Rapid Evidence Product

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Risk of Reinfection From SARS-CoV-2 – An Update of an Antibody Response Following SARS-CoV-2 Infection and Implications for Immunity: A Living Rapid Review

Questions for This Update

Key Question 2. What is the risk of reinfection from SARS-CoV-2 among adults with prior SARS-CoV-2 infection?

a. Does the risk of reinfection vary by patient characteristics (e.g., age, sex, race/ethnicity, and comorbidities), severity of the initial infection, initial antibody levels, SARS-CoV-2 variants, or vaccination status?
b. Is there a threshold level of detectable anti–SARS-CoV-2 antibodies necessary to confer immunity acquired by infection, and if so, does this threshold vary by patient characteristics (for example, age, sex, race/ethnicity, and comorbidities)?

Key Question 3. What is the duration of protection against reinfection among adults with prior SARS-CoV-2 infection?

a. Does the duration of protection vary by patient characteristics (e.g., age, sex, race/ethnicity, and comorbidities), severity of the initial infection, initial antibody levels, SARS-CoV-2 variants, or case identification method (e.g., surveillance, symptomatic testing only)?

What Did We Know?

In March 2021, we published a living rapid review that described the humoral (antibody) response after infection with the SARS-CoV-2 virus, but found little information on the duration of the response beyond 6 months or on antibody formation in asymptomatic patients or in those who are immunocompromised. At that time, only one study had measured the effect of immunity acquired by previous infection on the risk of reinfection and the relationship between features of the antibody response and the risk of reinfection.

What Is New?

Updated: 12/22/2021
Search current as of 11/30/2021

This update adds 18 cohort studies that compared the risk of reinfection in adults with prior SARS-CoV-2 infection to the risk of infection in adults without a prior infection. Our main findings are that:

- Prior infection with Alpha variant or wild-type SARS-CoV-2 reduced the risk of another infection by 80 to 97 percent (pooled estimate 87%, 95% confidence interval 84–90%) compared with

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uninfected individuals in studies with a median followup 8 months (range 4–13 months). Protection remains above 80 percent for at least 7 months. (High strength of evidence [SoE] for effect size and duration up to 7 months, low SoE for protection from 7–10 months, and insufficient evidence for longer periods.)

- There are also several gaps in the evidence (all low or insufficient SoE):
  - Data on reinfection risk in people who have asymptomatic primary infections is sparse and conflicting. Protection may be lower than for symptomatic primary infections.
  - Results for reinfection in the elderly were mixed. Overall, it seems more likely that protection for elderly individuals and younger adults is similar, but data are conflicting and additional evidence is needed.
  - There are no data about differences in protection from prior infection in immunocompromised individuals and people with other comorbidities, or among different race/ethnicity groups.
  - The studies were performed before vaccines became available. Additional data are needed to determine how vaccination increases the magnitude or duration of protection after infection, especially in people with asymptomatic or mildly symptomatic primary infections, elderly individuals, and people who are immunocompromised.
  - While evidence about the Alpha variant is reassuring, there are no data on reinfection risk with the Delta variant or other variants of concern.

Background and Purpose

The strength and expected duration of immunity, both from infection and from vaccination, are important for public health planning and clinical practice. Understanding the nature and duration of immunity acquired by previous infection to SARS-CoV-2 is a critical component of modeling the course of the pandemic and formulating public health policy.[1, 2] Better data on the risk for reinfection and on the relationship of antibody status to protection from reinfection can help guide practice policies regarding antibody testing and vaccination timing, particularly in immunocompromised patients and those with other comorbidities who have a higher risk of worse outcomes with COVID-19.

Between March and August 2021, several epidemiological studies have been published comparing infection risks between previously infected and uninfected adults, permitting analysis of protection against reinfection from SARS-CoV-2 in the general population and of factors that might be associated with symptomatic reinfection. The findings from this review will be used by the American College of Physicians (ACP) to update clinical practice pointers on the topic.[3]

Methods

The protocol for this living rapid review was registered at PROSPERO (CRD42020207098), and posted to the Agency for Healthcare Research and Quality (AHRQ) Effective Healthcare Site.[4, 5] Detailed methods can be found in Appendix A.

Data Sources, Searches, and Planned Updates

For this update, we modified our search strategies to focus on identifying longitudinal controlled studies of risk of reinfection. To find systematic reviews, we searched www.covid19reviews.org, a website that catalogs results of bibliographic database searches for systematic reviews related to SARS-CoV-2. To find relevant research studies, we searched (1) Ovid MEDLINE ALL, WHO COVID, and ClinicalTrials.gov roughly every 2 weeks on average: 4/6/2021, 4/13/2021, 04/26/2021, 5/14/2021, 6/1/2021, 7/1/2021, 8/16/2021, 9/22/2021, 10/15/2021, 11/5/2021, and on 11/30/2021 (2) reference lists of pertinent systematic reviews; and (3) publications from prospective cohort studies identified from ClinicalTrials.gov, other registries, and news items. A complete description of the search strategy can be found in Appendix A.

This is the first update of this living rapid review.[6] For each update, in consultation with the ACP and AHRQ, we prioritize questions for current and future updates based on whether evidence identified in bi-weekly searches will likely substantially change the conclusions or certainty of evidence of our last review.[7, 8]

As noted above, this update focuses on estimating the risk of reinfection among adults in the general population and on the duration of protection against reinfection (Key Questions 2 and 3). The next update, which is currently underway and is expected to be completed in spring 2022, will review new evidence about the antibody response to SARS-CoV-2 exposure (Key Question 1) and about behavior and beliefs regarding SARS-CoV-2 antibody testing (Key Question 4). For the complete set of Key Questions, see our protocol[4] and Appendix A.

Study Selection

We selected longitudinal studies that compared the risk of reinfection for individuals who had a documented infection with SARS-CoV-2 (the "positive" cohort) with the risk of new infections in individuals with no prior infection (the "negative" cohort).[9] Studies of the general population, healthcare workers, college students, and long-term care facilities were eligible, as were registry-based studies of patients with a specific condition. Studies that reported risk of reinfection but lacked an uninfected comparison cohort were ineligible, but we examined them to see whether they addressed populations or predictors of reinfection not adequately addressed in included studies. We used the Joanna Briggs Institute (JBI) cohort study checklist[10] to screen for methodological limitations that would almost certainly invalidate the study findings. Using this tool, we excluded two studies[11, 12] that used invalid criteria to allocate individuals to the positive or negative cohorts or did not follow participants an adequate length of time for reinfections to occur. As described below, for the remaining (included) studies, we performed a second risk of bias assessment designed to identify limitations specific to this topic.

While we originally planned to exclude preprints, we decided to include those that passed the methodological (JBI) screen because monitoring indicated a very high chance of acceptance to a journal. Preprints are marked in plots, and their impact on pooled measures of effect was examined in sensitivity analyses (Appendix C).

Data Extraction and Study Quality

We used a spreadsheet to extract the following information by study: study design, population, data sources, study inclusion/exclusion criteria, age, race, gender, comorbidities, immunoassay type and brand

(when applicable), definition of reinfection, followup test type and frequency of followup testing, primary infection symptom status, waiting period (if applicable), counts for all infection events/non-events, and main findings.

To assess study quality, we began by enumerating methodological challenges in studies of immunity acquired by infection that might bias effect sizes.[13] We then identified potential biases in four areas: sampling, cohort assignment, case definition, and ascertainment of cases during the followup period. We abstracted information relevant to these methodological features from each study, recording variations in methods that could have an impact on the observed effect. Some of the considerations for each of these areas are described below:

- *Sampling.* We assessed whether selection bias could arise from the data sources used to identify eligible individuals or the ways participants were selected. Selection bias could spuriously drive effect size up or down if some groups in the target population were less likely to be recruited, if the cohorts were differentially enriched with individuals having unusual risk profiles, or if cohort inception was poorly delineated.
- *Cohort assignment*. Within a given sample, the "positive" (infected) or "negative" (not infected) cohorts form the denominators for followup and analyses. We considered which tests were used (serologic, virologic, and clinical assessment), when they were performed in relation to illness onset, and whether they were applied to all participants. Misclassification can occur if, for example, the tests used to diagnose infection had poor sensitivity or if cohorts included individuals with incomplete testing.
- *Outcome ascertainment.* We assessed the methods used to ascertain new infections during the followup period, such as scheduled surveillance with polymerase chain reaction (PCR) tests, clinical surveillance, or identification of cases in clinical care without surveillance. In assessing ascertainment, we also considered, when applicable, whether surveillance for symptoms or access to medical evaluation differed among cohorts, as well as the frequency of, and adherence to, scheduled testing. Bias could also occur if the followup period was too short.
- *Classification of potential cases of reinfection during the followup period.* Ideally, a case is considered symptomatic reinfection only when a patient confirmed to have had an infection has a negative PCR test during the followup period and, later, presents with symptoms and a positive PCR test or genetic typing. In most studies, however, reinfection was diagnosed when an individual had a positive PCR test following a "waiting period" intended to give time for the initial episode to resolve clinically and virologically. Bias can occur if a positive PCR due to persistent viral shedding is counted as a reinfection, if the assay(s) used to confirm reinfection are not sensitive or specific, or if adjudication of reinfections in the positive cohort was more or less rigorous than adjudication of incident infections in the negative cohort.

In each of these four categories, we identified methodological variations that are likely to be associated with higher or lower quality (risk of bias). In rating the quality of each study, we used only the study characteristics for which we could reasonably anticipate the direction of bias. For example, in most studies, only individuals who had a negative evaluation for SARS-CoV-2 infection—serology, PCR, or both—were assigned to the uninfected (negative) cohort. In one study, however, untested individuals were included in the uninfected group, increasing the chance of misclassification. This type of misclassification would be expected to bias the estimate of protection to the null.

In many cases, however, the magnitude or direction of bias associated with the features of a particular protocol may be unknown, often because knowledge of the course of disease is still developing. For

example, as noted above, investigators must decide how long after cohort inception to count a positive PCR test as a reinfection. Different cutoffs for the waiting period between first and second positive tests influence the apparent rate of reinfection.[14] Starting the followup period too soon could misclassify persistent viral shedding as reinfection,[15] but waiting too long can exclude incident infections in the negative (previously uninfected) control group during a time when prior infection confers protection. In our judgment, all included studies employed reasonable time separations between assessments and adequate followup time. In this situation, *a priori* judgments about the risk of bias are suspect due to the novel nature of SARS-CoV-2 and lack of evidence to determine which decisions at the level of study design and methods could influence results.

