assessment), when they were done in relation to illness onset, and whether they were applied to all participants.

Outcome ascertainment. We assessed the methods used to ascertain new infections during follow-up, such as scheduled surveillance with PCR tests, clinical surveillance, or identification of cases in clinical care. In assessing ascertainment, we also considered whether surveillance for symptoms or access to medical evaluation differed among cohorts and (if applicable) adherence to scheduled testing. Bias could also occur if the follow-up period was too short.

Classification of potential cases of reinfection during the follow-up period. In most studies, reinfection was diagnosed when an individual had a positive result on a PCR test after a "waiting period" intended to give time for the initial episode to resolve clinically and virologically. Bias can occur if a positive PCR result due to persistent viral shedding is counted as a reinfection or if adjudication of reinfections is not equally rigorous in the positive and negative cohorts.

In each of these 4 categories, we identified methodological variations that are likely to be associated with higher or lower quality (risk of bias). In some cases, we did sensitivity analyses to assess how the overall protection estimate would change because of study-level factors. Such factors include study duration, the waiting period between cohort inception and the first reinfection assessment (8), median participant age, underlying prevalence (proxied by the proportion of new infections in the negative cohort), whether criteria for diagnosis of the initial infection would select only symptomatic infections, and whether serology, PCR, or both were used for cohort allocation.

In our original review and in each update, we report on studies identified by surveillance, particularly those that are not yet fully reported but may eventually be eligible for inclusion and those that are ineligible but can provide perspective on our results, such as uncontrolled studies of risk factors for reinfection in special populations or in the setting of emerging variants of concern. For this update, we summarize surveillance through 30 November 2021.

Data Synthesis and Strength of Evidence

The outcomes of interest were the effects of previous infection on the risk for symptomatic reinfection, risk for any reinfection, severity of reinfection, and duration of protection. These outcome metrics, termed "protection," are analogous to the end points used in studies of vaccine efficacy (9). Here, however, incident infections detected during the follow-up period in the positive cohort are reinfections, and those in the negative cohort are primary infections. The category "any reinfection" includes asymptomatic persons in whom virus has been detected.

Although many studies reported hazard ratios or relative rates of infection per person-time (often adjusted for various factors), our meta-analysis used absolute counts of events in both groups to obtain a relative risk estimate. We subsequently found a high degree of concordance between our calculated risk estimates and the rates reported in studies.

The primary analyses focused on the magnitude of protection against reinfection, quantified as the proportion or percentage of prevented infections. Each included study provided counts of reinfected individuals from the positive cohort and newly infected individuals from the negative cohort, which together yield an estimate of protection from reinfection—the difference in the proportion of incident infections between the negative and positive cohorts relative to the proportion observed in the negative cohort. We pooled these estimates via meta-analysis, both unstratified and stratified by population composition (general population, health care workers only, young adults only, or elderly persons only), to obtain combined effect estimates and corresponding 95% CIs. We used a continuity correction of 0.5 for 2 studies that reported 0 reinfections; this approach

imparts a small but acceptable null bias to the meta-analysis, leading to conservative inference. We generated uncorrected estimates for comparison. The empirical Bayes random-effects meta-analysis model was chosen for its robustness properties and low bias in small-sample settings (10, 11). Study heterogeneity within strata was assessed using the I^2 statistic (12). We assessed heterogeneity across strata using the Cochran Q_b statistic (13). Analysis was done using Stata, version 16.1 (StataCorp). (**Supplement** Item 2, available at Annals.org, provides further details.)

For some factors, including demographic variables, symptom status, health behaviors, vaccination, and variants, we could not examine their quantitative impact on effect sizes within a meta-analytic framework because of inconsistent reporting among studies. We abstracted information from study-specific sensitivity analyses and regression analyses when available, and we summarize these findings qualitatively.

Study-level factors that might influence estimates of protection include study duration, waiting interval between reinfection assessments, median participant age, underlying prevalence (proxied by the proportion of new infections in the negative cohort), and rigor in assessing positivity of infection (for example, whether asymptomatic infections were identified by surveillance and whether validation testing was done). We assessed these visually for relationships with effect sizes using scatter plots and nonparametric mean-smoothing of trends. We used meta-regression techniques to estimate R^2 values to examine each potential factor that may explain between-study heterogeneity. We also produced a L'Abbé and funnel plot as visual assessments of bias and sensitivity to study characteristics. The Harbord test was used to evaluate the evidence for asymmetry in the funnel plot (14).

We graded the strength of evidence to describe our confidence in effect estimates as high, moderate, low, or insufficient. The assessment is based on our analysis of the study limitations, directness, consistency, precision, dose-response, plausible confounding, and strength of association (15).

Role of the Funding Source

This work is based on a living rapid review done for the Agency for Healthcare Research and Quality. The funding source assigned the topic and contributed to the development of the review aims and scope but was not involved in data collection, analysis, manuscript preparation, or submission.

RESULTS

The updated literature search identified 635 citations (**Appendix Figure**, available at Annals.org). Eighteen eligible cohort studies provided estimates of the risk for reinfection in previously infected relative to uninfected persons. Two preprints (16, 17) were tentatively included in the review but lacked the data needed for our meta-analysis. We discuss 6 additional studies not included in the meta-analysis to provide additional context on how population-level factors, variants of concern, and vaccination may influence risk for reinfection (18–23).