We performed sensitivity analyses to assess whether 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, 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 include only symptomatic infections, and whether serology, PCR, or both were used for cohort allocation (Appendix C and Appendix Table B-1). We examined the relationship between these factors and protection estimates but lacked sufficient data to evaluate them in a meta-regression. We also repeated our main analysis excluding preprint studies.

Data Synthesis and Strength of Evidence

For Key Question 2, the main outcomes of interest were the effect of previous infection on the risk of symptomatic reinfection, any reinfection, and severity of reinfection. These outcome metrics, termed "protection," are analogous to the efficacy endpoints used in studies of vaccine efficacy.[16, 17] Here, however, incident infections detected during the followup period in the positive cohort are reinfections and those in the negative cohort are primary infections; in vaccine studies, all incident infections are considered primary infections. The category "any reinfection" includes individuals in whom virus is present, whether or not symptoms have been detected. For Key Question 3, the outcome of interest was the duration of protection as indicated by the length of followup and, in some cases, by within-study analyses of different followup time periods.

While 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 (Appendix A).

The primary analyses focused on the magnitude of protection against reinfection, quantified as the proportion or percentage of prevented infections (another analogue to vaccine studies). 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 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 (whether general population, health care workers only, young adult individuals only, or elderly individuals only), to obtain combined effect estimates and corresponding 95% confidence intervals. We used a continuity correction of 0.5 for two studies that reported zero 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[18] was chosen for its robustness properties and low bias in small-

sample settings.[19] Study heterogeneity within strata was assessed using the I^2 statistic.[20] We assessed heterogeneity across strata using Cochran's Q_b statistic.[21] Analysis was performed using Stata version 16.1 (*Stata Statistical Software: Release 16*; StataCorp LLC, College Station, TX), in particular the *meta* family of commands for meta-analysis. See Appendix A for further details.

For some factors that varied within studies or were specific to certain studies (including demographic variables, symptom status, health behaviors, vaccination, and genetic variants), we were unable to examine their quantitative impact on effect sizes within a meta-analytic framework due to inconsistent reporting among studies. We abstracted information from study-specific sensitivity analyses and regression analyses when available and 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 (whether asymptomatic infections were identified by surveillance, whether validation testing was performed, etc.). We assessed these visually for relationships with effect sizes using scatterplots 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.

We graded the strength of evidence (SoE) to describe our confidence in effect estimates as high, moderate, low, and insufficient evidence. The assessment is based on our analysis of the study limitations, directness, consistency, precision, dose-response, plausible confounding, and strength of association (see Appendix B for more details).[22] We used the same domains to grade the strength of evidence for age, baseline comorbidities, and other factors listed in Key Questions 2a and 3a that may influence effect estimates.

Results

Overview of Studies

The updated literature search identified 635 citations (Appendix B, Figure B-1). We identified 18 eligible cohort studies (including two preprints) that provided estimates of the risk of reinfection relative to uninfected individuals. Two additional preprints[23, 24] were included and are synthesized only narratively because they lacked the data needed for our meta-analysis. No studies included in our original review were eligible for this update. The total positive cohort n=465,206 and the total negative cohort n=12,505,204. Most included studies were of moderate to high quality (Appendix B, Table B-3).

Four studies were conducted in the United States,[23, 25-27] five in the United Kingdom,[9, 28-31] two in Italy,[32, 33] and one each in Austria,[34] Denmark,[35] France,[36] Qatar,[37] Switzerland,[38] Israel,[24] and Scotland.[39] The studies were methodologically diverse. Nine studies used antibody test results to assign patients to the "positive" or "negative" cohorts;[23, 26, 28, 30, 31, 33, 37-39] three used a combination of antibody test results and PCR;[9, 29, 36] and six used PCR alone (see Supplement Table 2).[24-27, 32, 34]Similarly, during the followup period, diagnostic method variations included scheduled PCR testing according to a protocol (versus detection in usual care); confirmation of PCR results by seroconversion and clinical adjudication (versus PCR alone); and classification of cases as "likely," "probable," and "suspected" (versus no classification) (Appendix B, Table B-1). None of the studies evaluated the Delta or Omicron variants.

Risk of Reinfection (Key Question 2)

Symptomatic and All Reinfections

In our meta-analysis, prior infection reduced the risk of symptomatic infection by 87 percent (95% confidence interval 84–90%) compared with uninfected individuals (High SoE, Appendix Table B-4). The protection for health care workers was similar to that of general populations (87% vs. 88%, respectively, Figure 1). Overall, there was no compelling evidence that population characteristics—whether the cohort was comprised of mostly young or old individuals, or enriched with health care-setting exposures or not—influenced the degree of protection afforded by prior infection ($Q_b(3) = 5.63$; $p = 0.13$), which was substantial in all settings (87% estimated protection overall). Across studies, estimates for young (median age ~20) and older adults (median age ~85) 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. Between-study differences in effect size relative to total variance was substantial ($I^2 = \sim 85\%$), 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 percent protection at minimum to ~100 percent at maximum, and are always indicative of very high protection, comparable to what has been reported for the vaccines currently in use in similar populations.[9, 24, 40] 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 (see FigureC-3). There may be substantial heterogeneity of effect sizes *within* this range, but the practical takeaway is that protection is always high in our included studies, regardless of variation in study methods and populations. Figure 1 summarizes these findings (an alternative version excluding preprints is available in Appendix C). All included studies found that reinfection was an uncommon event (range 0–2.2%). The highest reinfection proportion, 2.2 percent, was in a college student population; the control group risk of infection was also very high (12.1%).[25] In settings with high proportions of control group infection (10% or above), reinfection rates were also relatively high (approximately 1–2%). When control group incidence of infection was below 5 percent, reinfection incidence was relatively low (about 0.7% at most). The anomaly was in long-term care facilities, where despite very high control group incidence (20.4% and 37.5%), reinfection rates were low (1.8% and 0, respectively). This anomaly may be partially explained by increased adherence to preventative measures for previously infected individuals.

Asymptomatic Reinfections

Twelve studies reported the proportion of asymptomatic reinfections.[9, 23, 25, 27, 28, 30, 32, 33, 36-39] This proportion ranged from 0 percent to 100 percent, but absolute counts were often low (range 1–155 cases), and study followup methods were not always adequate to accurately detect symptoms that were present at the time of, or in the weeks after, a positive PCR test. The SARS-CoV-2 Immunity and Reinfection Evaluation (SIREN) study, a well-designed study of healthcare workers in the United Kingdom, had the highest number of reinfections (155) as well as the most reliable method to detect asymptomatic ones.[9] It found that 49 percent of reinfections were asymptomatic, versus 20 percent of incident infections in the negative cohort.

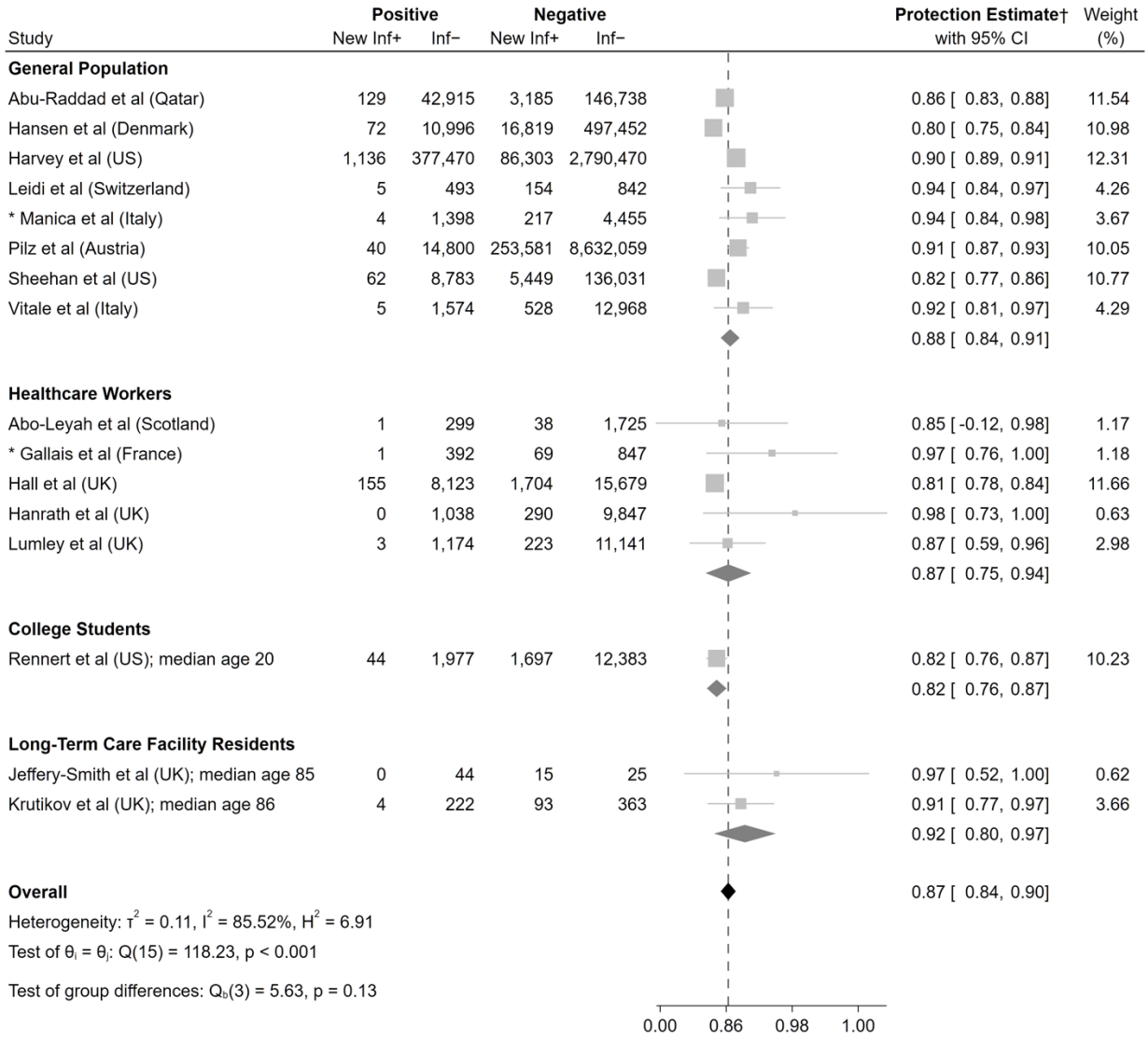
Across studies, prior infection clearly protected against asymptomatic reinfections, but whether this protection is as strong as it is for symptomatic reinfection is unclear. In the SIREN study, primary infection protected against both symptomatic and asymptomatic infections, but the degree of protection

was different (93% lower risk of symptomatic COVID-19 reinfection versus 52% lower risk of asymptomatic reinfection.)[9] In contrast, in a U.S.-based retrospective cohort study (Sheehan et al.), protection against symptomatic infections was 84.5 percent for symptomatic infections versus 81.8 percent when asymptomatic infections were included.[27]

Severity of Symptomatic Reinfection

Six studies provided information about the severity of symptomatic reinfections, but four of them described five or fewer cases.[28, 32, 33, 38] In the largest series, Sheehan et al., 31 patients had symptomatic reinfection.[27] While 18 of them were hospitalized within 30 days of the positive PCR test, only five had COVID-19 symptoms at the time of hospitalization and none of them required intensive care. In the other relatively large series, a study from Austria, five cases were described as moderate and 27 as mild.[34] The scarcity of data reflects the fact that, because prior infection prevented 80 percent or more symptomatic reinfections, severe reinfection is a rare event.