Overview of Eligible Studies

All of the studies were initiated in 2020 in the United States (16, 24–26), Europe (4, 27–37), or the Middle East (17, 38) and were completed before the emergence of the highly transmissible Delta and Omicron variants and before vaccine rollouts began. Nine studies used antibody test results to assign patients to the "positive" and "negative" cohorts (16, 25, 27, 29, 30, 32, 36–38), 3 used a combination of antibody test results and PCR (4, 28, 35), and 6 used PCR alone (**Supplement Table 2**, available at Annals.org) (17, 24–26, 31, 33). Study quality (risk of bias) ranged from moderate to high (**Supplement Table 3**, available at Annals.org).

All included studies found that reinfection was an uncommon event (range, 0% to 2.2%). The highest reinfection proportion was in a college student population, where the risk for infection in the control group was also very high (12.1%) (24). In settings with high proportions of control group infection (≥10%), reinfection risks were also relatively high (approximately 1% to 2%). When control group incidence of infection was below 5%, reinfection incidence was relatively low (about 0.7% at most).

Risk for Reinfection

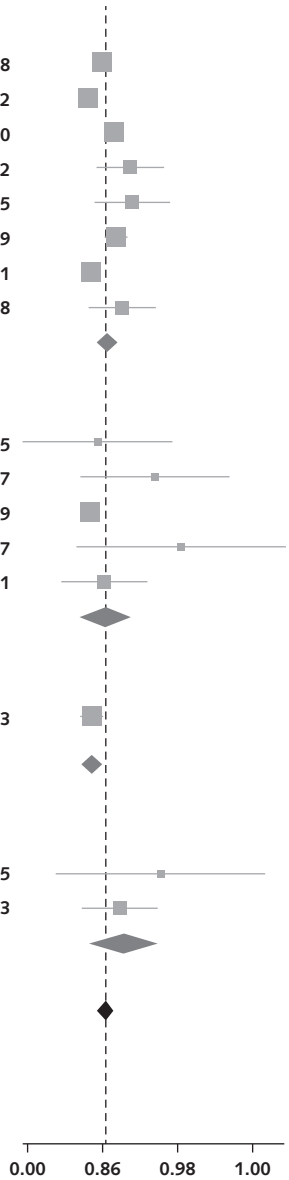
In our meta-analysis, prior infection reduced the risk for symptomatic infection by 87% (95% CI, 84% to 90%) compared with no prior infection (**Figure 1**). The estimate was similar in studies that used serology alone to identify infected persons (risk reduction among 8 studies, 89% [CI, 87% to 91%]). The protection for health care workers and general populations was similar (87% and 88%, respectively). The risk differences were −0.043 (CI, −0.071 to −0.015) (4.3 infections per 100 individuals) in the general population studies, −0.043 (CI, −0.069 to −0.016) in health care workers, −0.099 (CI, −0.107 to −0.090) in college students, and −0.266 (CI, −0.449 to −0.083) in care facilities. Repeating the analysis without the use of continuity correction of 0 counts resulted in numerical differences to the meta-analyzed protection estimates of 0.01 or less.

Between-study differences in effect size relative to total variance were substantial (I^2 = ∼85%), but this value should be interpreted in the context of high precision resulting from large sample sizes and low overall counts of reinfection. The effect sizes all fall within a narrow and high range, varying between 80% and about 100% protection, and are always indicative of very high protection. The L'Abbé plot shows no indication of systematic deviation from the meta-effect, no outlying studies, and no study suggesting a qualitatively different effect size (**Figure 2**). The Harbord test did not indicate that small-study effects or publication bias was present (P = 0.22).

Twelve studies reported the proportion of asymptomatic reinfections (4, 16, 24, 26, 27, 29, 31, 32, 35–38). Across studies, prior infection clearly protected against asymptomatic reinfection, but whether this protection is as strong as that against symptomatic reinfection is unclear. Follow-up methods were not always adequate to accurately detect symptoms that were present at the time of, or in the weeks after, a positive result on a PCR test. In the SIREN (SARS-CoV-2 Immunity and Reinfection Evaluation)

Figure 1. Risk for reinfection from SARS-CoV-2: meta-analysis.

Study, Year (Reference) (Location)	Positive		Negative		Protection Estimate (95% CI)*	Weight, %
	New Infection	No New Infection	New Infection	No New Infection		
General population						
Abu-Raddad et al, 2021 (38) (Qatar)	129	42 915	3185	146 738	0.86 (0.83 to 0.88)	11.54
Hansen et al, 2021 (34) (Denmark)	72	10 996	16 819	497 452	0.80 (0.75 to 0.84)	10.98
Harvey et al, 2021 (25) (US)	1136	377 470	86 303	790 470	0.90 (0.89 to 0.91)	12.31
Leidi et al, 2021 (36) (Switzerland)	5	493	154	842	0.94 (0.84 to 0.97)	4.26
Manica et al, 2021 (32) (Italy)	4	1398	217	4455	0.94 (0.84 to 0.98)	3.67
Pilz et al, 2021 (33) (Austria)	40	14 800	253 581	8 632 059	0.91 (0.87 to 0.93)	10.05
Sheehan et al, 2021 (26) (US)	62	8783	5449	136 031	0.82 (0.77 to 0.86)	10.77
Vitale et al, 2021 (31) (Italy)	5	1574	528	12 968	0.92 (0.81 to 0.97)	4.29
Heterogeneity: $T^2 = 0.12$; $I^2 = 90.04\%$; $H^2 = 10.04$					0.88 (0.84 to 0.91)	
Health care workers						
Abo-Leyah et al, 2021 (37) (Scotland)	1	299	38	1725	0.85 (–0.12 to 0.98)	1.17
Gallais et al, 2021 (35) (France)	1	392	69	847	0.97 (0.76 to 1.00)	1.18
Hall et al, 2021 (4) (UK)	155	8123	1704	15 679	0.81 (0.78 to 0.84)	11.66
Hanrath et al, 2021 (28) (UK)	0	1038	290	9847	0.98 (0.73 to 1.00)	0.63
Lumley et al, 2021 (27) (UK)	3	1174	223	11 141	0.87 (0.59 to 0.96)	2.98
Heterogeneity: $T^2 = 0.23$; $I^2 = 37.50\%$; $H^2 = 1.60$					0.87 (0.75 to 0.94)	
College students						
Rennert and McMahan, 2021 (24) (US); median age, 20 y	44	1977	1697	12 383	0.82 (0.76 to 0.87)	10.23
Heterogeneity: NA					0.82 (0.76 to 0.87)	
Long-term care facility residents						
Jeffery-Smith et al, 2021 (30) (UK); median age, 85 y	0	44	15	25	0.97 (0.52 to 1.00)	0.62
Krutikov et al, 2021 (29) (UK); median age, 86 y	4	222	93	363	0.91 (0.77 to 0.97)	3.66
Heterogeneity: $T^2 = 0.00$; $I^2 = 0.00\%$; $H^2 = 1.00$					0.92 (0.80 to 0.97)	
Overall					0.87 (0.84 to 0.90)	
Heterogeneity: $T^2 = 0.11$; $I^2 = 85.52\%$; $H^2 = 6.91$						
Test of $\theta_i = \theta_j$: $Q(15) = 118.23$; $P < 0.001$						
Test of group differences: $Q_b(3) = 5.63$; $P = 0.131$						

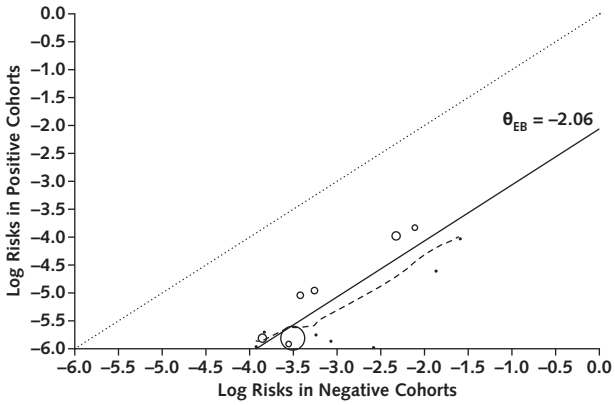


Positive indicates the group within a study where participants were polymerase chain reaction (PCR)–positive or seropositive at baseline. Negative indicates those within a study who were PCR-negative and/or seronegative at baseline. Estimates of relative risk (RR) ranged from 0.02 to 0.20; on the *x*-axis, 0.00 represents no effect, whereas 1.00 represents maximum protection. Study weighting and effect averaging were done using the empirical Bayes random-effects model. Continuity correction was used for counts of 0 (0.5 added to all counts). Studies were sorted alphabetically within categories by study author. Efficacy (1 − RR) can be interpreted as the proportion or percentage of infections that are prevented by the exposure. Median follow-up time was 8 mo (range, 4–13 mo). NA = not applicable; UK = United Kingdom; US = United States.* This plot shows estimates of protection, defined as 1 − RR.

study, which used the best methods, antibody-positive health care workers in England had lower risk for both symptomatic and asymptomatic infections than antibody-negative workers, but the degree of protection was different (93% lower risk for symptomatic reinfection vs. 52% lower risk for asymptomatic reinfection) (4). In contrast, in a retrospective cohort study based in the United States (26), protection was 84.5% for symptomatic infections versus 81.8% when asymptomatic infections were included (26).

Because prior infection prevented at least 80% of symptomatic reinfections, severe reinfection is a rare event (27, 31, 32, 36). In the largest series, 18 of 31 patients who had symptomatic reinfection were hospitalized within 30 days of diagnosis, but only 5 had COVID-19 symptoms at the time of hospitalization, and none required intensive

Figure 2. L'Abbé plot showing no indication of systematic deviation from the meta-effect, no outlying studies, and no study suggesting a qualitatively different effect size.



Point sizes are proportional to study precision.

care (26). In the other relatively large series, a study from Austria, 5 cases were described as moderate and 27 as mild (33).

Eight studies (26, 29, 33–38) that included more than 9 million participants in total (80 206 exposed and 9 696 466 control) examined whether the risk for reinfection varies over time (**Supplement Table 4**, available at Annals.org). All 8 found no evidence of waning protection during 6 to 13 months of follow-up. Further, 2 of the studies noted that the protection against reinfection may have increased over time (26, 38). There was no relationship between the length of the waiting interval and the reported duration of protection.