Figure 1. Protection estimate (risk of reinfection) after primary infection from SARS-CoV-2 with a median followup time of 8 months (range 4–13 months)



† This plot shows estimates of protection, defined as (1 − Relative Risk)
Estimates of Relative Risk ranged from 0.02 to 0.20; on the *x*-axis, 0.00 represents no effect, whereas 1.00 represents maximum protection
Study weights and effect averaging via empirical Bayes random-effects model
Continuity correction of zero counts (0.5 added to all counts)
Sorted alphabetically within categories by study author
* Preprint manuscript

Note: Positive indicates the group within a study where participants were PCR positive or seropositive at baseline. Negative indicates those within a study who were PCR negative and/or seronegative at baseline. Protection estimates (1 – RR) can be interpreted as the proportion or percentage of infections that are prevented by the exposure. Median followup time was 8 months (range 4–13 months).

Population and Methodological Factors Affecting the Risk of Reinfection

We conducted analyses of six additional factors that might affect reinfection risk, but which vary among studies because best practices for studying SARS-CoV-2 reinfection are not established. Study duration, waiting interval, median age of participants, underlying prevalence, inclusion of asymptomatic

people in the positive cohort, and tests used to allocate people to the two cohorts did not appear to have a strong relationship with the estimated effect size (Appendix C, Figure C-2). In our judgment, variation in these features of study design and conduct did not have a substantive influence on the estimates of protection. R^2 values for effect size for other potential sources of variation in those estimates were low: cohort allocation criterion (13.2%; QB=2.85; p=0.241), median age of participants (6.7%), infection proportion in negative group (<0.1%), waiting period (<0.1%), total followup (<0.1%), and symptom status at baseline (<0.1%; see Figure C-2).Protection against reinfection was only slightly lower in studies that used the most reliable methods to ascertain and characterize reinfections.[9, 35]

Some studies reported their own sensitivity analyses or mathematical modeling of the impact of these methodological factors.[9, 23, 28, 30, 35, 38] Overall, protection against reinfection was not correlated with the asymptomatic testing rate, cohort assignment criteria, or method for assessment of infection during the followup period.[9, 30, 38] Appendix Table B-5 summarizes findings and overall confidence rating for additional factors that may affect reinfection.

Baseline Factors

Age, Sex, and Race

In the Denmark study, there was no difference in the estimates of protection against repeat infection by sex, but there was a striking difference in protection against repeat infection in the elderly.[35] Among individuals aged 0–64 years, estimated protection was 80–82 percent, whereas in individuals older than 65, it was 47.1 percent (confidence interval [CI] 24.7–62.8%). Among those older than 65 who had a previous infection, the infection rate was 8.01 per 100,000 person-days of followup 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 it was in the younger groups (16.92 per 100,000 person-days versus 27.42 to 38.13 in the younger groups.) The low infection rate in the elderly controls relative to other controls 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 of reinfection among those older than 60 years old compared with those younger (>60 years old hazard ratio=0.44, 95% CI: 0.14–1.4; <60 years old hazard ratio=0.05, 95% CI 0.01–0.20).[38] The study in Israel compared protection among age groups and found a slight decrease in the protection conferred by immunity acquired from previous infection for those greater than 80 years of age (overall protection: 94.8%, 95% CI 94.4–95.1; over-80 protection: 91.4%, 95% CI 85.5–94.9).[24]

These findings on age are in conflict with 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, other populations (Figure 1).[30, 31]

Studies offered very little information about the effect of race and ethnicity on protection from reinfection. Of the four U.S.-based studies, two did not mention race.[25, 27] A third stated that race and ethnicity had been deleted from the aggregated health system dataset before analysis to prevent Health Insurance Portability and Accountability Act (HIPAA) violations.[26] The fourth, a preprint, reported adjustment for race but has not yet reported the regression results.[23] The European studies had low proportions of individuals identified as Black, Hispanic, or Asian, whereas the largest U.S. studies did not report results by race or ethnicity.

Immunocompromised Patients and Other Comorbidities

While some studies adjusted for immunosuppression or other comorbidities, none reported on the incidence of reinfections in these subgroups. We expected to find registry studies of risk of reinfection in immunosuppressed patients but did not. A study that was ineligible for inclusion in our meta-analysis investigated characteristics of 23 suspected reinfections in electronic health records (EHR) and found 83% of presumed reinfections were in those with immunocompromised conditions. [41]

Initial Antibody Levels

Eleven studies provided information about the antibody response to the initial infection.[9, 23, 26, 28-31, 36-39] Additional analyses from these cohorts may shed light on the relationship of the initial antibody response or the persistence of antibodies to protection against reinfection. Seven studies did not include analyses of the antibody response.[25, 27, 30, 32-35]

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 were either not recorded or were 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.[28, 32, 36, 38, 39] with those that recruited only symptomatic people[26, 27, 29, 34] did not reveal a clear relationship between the recruitment method and protection against reinfection. A recently published cohort study found that mild COVID-19 illness was associated with protection against reinfection and generally supports our conclusions, though no reinfections were observed, and the sample was relatively small (N=653). [42]

Variants

As of August 10, 2021, the U.S. Centers for Disease Control and Prevention (CDC) identified four "variants of concern," defined as "variants for which there is evidence of an increase in transmissibility, more severe disease (e.g., increased hospitalizations or deaths), significant reduction in neutralization by antibodies generated during previous infection or vaccination, reduced effectiveness of treatments or vaccines, or diagnostic detection failures." [43]

The B.1.1.7 (Alpha) variant was studied in four of the studies meta-analyzed. While evidence is sparse, there is no indication of increased risk of reinfection for this variant. In the SIREN study, a cohort study of health care workers in the United Kingdom, an increased prevalence of the Alpha variant, which accounted for most infections during the followup period, did not affect risk of reinfection.[9] Of two additional studies that reported on the Alpha variant, neither indicated an effect of the variant on reinfection.[24, 30] In an ecologic study among 36,920 United Kingdom 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. [44] The remaining 15 studies included within our review did not include analyses of variants.[23, 25-36, 38, 39]

These results do not, of course, rule out the possibility that another variant of concern could evade immunity acquired by previous infection. In this regard, the rapidly changing variant causing outbreaks in Brazil is considered to be the most concerning. [45] A study from Brazil suggested higher reinfection

risks due to the P.1 (Gamma) variant, but was not included in our review because it reported increasing antibody levels instead of seroconversion or a positive PCR test as a possible signal for reinfection.[11]

In July 2021, the Delta variant became the dominant strain among new infections in the United States. Data on reinfection risk in the setting of the B.1.617.2 (Delta) variant are sparse and still developing, but, recently, a preprint from Israel, surveillance data from Kentucky, and an outbreak investigation in Texas indicated that immunity acquired by infection provided protection consistent with our estimates after the Delta variant became predominant.[46-49] 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.[49]

Vaccination

An important clinical question is whether vaccination reduces risk of reinfection in those who have had an infection. Only four of the studies reported on vaccinations in their sample populations, and none reported the impact of vaccination on risk of reinfection.[9, 24, 30, 36] In the SIREN study, 13,401 participants were vaccinated during the followup period, but followup after vaccination was too short to assess the protective effect of previous infection and vaccination separately.[9] The remaining 14 studies did not include vaccinated individuals within their study population.[23, 25-29, 31-35, 37-39]

Because prior infection and vaccination both provide strong protection against infection, large sample sizes or a case-control design would be needed to determine whether vaccination augments protection from prior infection. In August 2021, a case-control study in Kentucky of patients with previous COVID-19 infection reported that being unvaccinated was associated with an increased odds of being reinfected compared with being fully vaccinated (odds ratio=2.34; 95% CI = 1.58–3).[46] This study had important limitations (five of which the authors noted), but, even if the odds ratio estimate is valid, it is important to recognize that the odds ratio is consistent with our finding that immunity acquired by previous infection confers a high degree of protection from reinfection. That is, even if a reinfected individual is approximately twice as likely not to be vaccinated as a matched individual who was not reinfected, doesn't mean a randomly chosen unvaccinated individual with a prior infection was twice as likely as a similar but vaccinated individual to get a reinfection. Both have a very high probability of escaping reinfection. For example, based on State of Kentucky data from public sources, [50] the result is consistent with an estimate that immunity acquired by infection was around 91 percent protective, similar to the studies we reviewed, and protection for immunity acquired by infection plus vaccination might have been around 95 percent or possibly higher, also within the range of studies of immunity acquired by infection alone. It is also worth noting that, contrary to some reports in the media, this study did not compare the efficacy of vaccination with the protection from immunity acquired by previous infection: the comparison was between vaccination and no or partial vaccination in people who had been previously infected.[9, 24, 30, 36]

Concordance With Risk of Reinfection in Uncontrolled Studies

Studies that followed a group of infected patients but did not compare their outcomes with those of a control group (Appendix Table B-5) used large databases to make crude estimates of reinfection risk. For example, an abstract of an analysis from the Epic Health Research Center found that 4 per 1,000 individuals who had an initially positive PCR had another positive PCR 90 or more days later.[38] In an analysis using a dataset from 62 U.S. health systems that use a Cerner EHR, the criteria for reinfection were a positive PCR test followed by at least two negative PCRs, and then a positive PCR test at least 90

days after the initial positive PCR test.[14] A large proportion of patients in the dataset were excluded from the analysis due to lack of serial tests. A total of 63 (0.7%) of 9,119 patients had a reinfection. In this analysis, reinfection was associated with pre-existing asthma (odds ratio [OR] 1.9, 95% CI 1.1–3.2) and nicotine dependence/tobacco use (OR 2.7, 95% CI 1.6–4.5), but not with age. Among reinfected individuals, 37 percent were White, 16 percent were African American, and 25 percent were Hispanic, versus 36.1 percent, 17.7 percent, and 34.3 percent, respectively, among patients without reinfection.

Duration of Protection (Key Question 3)

Eight studies[27, 30, 34-39] that included over 9 million participants in total (80,206 exposed, 9,696,466 control) examined whether the risk of reinfection varies over time. All eight found no evidence of waning protection during 6 to 13 months of followup. Further, two of the studies noted that the protection against reinfection may have increased over time.[27, 37] Sheehan et al. found that 6 months after primary infection, protection against symptomatic disease increased from 84.5 percent for all time points to over 90 percent for events at more than 6 months.[27] Abu-Raddad et al. saw incidence rates of reinfection slightly decreasing over time, implying increased protection over time, though this may alternately be explained by national population-level decreases in infection incidence rates during that time period.[37] Appendix Table B-7 summarizes findings for duration of protection against reinfection findings by study.

These findings are based on the variants in circulation around the world during the timeframe of these studies. At present, these studies have not reported extensively on factors that could affect the duration of protection partly because, within the range of followup durations that have been studied, late reinfection is a rare event. These results could change dramatically as the studies report longer followup times or new variants.

Statements From Public Health Organizations

The CDC states that, based on experience with other human coronaviruses,

> *"…the probability of SARS-CoV-2 reinfection is expected to increase with time after recovery from initial infection because of waning immunity and the possibility of exposure to virus variants…. The risk of reinfection may be increased in the future with exposure to SARS-CoV-2 variant virus strains that are not neutralized by immune antisera, such as one recently described in South Africa…. The risk of reinfection also depends on the likelihood of re-exposure to infectious cases of COVID-19. Continued widespread transmission makes it more likely that reinfections will occur."*[15]

The World Health Organization (WHO) does not have a recent statement about reinfection.

Future Research and Ongoing Studies

Longer followup from the included studies should assess whether protection lasts for periods longer than 7 to 10 months, whether variants that were not prevalent in current studies can evade immunity acquired by previous infection, and whether vaccination adds significant protection among individuals who have been infected. Additional studies are needed to address protection against reinfection in the

young, in the elderly, in patients who tested positive for SARS-CoV-2 but had no symptoms, and in immunocompromised patients and those with other comorbidities.

The populations studied to date are also relatively homogenous racially, ethnically, and geographically. Analysis of larger, more diverse cohorts of previously infected individuals could help verify whether the estimates of reinfection rates we found are applicable in other populations, social circumstances, and settings.

Ongoing studies of immune responses and risk of reinfection (Appendix D) may address some of these gaps. Three of these studies are examining COVID-19 survivors under the age of 18, contributing to the substantial knowledge gap in pediatric populations. Additionally, three studies will include groups of vaccinated individuals in their cohorts.

Discussion

The findings provide strong evidence that the immunity acquired by previous infection reduced the risk of symptomatic infections from wild-type and Alpha variants by 84% to 90% for at least 7 months (see Appendix Table B-4 for SoE assessment). The evidence for an overall effect is consistent, and the effect sizes are too large to be accounted for by biases. In the evidence we reviewed, most investigators described their decision-making regarding study methods, and many conducted sensitivity analyses or alternative cohort analyses to minimize error and detect biases that are inherent in studying immunity acquired by previous infection.

Nevertheless, it is not clear that they overcame every challenge. 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 perform protocolized followup testing designed to capture all incident infections and reinfections. While widely used in the literature, the term "asymptomatic infection" and "asymptomatic reinfection" are poorly defined, and methods to distinguish symptomatic reinfections from virological recurrence without clinical evidence for infection were problematic.[51] Study methods and knowledge of SARS-CoV-2 are not sufficiently developed to distinguish which people with "asymptomatic infections" are "pre-symptomatic" on the one hand, or "colonized" on the other. 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 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 (e.g., for surveillance in a study setting) and convert to a positive one, or 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 the prognostic value of the more widely used PCR test, which, it should be noted, has additional value because it not only tells us about reinfection risk but also about transmission risk.

A key limitation of this literature is that it does not apply to antibody testing in people and clinical settings when 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, or 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.

None of the studies could account directly for the behavioral and occupational variables that affect infection risk and might well 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. While possible, this and other scenarios that can be imagined seem unlikely and would require that all of the studies suffered from 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.

Of less concern, but worth noting, results do not address protection conferred by a first infection that occurred between or after high incidence surges. Many of the studies measured reinfections as new cases happening within the second pandemic wave in a particular geographic location. This approach avoids the time confounding that might exist should cases have been considered continuously. That is, because public health restrictions, variants, and other potential confounders changed frequently over time, no study could reasonably account for these changes analytically in continuous time. This means that the degree of protection afforded by immunity acquired from recent infection between waves has not been thoroughly studied.

The results may also be difficult to apply when there is uncertainty about how much time has elapsed since initial infection, as is often the case in clinical practice. Also, as the vast majority of timepoints included in studies were prior to the emergency use authorization of any vaccines in late 2020, the results may be less applicable in populations with high vaccination rates.

All the included studies were conducted in highly developed countries, and our findings may not be as applicable to less-developed countries where exposures may differ due to preventative public health measures not being as widespread or feasible. It is reassuring that the results apply to frail individuals residing in long-term care facilities, but results may also be less applicable to groups that were not well-represented in the studies, especially immunocompromised patients.

Our results do not in any way argue for infection rather than vaccination as a means of obtaining individual or herd immunity. Followup studies of protection against reinfection do not include people who died from COVID-19 and do not consider that morbidity from COVID-19 far outweighs any potential advantage conferred by immunity acquired from recent 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, the findings provide strong evidence that the immunity afforded by previous infection confers strong protection against reinfection for at least 7 months. At present, recent infection is a reliable marker of protection against symptomatic reinfection with SARS-CoV-2.

Appendix A. Methods

Deferred Key Questions

Updates of the protocol, including the deferred key questions regarding antibody response (KQ1) and the consequences of antibody testing (KQ4) are available at PROSPERO, The International Prospective Register of Systematic Reviews (registration number: CRD42020207098).

Search Strategy

The searches included free-text words related to COVID-19, SARS-COV-2, reinfection, and immunity. This updated review's search strategy changed from its previous iteration to mirror the strategy described in Hansen et al.'s SARS-Cov-2 publication.[35]

The reference lists of relevant existing systematic reviews were scanned to identify additional eligible studies. We also monitored the University of Washington's Alliance for Pandemic Preparedness COVID-19 Literature report weekly. [52] Additional articles suggested to us from any source, including peer and public review, were screened applying identical eligibility criteria.

Ovid MEDLINE ALL 1946 to November 30, 2021

Date searched: November 30, 2021

1 ("SARS-CoV-2" or "COVID-19" or "COVID" or "coronavirus").mp. (137407)

2 reinfection.mp. (8500)

3 immunity.mp. (306602)

4 and/1-3 (142)

Ovid Medline Syntax

.mp = Multi-purpose field (searches title, original title, abstract, subject heading, name of substance, and registry word fields)

WHO COVID (https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/)

Date searched: November 30, 2021

tw:((tw:("SARS-CoV-2" OR "COVID-19" OR "COVID" OR coronavirus)) AND (tw:(reinfection)) AND (tw:(immunity))) AND db:("COVIDWHO") (36)

ClinicalTrials.org
(https://clinicaltrials.gov/ct2/results?show_xprt=Y&xprt=reinfection+AND+immunity+AND+AREA%5BConditionSearch%5D+%28+SARS-CoV-2+OR+COVID-19+OR+COVID+OR+coronavirus+%29)

Date searched: November 30, 2021

reinfection AND immunity AND AREA[ConditionSearch] (SARS-CoV-2 OR COVID-19 OR COVID OR coronavirus) (16)

COVID19reviews.org (https://www.covid19reviews.org/)

Date searched: November 30, 2021

reinfection OR immunity (1)

Study Selection

Title and abstract screening was completed by a single screener and exclusion decisions confirmed by a second screener. Full-text screening was completed by two reviewers and any conflicts resolved by a third independent reviewer. The JBI Checklist for cohort studies was used as an additional level of screening. Consensus was required for exclusion reasons and any conflicts were resolved by a third independent reviewer.

Table A-1. Study selection criteria*

PICOTS	Inclusion and Exclusion Criteria
Population	**Include**: **KQs 1-4**: Adults with documented COVID-19 infection compared with a concurrent control group. Index infection can be determined by RT-PCR or serologic testing for SARS-CoV-2 in the setting of a wave or outbreak of COVID-19. **Exclude**: Children less than 18 years of age.

Outcomes	**Include:**
	KQ 1:
	• Length of time anti-SARS-CoV-2 antibodies remain detectable.
	