We analyzed 6 additional factors that might affect reinfection risk, but they varied among studies because best practices for studying SARS-CoV-2 reinfection are not established (**Supplement Table 5**, available at Annals.org). Study duration, waiting interval, median age of participants, underlying prevalence, inclusion of asymptomatic people in the positive cohort, and type of test used to allocate people to the 2 cohorts did not seem to have a strong relationship with the estimated effect size (**Figure 3**). R^2 values for effect size were low for other potential sources of variation in those estimates: cohort allocation criterion (13.2%;$Q_B = 2.85$;$P = 0.241$), median age of participants (6.7%), infection proportion in negative group (<0.1%), waiting period (<0.1%), total follow-up (<0.1%), and symptom status at baseline (<0.1%) (**Figure 3**). Protection against reinfection was slightly lower in 2 studies that used the most reliable methods to characterize reinfections (0.81 and 0.80 vs. 0.86 overall), but other factors could account for this difference (4, 34).

Some studies reported their own sensitivity analyses or mathematical modeling of the effect of these methodological factors (4, 16, 27, 29, 34, 36). Overall, protection against reinfection was not correlated with the asymptomatic testing rate, cohort assignment criteria, or method for assessment of infection during the follow-up period (4, 29, 36).

Population Factors Affecting the Risk for Reinfection

We saw no gender differences in protection against reinfection.

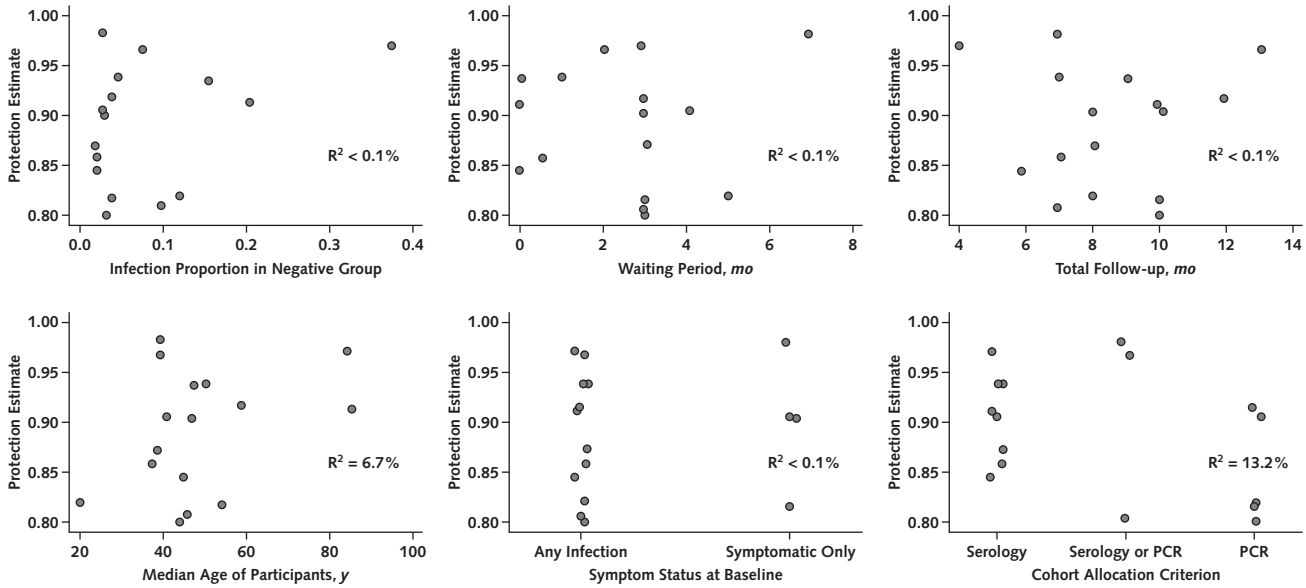
Studies offered no useful information about the effect of race and ethnicity on protection from reinfection. Although some studies adjusted for immunosuppression or other comorbid conditions, none of our included studies reported on the incidence of reinfections in immunocompromised persons or other comorbidity subgroups. A study that was ineligible for inclusion in our meta-analysis investigated characteristics of 23 suspected reinfections in electronic health records and found that 83% of presumed reinfections were in those with immunocompromised conditions (19).

Age

Results for age are conflicting. In the meta-analysis, there was no compelling evidence that cohort composition (that is, whether mostly young or mostly old) influenced the degree of protection afforded by prior infection ($Q_b(3) = 5.63$;$P = 0.131$). Across studies, estimates for young (median age, ~20 years) and older (median age, ~85 years) adults were also qualitatively similar (82% for young vs. 92% for old), although for both estimates there were few studies and sample sizes for the available studies were not large. A large, population-based study from Denmark found no difference by sex in estimates of protection against repeated infection but a striking difference in protection against repeated infection in the elderly (34). Among persons aged 0 to 64 years, estimated protection was 80% to 82%, whereas in those older than 65 years, it was 47.1% (CI, 24.7% to 62.8%). Among those older than 65 years who had a previous infection, the infection rate was 8.01 per 100 000 person-days of follow-up, compared with 4.25 to 5.92 per 100 000 person-days in the younger age groups. However, in the negative control cohort, the infection rate in the elderly was much lower than in the younger groups (16.92 vs. 27.42 to 38.13 per 100 000 person-days). The low infection rate in the elderly control participants relative to other control participants could be related to public health approaches to opening up after lockdown (perhaps selective isolation of more vulnerable groups), but this explanation does not account for the relatively high rate of reinfection in the positive cohort. Another study in Switzerland found a higher risk for reinfection among those older than 60 years compared with younger persons (>60 years old: hazard ratio, 0.44 [CI, 0.14 to 1.4]; <60 years old: hazard ratio, 0.05 [CI, 0.01 to 0.20]) (36). A study in Israel compared protection among age groups and found a slight decrease in protection for those older than 80 years (overall protection: 94.8% [CI, 94.4% to 95.1%]; over-80 protection: 91.4% [CI, 85.5% to 94.9%]) (17).