	KQ 2:
	• Incidence of re-infection. Primary outcome is clinical re-infection; secondary outcomes are any reinfection and severity of reinfection. Re-infection is determined through either:
	  ○ Genomic sequencing;
	  ○ A repeat positive RT-PCR test result 45 or more days following negative RT-PCR testing; or
	  ○ Positive RT-PCR test result 45 or more days following detection of anti-SARS-CoV-2 antibodies
	KQ 3:
	• Duration of immunity (i.e., length of time between an initial RT-PCR-confirmed or clinically diagnosed SARS-CoV-2 infection following documented clinical recovery to a repeat SARS-CoV-2 infection)
	
	KQ 4:
	• Unintended consequences of antibody testing after SARS-CoV-2 infection (e.g., discontinuation of recommended safety practices such as wearing masks or social distancing due to misinterpretation of positive antibody test results as indicative of immunity)
	
	We will stratify outcomes by the following factors:
	• Patient characteristics (i.e., age, gender, race/ethnicity, comorbidities)
	• Severity of COVID-19 infection (i.e., mild, moderate, severe, and critical as defined in NIH COVID-19 treatment guidelines)[53]
	• Presence of symptoms (asymptomatic or symptomatic)
	• How reinfection or suspected reinfection was defined (genetic testing, repeat positive RT PCR, serologic testing)

Eligible study designs	**Include:** **KQs 1-3**: Large, population-based observational (cohort or case-control) studies. Systematic reviews that meet criteria for timeliness, relevance, and quality. **KQ4:** None at present. **Exclude:** Observational studies without an uninfected comparison group; case series, case reports, editorials, non-systematic reviews. For KQ1 we excluded non-peer reviewed articles. For KQ2-3, we excluded non-peer reviewed articles that failed pass a methodological screen.
Study settings	**Include**: Studies in the general population and settings of increased exposure rates (health care workers, communal living situations such as college dormitories or military barracks) **Exclude**: Studies in specific settings that don't have increased exposure rates

*Criteria presented represent the PICOTs that were used to formulate the current update. The most up-to-date PICOTs criteria is available at PROSPERO (registration number: CRD42020207098)

Data Abstraction

Data was abstracted by a single reviewer and verified by a second reviewer. Any discrepancies were resolved verbally, and any conflicts were resolved by a third independent reviewer. We classified studies into two groups based on whether primary infection status at group assignment included symptomatic people only or any infection event. Those classified as 'symptomatic only' included studies where people were only able to be recruited if they presented to a clinic with symptoms seeking a test. Those classified as 'any infection event' included studies where recruitment was done with some sort of surveillance screening not based on symptoms.

Statistical Analysis

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 proportion of incident infections between the negative and positive cohorts relative to the proportion observed in the negative cohort. This estimate is formally one minus the relative risk (RR); i.e., protection estimate = 1 – RR. We pooled these estimates via meta-analysis, both unstratified and stratified by population composition (whether general population, health care workers only, young adult individuals only, or elderly individuals only), to obtain combined effect estimates and corresponding 95% confidence intervals both for each population type and overall.

As a sensitivity analysis, we fitted the meta-analytic model with preprint studies excluded. We also performed a version of the meta-analyses stratified by cohort type, beginning with healthcare worker status, to assess the influence this characteristic may have had. We performed similar stratifications over studies observing very young (college-age) and very old (elderly-care facility resident) cohorts. We identified several other study-level factors that might influence estimates of protection, including study duration, length of waiting interval between reinfection assessments, median age of participant, underlying prevalence (proxied by the proportion of new infections in the negative cohort), and rigor in assessing positivity of infection (whether asymptomatic infections were identified by surveillance, whether validation testing was performed, etc.). We were unable to incorporate these in the meta-analytic model but plotted each factor against the effect sizes to visually assess association. Smooth regression lines were calculated using mean smoothing via nonparametric kernel regression (default Epanechnikov kernel) with bandwidth chosen empirically (see Appendix C).

Control for demographic characteristics and other confounders varied across studies, and studies additionally differed by whether they reported rates adjusted for person-time under observation or simply reported infection proportions. In the interest of robustness and simplicity of interpretation, we opted to ignore study-level adjustments and instead meta-analyze the crude proportions observed over the study period, however long or short, for each study. In a similar vein, we did not consider person-time to be a coherent normalization for this question because of its strong assumption of constant hazard and its population-level rather than person-level orientation. Rates of infection by unit person-time are appropriate for predicting the number of events showing up in a population registry but not directly predictive of individual risk in this context because a first exposure changes the nature of subsequent observation and the probability

of subsequent exposure. Our interest is primarily in how many of the previously infected are spared subsequent infection, on average across unknown and varying levels of exposure over sufficiently long durations to be relevant for public health policy. Ratios of crude proportions are the best fit for addressing this question. Note, however, that most of the studies considered in this report published protection estimates that were both weighted by person-time and adjusted for individual-level and cohort-level factors that may affect infection risk (such as age, socioeconomic conditions, seasonal changes in prevalence, changes to public policy, and so on). Results were reported variously as hazard ratios, odds ratios, relative rates, or adjusted incidence rate ratios. Despite the variety of metrics and adjustment models chosen to quantify the degree of protection afforded, the concordance between our crude proportions and the corresponding adjusted efficacy rates variously reported by the studies was >0.85 by Lin's concordance coefficient,[54] suggesting a broad-based robustness to these adjustments.

A random effects meta-analysis model was chosen because it explicitly estimates a between-study component of variance in addition to pooling the within-study estimates of variance provided by each study, and we employed the empirical Bayes (aka Paule-Mandel) estimator for between-study variance. (An exhaustive recent comparative review[19] of the performance of alternative estimators of between-study variance in the meta-analytic context concluded that the empirical Bayes estimator has lower bias on average than the other alternatives, particularly the popular DerSimonian-Laird and REML estimators, while maintaining good properties such as robustness of estimation under small sample sizes and violations of distributional assumptions, and also has less variance than many alternative estimators.) Study heterogeneity within strata was assessed using the I^2 statistic, which estimates the fraction of total outcome variance that can be attributed to fundamental differences in effect estimates between studies as opposed to within-study sampling variance. Study heterogeneity across strata was assessed using Cochran's Q_b statistic, which follows a chi-squared distribution (degrees of freedom = #subgroups – 1) and uses a null hypothesis that stratum-specific estimates do not differ. Some additional measures of heterogeneity ($\tau 2$,[21] the model-based estimate of between-study variance, and H2, the ratio of total variance to pooled within-study variance[55]) and a standard test (Cochran's Q) of overall homogeneity are provided on forest plots.[56] Cochran's Q has a chi-squared distribution (degrees of freedom = #studies – 1) under the null hypothesis that all study-specific effect sizes are equal to the mean effect size across studies.

Analysis was performed using Stata version 16.1 (Stata Statistical Software: Release 16; StataCorp LLC, College Station, TX), in particular the meta family of commands for meta-analysis.

Appendix B. Results

See supplemental Excel files: Table B-1. Observational studies examining reinfection for those with SARS-CoV-2

Figure B-1. PRISMA flow diagram

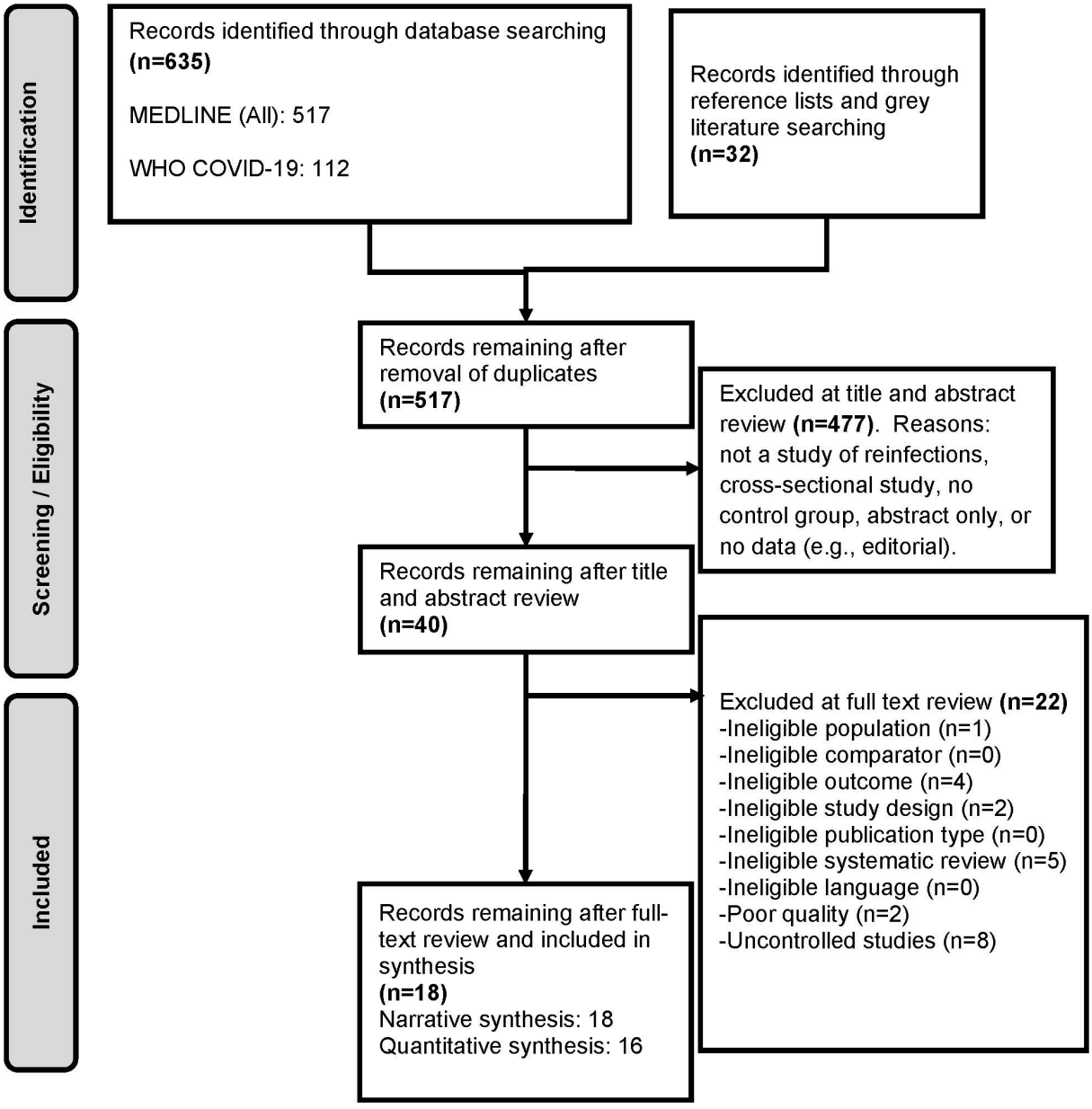


Table B-2. Joanna Briggs Institute cohort checklist used in study screening

Author, Year	1	2	3	4	5	6	7	8	9	10	11
Abo-Leyah, 2021[14]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Abu-Raddad, 2021[37]	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y
Finch, 2021[23]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y
Gallais, 2021[36]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Goldberg, 2021[24]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y
Hall, 2021[9]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Hanrath, 2021[29]	Y	N	Y	Y	N	Y	Y	Y	N	Y	U
Hansen, 2021[35]	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Harvey, 2020[26]	Y	N	Y	Y	N	Y	Y	Y	Y	N	Y
Jeffery-Smith, 2021[31]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Krutikov, 2021[30]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Leidi, 2021[38]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Letizia, 2021[12]	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Lumley, 2021[28]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Manica, 2021[33]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Pilz, 2021[34]	Y	N	Y	N	N	Y	Y	Y	Y	NA	Y
Prete, 2021[11]	U	N	N	Y	Y	Y	N	Y	Y	NA	Y
Rennert, 2021[25]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Sheehan, 2021[3]	Y	N	Y	Y	Y	Y	Y	Y	Y	U	Y
Vitale, 2021[32]	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y

Abbreviations: N= no; NA= not applicable; U= unclear; Y= yes.