These findings on age conflict with results from studies of presumably frail elderly patients in long-term care facilities, where rates of infection in the control groups were far higher and rates of reinfection in the positive groups were as low as, or lower than, those in other populations (**Figure 1**) (29, 30).

Figure 3. Scatter plots conveying the influence of various factors on the protective effect of prior SARS-CoV-2 infection.



The factors are infection proportion in the negative group, waiting period (in months), total follow-up (in months), median age of participants (in years), symptom status at baseline (any infections vs. symptomatic only), and cohort allocation criterion (serology, serology or PCR, and PCR). In all plots, the *y*-axis is efficacy (1 − relative risk), which can be interpreted as the proportion or percentage of infections that are prevented by the exposure. Points have been jittered slightly for visual display. PCR = polymerase chain reaction.

Symptom Severity of Initial Infection

Assessments of the relationship between the severity of the initial infection and protection against reinfection were limited. In most studies, initial infections were not detected until antibodies had formed and information about symptoms was either unrecorded or subject to recall bias. Hospitalization during the initial infection could also be a proxy for severity, but in most studies the number of hospitalized patients was too small for analysis. Comparing studies that used sampling methods that detected people with no or mild symptoms (27, 31, 35–37) with those that recruited only symptomatic people (25, 26, 28, 33) did not show a clear relationship between recruitment method and protection against reinfection. A recently published cohort study found that mild COVID-19 was associated with protection against reinfection and generally supports our conclusions, although no reinfections were observed and the sample was relatively small (23).

Variants of Concern

The B.1.1.7 (Alpha) variant was studied in 4 of the studies meta-analyzed. Although evidence is sparse, there is no indication of increased risk for reinfection for this variant (4). Of 2 additional studies that reported on the Alpha variant, neither indicated an effect of the variant on reinfection (17, 29). In an ecologic study among 36 920 U.K. users of the COVID-19 Symptom Study app, the rate of "possible reinfection" was 0.7 and did not change after the Alpha variant became prevalent (18).

Data on reinfection risk in the setting of the B.1.617.2 (Delta) variant are sparse and are still developing, but a preprint from Israel, surveillance data from Kentucky, and an outbreak investigation in Texas recently indicated that immunity acquired by infection provided substantial protection after the Delta variant became predominant (20–22, 39). Preliminary data on Omicron raise the possibility that protection against symptomatic (but not serious) reinfection may be lower than that observed in the studies we reviewed (39).

Vaccination

Vaccination during follow-up could bias estimates of protection, particularly if vaccination rates differ between the positive and negative cohorts. In 5 of the studies included in our meta-analysis, the follow-up period traversed the first vaccine rollout. However, most were nearly completed at the time of the vaccine rollout, and none had sufficient data to assess how vaccination influenced the estimate of protection (4, 17, 29, 35). For example, in the SIREN study, which had the largest subgroup of vaccinated participants (n = 13 401), only 0.4% of the study's person-time of follow-up included participants who would be considered to have protection as the result of vaccination.

Discussion

Immunity acquired by previous infection reduced the risk for symptomatic infections from wild-type and Alpha variants by 84% to 90% for at least 7 months (high strength of evidence; see **Supplement Table 6**, available at Annals.org). Longer follow-up and the emergence of new variants may reduce the protective effect of prior infection.

Protection against asymptomatic infection is also substantial, but the evidence is inherently weaker. Study methods and knowledge of SARS-CoV-2 are not sufficiently developed to distinguish which people with "asymptomatic infections" are "presymptomatic" and which are "colonized" (40). Also, many of the studies used surveillance methods that were not adequate for detection of all asymptomatic infections. Nevertheless, the protection estimates for asymptomatic and symptomatic infection were similar, and the result was not sensitive to these and other potential methodological weaknesses.

Antibody testing has been proposed as a potential marker or correlate of protection against infection. In our analysis, seroconversion or a positive antibody test result obtained soon after the onset of infection was strongly associated with protection against reinfection. This finding applies only to people who have had a negative antibody test result (for example, for surveillance in a study setting) and convert to a positive one, and to people who have never been infected and develop antibodies during or immediately after a wave. In these situations, the prognostic value of antibody testing was identical to that of the more widely used PCR test, which has additional value because it tells us about not only reinfection risk but also transmission risk.

A key limitation of this literature is that it does not apply to antibody testing in people and clinical settings where the timing of testing in relation to infection is unknown. Ongoing research may provide better information about the utility of antibody testing in actual practice. Specific gaps in current evidence are whether failure to develop antibodies, antibody titers or levels, the loss of antibodies, and the antibody target (which spike proteins it binds to) provide useful information about reinfection risk. A particularly important gap is how much protection infection confers in immunocompromised people who do or do not develop antibodies (or high titers of antibodies) after infection. Until ongoing research addresses these gaps, our results shed little light on the role of antibody testing in actual practice.

The studies included in our analysis had important weaknesses. With respect to cohort composition, no feasible study design can ensure that—within the target population—all infected individuals, regardless of symptoms, are identified and allocated appropriately, or that exclusions of individuals who lacked required tests for allocation would not bias the results. Most studies did not do protocolized follow-up testing designed to capture all incident infections and reinfections.

None of the studies could account directly for the behavioral and occupational variables that affect infection risk and might be unevenly distributed between the positive and negative cohorts. It is also possible that a group of people at higher reinfection risk—perhaps because they engaged in much riskier behavior than most people—were less likely to be recruited—perhaps because they avoided the testing that would make them eligible and countable in these studies. Although possible, this and other imaginable scenarios seem unlikely and would require that all of the studies had large, undetected confounding. Despite evidence of heterogeneity, our results were consistent across a wide range of methodological diversity, increasing our confidence in the main findings and in the robustness of the results of the antibody-only studies.

Our results do not in any way argue for infection rather than vaccination as a means of obtaining individual or herd immunity. Follow-up studies of protection against reinfection do not include people who died of COVID-19 and do not consider that death from COVID-19 far outweighs any potential advantage conferred by immunity acquired by infection. Nor do our results provide evidence that immunity acquired by infection is longer-lasting or in other ways superior to immunity acquired by vaccination.

Despite the noted limitations, our findings provide strong evidence that the immunity afforded by recent infection conferred substantial protection against symptomatic reinfection with the wild-type or Alpha variant for at least 7 months. The evidence we have to date supports that recent infection is a reliable marker of protection against symptomatic reinfection with the wild-type or Alpha variant of SARS-CoV-2.

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References

1. **Arkhipova-Jenkins I, Helfand M, Armstrong C, et al.** Antibody response after SARS-CoV-2 infection and implications for immunity. A rapid living review. Ann Intern Med. 2021;174:811-821. [PMID: 33721517] doi:10.7326/M20-7547

2. **Krammer F.** A correlate of protection for SARS-CoV-2 vaccines is urgently needed. Nat Med. 2021;27:1147-1148. [PMID: 34239135] doi:10.1038/s41591-021-01432-4