Note: Shaded rows = excluded (Letizia[12] and Prete[11]).

Criteria (From the Joanna Briggs Institute Checklist for Cohort Studies[10]):

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
7. Were the outcomes measured in a valid and reliable way?
8. Was the followup time reported and sufficient to be long enough for outcomes to occur?
9. Was followup complete, and if not, were the reasons to loss to follow up described and explored?
10. Were strategies to address incomplete follow up utilized?
11. Was appropriate statistical analysis used?

Table B-3. Risk of bias and overall study quality ratings

Author	Sampling Risk of Bias	Cohort Allocation Risk of Bias	Outcome Ascertainment Risk of Bias	Outcome Classification Risk of Bias	Risk of Bias Overall Rating	Study Quality Rating
Abo-Leyah[39]	Low	Low	Moderate	Moderate	Low	High quality
Abu-Raddad[37]	Low	Moderate	Moderate	Moderate	Moderate	Moderate quality
Finch[23]	Low	Moderate	Moderate	Moderate	Moderate	Moderate quality
Gallais[36]	Low	Low	Low	Moderate	Low	High quality
Goldberg[24]	Low	Low	Low	Moderate	Low	High quality
Hall[9]	Low	Low	Low	Moderate	Low	High quality
Hanrath[29]	Moderate	Low	Moderate	Moderate	Moderate	Moderate quality
Hansen[35]	Low	Low	Moderate	Moderate	Low	High quality
Harvey[26]	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate quality
Jeffery-Smith[31]	Low	Low	Low	Moderate	Low	High quality
Krutikov[30]	Low	Moderate	Low	Low	Low	High quality
Leidi[38]	Low	Moderate	Moderate	Low	Low	High quality
Lumley[28]	Low	Moderate	Low	Moderate	Low	High quality
Manica[33]	Low	Moderate	Moderate	Moderate	Low	High quality
Pilz[34]	Moderate	Serious	Moderate	Moderate	High	Poor quality
Rennert[25]	Low	Low	Low	Low	Low	High quality
Sheehan[27]	Moderate	Low	Moderate	Moderate	Moderate	Moderate quality
Vitale[32]	Low	Low	Moderate	Low	Low	High quality

Table B-4. Strength of evidence assessments for the statement "prior infection reduces the risk of both symptomatic and asymptomatic reinfections for at least 7 months" (KQ2 and KQ3)*

Outcome	N Studies, N Total Cohort	Study Limitations	Directness	Precision	Consistency	Dose Response	Plausible Confounding	Strength of Association	Strength of Evidence
Risk of reinfection	**18 studies; N= 12,968,006** Abo-Leyah 2021,[39] Abu-Raddad 2021,[37] Finch 2021,[23] Gallais 2021,[36] Goldberg 2021,[24] Hall 2021,[9] Hanrath 2021,[29] Hansen 2021,[35] Harvey 2021,[26] Jeffery-Smith 2021,[31] Krutikov 2021,[30] Leidi, 2021,[38] Lumley 2020,[28] Manica, 2021,[33] Pilz 2021,[34] Rennert 2021,[25] Sheehan 2021,[27] Vitale 2021[32]	Moderate	Direct	Precise	Consistent	Undetected	Present	Strong	**High**

*This statement refers to the pooled estimate of protection against reinfection conferred by immunity acquired by previous infection of 87% (95% confidence interval 84%-90%). For this estimate, strength of evidence is low for 7-10 months and insufficient for >10 months.

Table B-5. Overall confidence assessments and narrative summary statements for additional factors that may impact the risk of reinfection

Additional Factors That May Impact Risk of Reinfection	N Studies, N Total Cohort	Narrative Summary Statement	Overall Confidence Rating
Initial antibody levels	**11 studies; N= 3,241,686** Abo-Leyah 2021,[39] Abu-Raddad 2021,[37] Finch 2021,[23] Gallais 2021,[36] Hall 2021,[9] Hanrath 2021,[29] Harvey 2021,[26] Leidi 2021,[38] Lumley 2020,[28] Krutikov 2021,[30] Jeffery-Smith 2021,[31]	Very uncertain about how initial antibody levels could impact reinfection. Subsequent update will aim to fill this gap.	**Insufficient**
Age	**5 studies; N= 529,105** Hansen 2021,[35] Krutikov 2021,[30] Jeffery-Smith 2021,[31] Leidi 2021,[38] Goldberg 2021,[24]	Overall, it is more likely that protection for elderly individuals and younger adults is similar, but additional evidence is needed to resolve the issue.	**Low**
Gender	**18 studies; N= 12,968,006** Abo-Leyah 2021,[39] Abu-Raddad 2021,[37] Finch 2021,[23] Gallais 2021,[36] Goldberg 2021,[24] Hall 2021,[9] Hanrath 2021,[29] Hansen 2021,[35] Harvey 2021,[26] Jeffery-Smith 2021,[31] Krutikov 2021,[30] Leidi, 2021,[38] Lumley 2020,[28] Manica, 2021,[33] Pilz 2021,[34] Rennert 2021,[25] Sheehan 2021,[27] Vitale 2021[32]	Both males and females were adequately represented in the cohorts, and effects for both were large and consistent.	**High**
Race/Ethnicity	**1 study; N= 4,411** Finch 2021[23]	Blacks were under-represented in the cohorts, and the impact of race on risk of reinfection is uncertain.	**Insufficient**
Comorbidities	**0 studies**	There is little evidence on how comorbidities may impact risk of reinfection.	**Insufficient**
Severity of primary infection	**10 studies; N= 12,345,502** Lumley 2020,[28] Leidi 2021,[38] Gallais 2021,[36] Vitale 2021,[32] Abo-Leyah 2021,[39] Pilz 2021,[34] Sheehan 2021,[27] Harvey 2021,[26] Hanrath 2021,[29] Hall 2021[9]	Mild or asymptomatic initial infections may be associated with a higher risk of reinfection, but evidence is inconsistent and incomplete.	**Low**
Variants	**3 studies; N= 27,772** Hall 2021,[9] Goldberg 2021,[24] Krutikov 2021,[30]	The Alpha variant did not affect the protection against reinfection, but this result does not apply to variants not represented in the studies (such as the Delta variant).	**Low**
Vaccination	**4 studies; N= 29,081** Gallais 2021,[36] Hall 2021,[9] Goldberg 2021,[24] Krutikov 2021,[30]	It is uncertain how vaccination may impact risk of reinfection.	**Insufficient**

Table B-6. Uncontrolled studies of reinfection from SARS-CoV-2

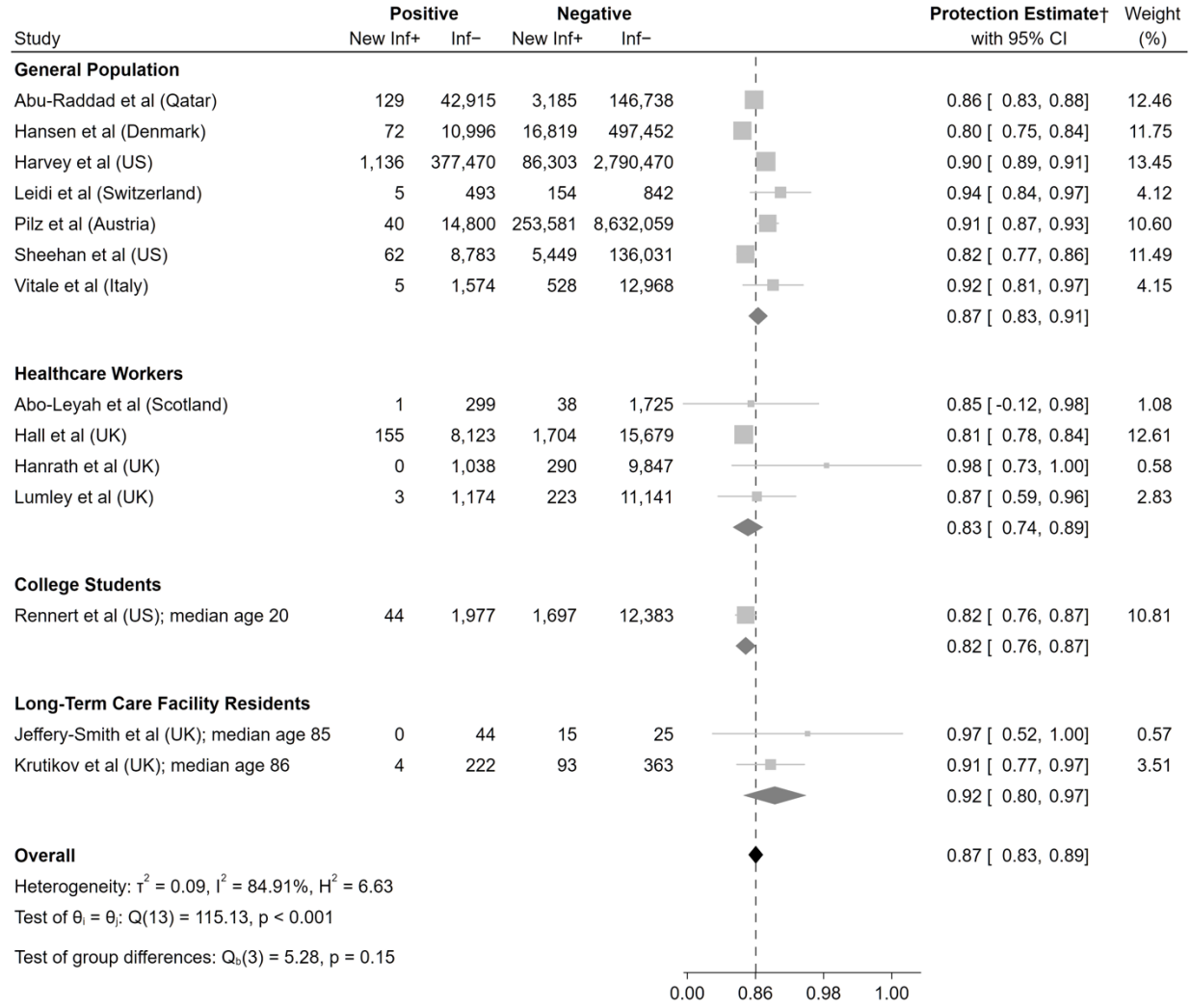
Author	Title	Country	Population
Graham, 2021[44]	Changes in symptomatology, reinfection, and transmissibility associated with the SARS-CoV-2 variant B.1.1.7: an ecological study	United Kingdom	General population
Qureshi, 2021[14]	Re-infection with SARS-CoV-2 in Patients Undergoing Serial Laboratory Testing	United States	General population
Brouqui, 2021[57]	COVID-19 re-infection	France	General population
Thompson, 2021[58]	Rapid Emergence and Epidemiologic Characteristics of the SARS-CoV-2 B.1.526 Variant — New York City, New York, January 1–April 5, 2021 | MMWR (cdc.gov)	United States	General population
Murillo-Zamora, 2021[59]	Predictors of severe symptomatic laboratory-confirmed SARS-CoV-2 reinfection - ScienceDirect	Mexico	General population