3. **Agency for Healthcare Research and Quality.** Immunity After COVID-19. 10 September 2020. Accessed at https://effectivehealthcare.ahrq.gov/products/immunity-after-covid/protocol on 11 June 2021.
4. **Hall VJ, Foulkes S, Charlett A, et al; SIREN Study Group.** SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: a large, multicentre, prospective cohort study (SIREN). Lancet. 2021;397:1459-1469. [PMID: 33844963] doi:10.1016/S0140-6736(21)00675-9
5. **Johanna Briggs Institute.** Critical Appraisal Checklist for Cohort Studies. 2017.
6. **Prete CA, Buss LF, Abrahim CMM, et al.** Reinfection by the SARS-CoV-2 P.1 variant in blood donors in Manaus, Brazil. medRxiv. Preprint posted online 12 May 2021. doi:10.1101/2021.05.10.21256644
7. **Letizia AG, Ge Y, Vangeti S, et al.** SARS-CoV-2 seropositivity and subsequent infection risk in healthy young adults: a prospective cohort study. Lancet Respir Med. 2021;9:712-720. [PMID: 33865504] doi:10.1016/S2213-2600(21)00158-2
8. **Qureshi AI, Baskett WI, Huang W, et al.** Re-infection with SARS-CoV-2 in patients undergoing serial laboratory testing. Clin Infect Dis. 2021. [PMID: 33895814] doi:10.1093/cid/ciab345
9. **Hodgson SH, Mansatta K, Mallett G, et al.** What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2. Lancet Infect Dis. 2021;21:e26-e35. [PMID: 33125914] doi:10.1016/S1473-3099(20)30773-8
10. **Berkey CS, Hoaglin DC, Mosteller F, et al.** A random-effects regression model for meta-analysis. Stat Med. 1995;14:395-411. [PMID: 7746979]
11. **Veroniki AA, Jackson D, Viechtbauer W, et al.** Methods to estimate the between-study variance and its uncertainty in meta-analysis. Res Synth Methods. 2016;7:55-79. [PMID: 26332144] doi:10.1002/jrsm.1164
12. **Higgins JP, Thompson SG, Deeks JJ, et al.** Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-60. [PMID: 12958120]
13. **Borenstein M, Hedges LV, Higgins JPT, et al.** Introduction to Meta-Analysis. J Wiley; 2009.
14. **Harbord RM, Egger M, Sterne JA.** A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. Stat Med. 2006;25:3443-57. [PMID: 16345038]
15. **Berkman ND, Lohr KN, Ansari M, et al.** Grading the strength of a body of evidence when assessing health care interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: an update. In: Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Agency for Healthcare Research and Quality; 2013.
16. **Finch E, Lowe R, Fischinger S, et al.** SARS-CoV-2 infection and reinfection in a seroepidemiological workplace cohort in the United States. medRxiv. Preprint posted online 6 May 2021. doi:10.1101/2021.05.04.21256609
17. **Goldberg Y, Mandel M, Woodbridge Y, et al.** Protection of previous SARS-CoV-2 infection is similar to that of BNT162b2 vaccine protection: a three-month nationwide experience from Israel. medRxiv. Preprint posted online 24 April 2021. doi:10.1101/2021.04.20.21255670
18. **Graham MS, Sudre CH, May A, et al; COVID-19 Genomics UK (COG-UK) Consortium.** Changes in symptomatology, reinfection, and transmissibility associated with the SARS-CoV-2 variant B.1.1.7: an ecological study. Lancet Public Health. 2021;6:e335-e345. [PMID: 33857453] doi:10.1016/S2468-2667(21)00055-4
19. **Dong X, Zhou Y, Shu X, et al.** Comprehensive characterization of COVID-19 patients with repeatedly positive SARS-CoV-2 tests using a large US electronic health record database. medRxiv. Preprint posted online 13 June 2021. doi:10.1101/2021.06.10.21256915
20. **Cavanaugh AM, Spicer KB, Thoroughman D, et al.** Reduced risk of reinfection with SARS-CoV-2 after COVID-19 vaccination — Kentucky, May–June 2021. MMWR Morb Mortal Wkly Rep. 2021;70:1081-1083. [PMID: 34383732] doi:10.15585/mmwr.mm7032e1
21. **Gazit S, Shlezinger R, Perez G, et al.** Comparing SARS-CoV-2 natural immunity to vaccine-induced immunity: reinfections versus breakthrough infections. medRxiv. Preprint posted online 25 August 2021. doi:10.1101/2021.08.24.21262415
22. **Hagan LM, McCormick DW, Lee C, et al.** Outbreak of SARS-CoV-2 B.1.617.2 (Delta) variant infections among incarcerated persons in a federal prison — Texas, July–August 2021. MMWR Morb Mortal Wkly Rep. 2021;70:1349-1354. [PMID: 34555009] doi:10.15585/mmwr.mm7038e3
23. **Schuler CF 4th, Gherasim C, O'Shea K, et al.** Mild SARS-CoV-2 illness is not associated with reinfections and provides persistent spike, nucleocapsid, and virus-neutralizing antibodies. Microbiol Spectr. 2021;9:e0008721. [PMID: 34468184] doi:10.1128/Spectrum.00087-21
24. **Rennert L, McMahan C.** Risk of SARS-CoV-2 reinfection in a university student population. Clin Infect Dis. 2021. [PMID: 33993225] doi:10.1093/cid/ciab454
25. **Harvey RA, Rassen JA, Kabelac CA, et al.** Association of SARS-CoV-2 seropositive antibody test with risk of future infection. JAMA Intern Med. 2021;181:672-679. [PMID: 33625463] doi:10.1001/jamainternmed.2021.0366
26. **Sheehan MM, Reddy AJ, Rothberg MB.** Reinfection rates among patients who previously tested positive for coronavirus disease 2019: a retrospective cohort study. Clin Infect Dis. 2021;73:1882-1886. [PMID: 33718968] doi:10.1093/cid/ciab234
27. **Lumley SF, O'Donnell D, Stoesser NE, et al; Oxford University Hospitals Staff Testing Group.** Antibody status and incidence of SARS-CoV-2 infection in health care workers. N Engl J Med. 2021;384:533-540. [PMID: 33369366] doi:10.1056/NEJMoa2034545
28. **Hanrath AT, Payne BAI, Duncan CJA.** Prior SARS-CoV-2 infection is associated with protection against symptomatic reinfection [Letter]. J Infect. 2021;82:e29-e30. [PMID: 33373652] doi:10.1016/j.jinf.2020.12.023
29. **Krutikov M, Palmer T, Tut G, et al.** Incidence of SARS-CoV-2 infection according to baseline antibody status in staff and residents of 100 long-term care facilities (VIVALDI): a prospective cohort study. Lancet Healthy Longev. 2021;2:e362-e370. [PMID: 34104901] doi:10.1016/S2666-7568(21)00093-3
30. **Jeffery-Smith A, Iyanger N, Williams SV, et al.** Antibodies to SARS-CoV-2 protect against re-infection during outbreaks in care homes, September and October 2020. Euro Surveill. 2021;26. [PMID: 33541486] doi:10.2807/1560-7917.ES.2021.26.5.2100092
31. **Vitale J, Mumoli N, Clerici P, et al.** Assessment of SARS-CoV-2 reinfection 1 year after primary infection in a population in Lombardy, Italy [Letter]. JAMA Intern Med. 2021;181:1407-1408. [PMID: 34048531] doi:10.1001/jamainternmed.2021.2959
32. **Manica M, Pancheri S, Poletti P, et al.** The risk of symptomatic infection during a second COVID-19 wave, in SARS-CoV-2 seropositive individuals. Clin Infect Dis. 2021. [PMID: 34134145] doi:10.1093/cid/ciab556
33. **Pilz S, Chakeri A, Ioannidis JP, et al.** SARS-CoV-2 re-infection risk in Austria. Eur J Clin Invest. 2021;51:e13520. [PMID: 33583018] doi:10.1111/eci.13520
34. **Hansen CH, Michlmayr D, Gubbels SM, et al.** Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. Lancet. 2021;397:1204-1212. [PMID: 33743221] doi:10.1016/S0140-6736(21)00575-4
35. **Gallais F, Gantner P, Bruel T, et al.** Anti-SARS-CoV-2 antibodies persist for up to 13 months and reduce risk of reinfection. medRxiv. Preprint posted online 17 May 2021. doi:10.1101/2021.05.07.21256823
36. **Leidi A, Koegler F, Dumont R, et al; SEROCoV-POP study group.** Risk of reinfection after seroconversion to SARS-CoV-2: a population-based propensity-score matched cohort study. Clin Infect Dis. 2021. [PMID: 34043763] doi:10.1093/cid/ciab495