Table B-7. Duration of protection against reinfection findings by study

Finding	Study	Overall Followup Time (months)	Duration of Protection Finding
Evidence of no change in protection over time	Abo-Leyah, 2021[39]	6 months	No variation in protection estimate over time.
	Gallais, 2021[36]	13 months	"Altogether, our findings indicate that although anti-SARS-CoV-2 antibody titers do indeed decline, the risk of reinfection within a year post-infection remains low."
	Hansen, 2021[35]	10 months	No difference in protection estimate over time (3–6 months of followup 79·3% [74·4–83·3] vs ≥7 months of followup 77·7% [70·9–82·9]).
	Leidi, 2021[38]	9 months	No variation in protection estimate over time.
	Pilz, 2021[34]	10 months	Descriptive analyses found "no clear sign" reinfection odds changed over time.
	Krutikov, 2021[30]	10 months	No variation in the protection estimate over time.
Suggests potential increase of protection over time	Abu-Raddad, 2021[37]	7 months	Reinfection rate decreased over time, implying a potential increase in protection.
	Sheehan, 2021[27]	10 months	Reinfection rate decreased over time, implying a potential increase in protection.

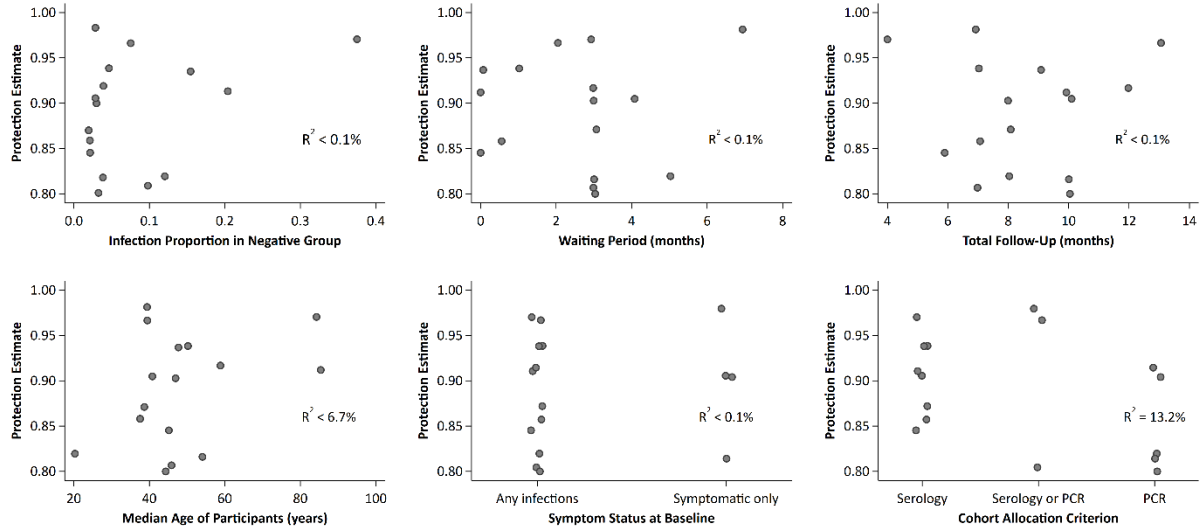
Appendix C. Sensitivity Analyses

Figure C-1. Protection estimate (risk of reinfection) excluding preprint studies



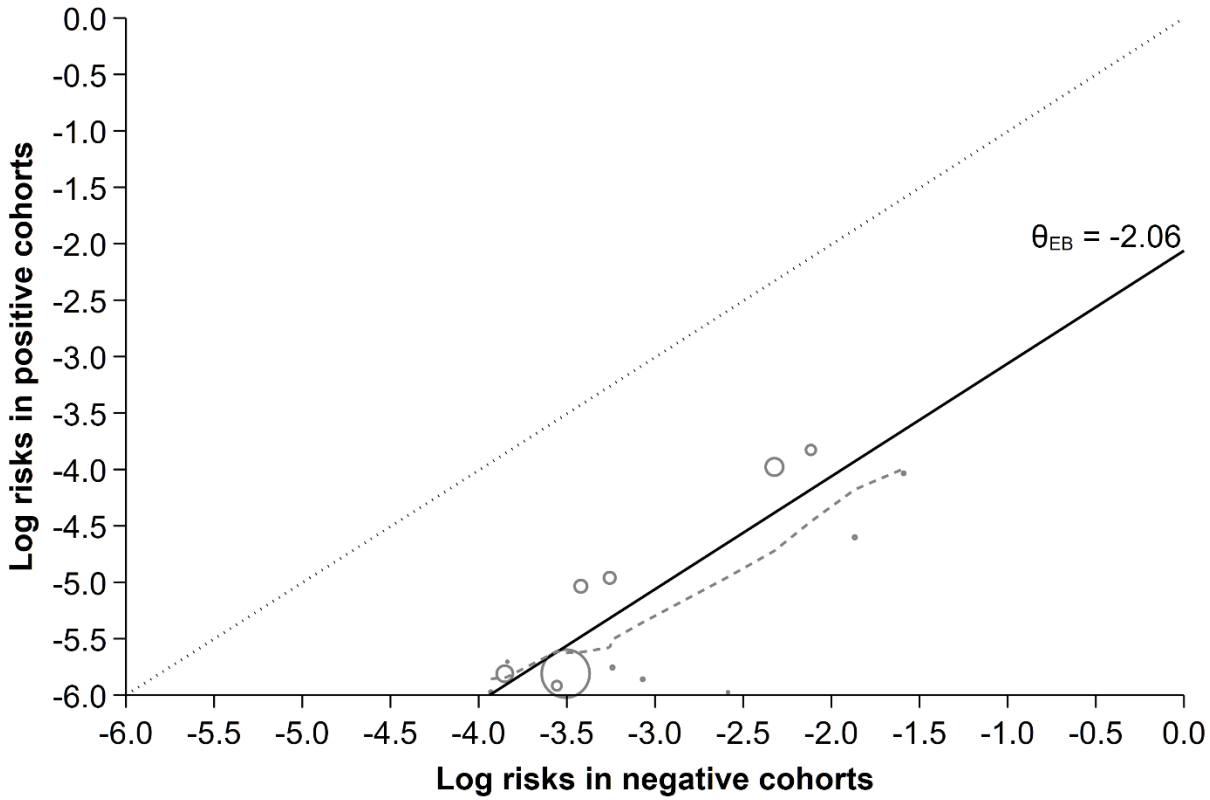
† This plot shows estimates of protection, defined as (1 − Relative Risk)
Estimates of Relative Risk ranged from 0.02 to 0.20; on the *x*-axis, 0.00 represents no effect, whereas 1.00 represents maximum protection
Study weights and effect averaging via empirical Bayes random-effects model
Continuity correction of zero counts (0.5 added to all counts)
Sorted alphabetically within categories by study author

Figure C-2. Methodological and other factors and their influence on protective effect of prior SARS-CoV-2 infection estimates



Points have been jittered slightly for visual display

Figure C-3. Assessment of study heterogeneity



Point sizes proportional to study precision

Appendix D. Ongoing Studies

Study Title ClinicalTrials.gov NCT Number	Study Design Country	Population Description	Expected Outcomes	Status per Last Update on Clinical Trials.gov	Anticipated Primary Completion Date
Humoral Immunity Against SARS-CoV-2 in Liver Transplanted Patients After COVID-19 in Comparison With Immunocompetent Patients NCT04410471	Case-control Spain	Liver transplant and control patients	Incidence of IgG against SARS-CoV-2; titration and evolution of humoral response (IgG) along first 12 months after having COVID-19; Reinfection of COVID-19; mortality	Recruiting as of June 2, 2020	May 29, 2020
Immune Response to COVID-19 in 300 Health Care Workers With Mild Symptoms NCT04356586	Observational Cohort Belgium	HCW previous tested for COVID-19 with mild symptoms in Jessa Ziekenhuis, Belgium	Percentage of serological positive healthcare workers; Percentage of HCW with positive Saliva-sabs	Completed as of September 7, 2020	August 21, 2020
COVID-19: Investigation of Transmission and Immunisation Among Hospital Staff NCT04346186	Observational Cohort Denmark	*Group 1:* hospital staff in the capital region of Denmark *Group 2*: healthy volunteer blood donors	Positive IgM/IgG tests at baseline, 1 month, 5 month; comparison of the point of care test and ELISA at baseline, 1 month, 5 months; reinfection rate at 180 and 360 days; IgM/IgG positive participants on followup test at 1 month and 5 months	Enrolling by invitation as of September 25, 2020	October 1, 2020
Validating an ELISpot for Early Detection of an Active Immune Response Against COVID-19 NCT04418206	Cohort France	COVID-19 patients will be selected in the 4 participating centers. Contact subjects and healthy volunteers will be selected only in the coordinating center (Centre Hospitalier Universitaire de Nice)	Proportion of subjects with IgA-specific cells of SARS-CoV-2's Spike 1 protein at inclusion and 7 +/-2 days later	Recruiting as of November 9, 2020	December 1, 2020