37. **Abo-Leyah H, Gallant S, Cassidy D, et al.** The protective effect of SARS-CoV-2 antibodies in Scottish healthcare workers. ERJ Open Res. 2021;7. [PMID: 34104643] doi:10.1183/23120541.00080-2021

38. **Abu-Raddad LJ, Chemaitelly H, Coyle P, et al.** SARS-CoV-2 antibody-positivity protects against reinfection for at least seven months with 95% efficacy. EClinicalMedicine. 2021;35:100861. [PMID: 33937733] doi:10.1016/j.eclinm.2021.100861

39. **Pulliam JRC, van Schalkwyk C, Govender N, et al.** Increased risk of SARS-CoV-2 reinfection associated with emergence of the Omicron variant in South Africa. medRxiv. Preprint posted online 2 December 2021. doi:10.1101/2021.11.11.21266068

40. **Buitrago-Garcia D, Egli-Gany D, Counotte MJ, et al.** Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: a living systematic review and meta-analysis. PLoS Med. 2020;17:e1003346. [PMID: 32960881] doi:10.1371/journal.pmed.1003346

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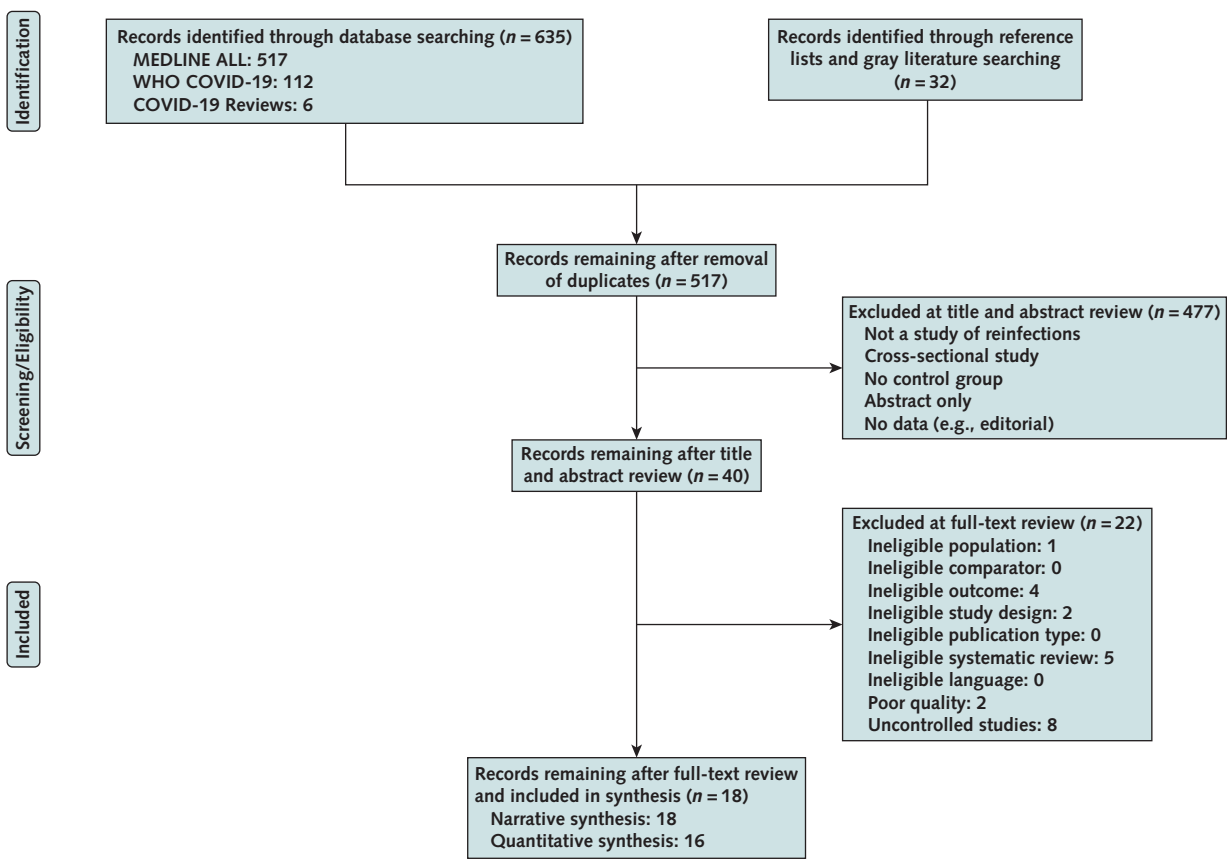
Appendix Figure. Evidence search and selection.



WHO = World Health Organization.