Study Title ClinicalTrials.gov NCT Number	Study Design Country	Population Description	Expected Outcomes	Status per Last Update on Clinical Trials.gov	Anticipated Primary Completion Date
Clinical and Immunological Evolution of COVID-19 Occurring in a Context of Non-Hodgkin Lymphoma NCT04641806	Observational case-control France	*Lymphoma cases*: Adults aged at least 18 years, with a COVID-19 confirmed by PCR, diagnosed between February and May 2020. Past history of B-cell NHL in remission, active surveillance or during first-line or second-line treatment Affiliated with a social security, consenting to the study *Control group*: Adults aged at least 18 years, with a COVID-19 confirmed by PCR, diagnosed between February and May 2020. No past history of lymphoma. Affiliated with a social security, consenting to the study	Immunological response to SARS Cov2 (Quantification of IgG anti-SARS-Cov-2 by ELISA.); Clinical evolution 6 months after COVID-19 diagnosis (length(s) of stay(s) for COVID-19 in hospitalization and intensive care)	Not yet recruiting as of November 24, 2020	April 16, 2021
Evaluation and Longitudinal Follow-up of Biomarkers Predictive of Severe Forms of COVID-19 NCT04648709	Observational Cohort France	Patients with COVID-19 infection documented by PCR and/or antigenic testing will be included. *Group 1:* asymptomatic patients with PCR-positive PCR *Group 2:* patients with mild symptoms and PCR positive *Group 3*: seriously symptomatic patients with PCR positive *Group 4*: patients in resuscitation with positive PCR *Group 5*: heathy volunteer as control	*T cell immune response*: Characterize T-cell immune response in patient with COVID-19 infection *B cell immune response*: Characterize B-cell immune response in patient with COVID-19 infection *Platelet immune response*: Characterize platelet immune response in patient with COVID-19 infection *Immune response and chronic forms*: Immune response and chronic forms	Recruiting as of April 20, 2021	June 2021

Study Title ClinicalTrials.gov NCT Number	Study Design Country	Population Description	Expected Outcomes	Status per Last Update on Clinical Trials.gov	Anticipated Primary Completion Date
Cellular-Mediated Immunity in COVID-19 (DEMETRA) NCT04746521	Cross-sectional Italy	*Group 1*: Patients with previous Sars-CoV-2 infection who did not undergo vaccination *Group 2*: Patients with previous Sars-CoV-2 infection who undergone vaccination *Group 3*: Subjects without previous Sars-CoV-2 infection who undergone vaccination	Detection of Cellular-Mediated Immune Response; detection of T cell subpopulation maturation	Completed as of July 14, 2021	June 14, 2021
Convalescent Plasma as Therapy for COVID-19 Severe SARS-CoV-2 Disease (CONCOVID Study) NCT04342182	Randomized Comparative Trial Netherlands	Patients with PCR confirmed COVID-19 disease, age >18 years. Donors will be included with a known history of COVID-19 who have been asymptomatic for at least 14 days.	Overall mortality until discharge from the hospital or a maximum of 60 days after admission whichever comes first—the mortality in the 300ml convalescent plasma group will be compared with the control arm	Active, not recruiting as of November 16, 2020	July 1, 2021
COVID-19 IgG Antibodies in the Serum of Recovered Patients NCT04470414	Observational Cohort Egypt	Patients recovered from COVID-19 infection within three months before the start of the study.	Levels of IgG in the serum of recovered COVID-19 patients (at 3, 6, 12 months post infection); Factors related to IgG level at 1 year	Not yet recruiting as of July 16, 2020	July 1, 2021
Post COVID-19 Cardiopulmonary and Immunological Changes NCT04388436	Observational Cohort Egypt	COVID-19 PCR positive survivors	Measurement of pulmonary function changes either obstructive or restrictive also lung diffusion and if there is remaining interstitial fibrosis; measurement for cardiac function and ejection fraction changes and if there are changes in pulmonary artery pressure; assessment of IGM and IGG level and if there are immunological changes	Active, not recruiting as of May 19, 2020	July 10, 2021

Study Title ClinicalTrials.gov NCT Number	Study Design Country	Population Description	Expected Outcomes	Status per Last Update on Clinical Trials.gov	Anticipated Primary Completion Date
BNT162b2 Vaccination With Two Doses in COVID-19 Negative Adult Volunteers and With a Single Dose in COVID-19 Positive Adult Volunteers NCT04824638	Non-Randomized interventional trial France	*Group 1*: SARS-CoV-2 naive participants (participants without antecedent of SARS-CoV-2 infection) *Group 2:* Previously SARS CoV-2 infected participants (participants with antecedent of SARS-CoV-2 infection [more than 6 months])	IgG humoral response to vaccine 28 days post vaccination; humoral response to vaccine; T cells response to vaccine; Mucosal response to vaccine; B cell response to vaccine; predictive determinants of vaccine response; Safety of BNT162b2 vaccine; SARS-CoV-2 infection	Recruiting as of April 1, 2021	August 8, 2021
Study of Kinetics and Efficacy of the Immune Response Against COVID-19 Among Hospital Staff NCT04408001	Observational Cohort France	Percy hospital staff having (symptomatic individuals group) or not (asymptomatic individuals group) presented COVID-19 infection symptoms *Group 1*: Hospital staff identified by the COVID-19 case census cell who have been infected, confirmed by positive PT-PCR; or who show clinical signs of COOVID-19 despite negative PT-PCR *Group 2*: Hospital staff who have not been identified by the COVID-19 case census cell (asymptomatic)	Induced SARS-CoV2 immunity Long-term protection of induced SARS-CoV2 immunity at 6 months; long-term protection of induced SARS-CoV2 immunity at 1 year; anti-SARS-CoV2 antibodies kinetics in blood throughout the study; anti-SARS-CoV2 antibodies kinetics in saliva throughout the study; kinetics of serum neutralization in blood throughout the study	Active, not recruiting as of July 7, 2021	September 30, 2021
DCI COVID-19 Surveillance Project NCT04780698	Cohort United States	Patients who receive in-center chronic dialysis (>3 months) at DCI Henry Avenue (Philadelphia, PA)	Incidence of COVID-19 infection in the cohort; Link the presence of COVID-19 infection to COVID-19 antibody formation (seroconversion) from quantitative and qualitative testing; Incidence of COVID-19 reinfection; presence of antibodies in cases of reinfection	Recruiting as of June 23, 2021	October 2021

Study Title ClinicalTrials.gov NCT Number	Study Design Country	Population Description	Expected Outcomes	Status per Last Update on Clinical Trials.gov	Anticipated Primary Completion Date
Immunity Against Severe Acute Respiratory Syndrome Coronavirus 2 Disease (COVID-19) in the Oncology Outpatient Setting NCT04779346	Observational Cohort Germany	Outpatient cancer patients: Cancer patients who are regularly treated in the Oncology Outpatient Clinic of the University Medical Center Hamburg-Eppendorf (UKE)	Rate of SARS-CoV-2 antibody positive patients; Rate of SARS-CoV-2 antibody positivity after 3, 6, 9, 12 months in previously SARS-CoV-2 antibody positive patients; Rate of SARS-CoV-2 antibody positivity after 3, 6, 9, 12 months in previously SARS-CoV-2 vaccinated patients	Recruiting as of March 22, 2021	December 31, 2021
Medical and Serological Follow-up of the Staff of the Paris Saint-Joseph Hospital Group Infected with Severe Acute Respiratory Syndrome Coronavirus 2 NCT04488484	Nonrandomized prospective cohort France	The Paris Saint- Joseph Hospital Group staff	Immune Response description and evolution of the SARS-CoV2 over time	Active, not recruiting as of August 12, 2020	December 31, 2021
Study of COVID-19 Outbreak in Hospital Departments of Bamako, Mali NCT04710316	Non-Randomized interventional trial Mali	*Group 1:* Hospitalized patients in one of the four centers in Bamako, with clinical signs of infection of the upper or lower respiratory tracts with fever or feeling of fever or any other signs of SARS-Cov-2 infection or who have been in close contact with a SARS-CoV-2 infected person without effective protective measures *Group 2:* Caregivers of one of the four centers in Bamako. Serological screening: all. Molecular screening: with clinical signs of infection of the upper or lower respiratory tracts with fever or feeling of fever or any other signs of SARS-Cov-2 infection or who have seroconverted to SARS-CoV-2 or who have been in close contact with a SARS-CoV-2 infected person without effective protective measures	Incidence rate of positive SARS-Cov-2 RT-PCR in Bamako hospital departments during the study (and up to 15 months after study start date) – positive SARS-Cov-2 RT-PCRs are defined by the detection of SARS-Cov-2 genome after amplification using a test targeting 2 regions of the genome.	Not yet recruiting as of January 14, 2021	April 30, 2022

Study Title ClinicalTrials.gov NCT Number	Study Design Country	Population Description	Expected Outcomes	Status per Last Update on Clinical Trials.gov	Anticipated Primary Completion Date
Patients and Health Staff of Cancer Centres During the COVID-19 Pandemic NCT04421625	Cohort France	Population in Cancer centers responding to one of these 3 definitions: patients having a treatment in process, patients under surveillance (having completed their treatment for more than a year), health staff.	Establishment of a clinical (12 months) and biological (15 days) basis for to describe the number and severity of COVID-19 infections in Cancer centers staff and patients. Establishment of a biological basis for to describe the number and severity of COVID-19 infections in Cancer centers staff and patients (3, 6, 9, and 12 months.	Recruiting as of May 5, 2021	June 15, 2022
Longitudinal Follow-up of a Population Cohort in a French City With High SARS-CoV-2 Circulation, in Early 2020 COVID-19 NCT04644159	Observational Cohort France	Residents of a city in Northern France *Group 1*: Pupils, teachers and non-teaching staff who attended schools of the city during the 2019-2020 school year and members of their households *Group 2*: Residents and patients from retirement homes and long-term care units *Group 3*: Staff of health care institutions	Presence of specific anti-SARS-CoV-2 antibodies in the different study groups.	Recruiting as of November 27, 2020	June 30, 2022
Immunity Against SARS-CoV2 in Children and Their Parents COVID-19 NCT04355533	Nonrandomized interventional France	*Group 1:* hospitalized children or consulting at hospital *Group 2:* parents of included child *Group 3*: children with potential COVID-19 during first wave *Group 4:* SARS-cov2 positive school children *Group 5*: person living under same room as children included in study	Seroconversion against SARS-CoV2	Recruiting as of March 26, 2021	July 2022

Study Title ClinicalTrials.gov NCT Number	Study Design Country	Population Description	Expected Outcomes	Status per Last Update on Clinical Trials.gov	Anticipated Primary Completion Date
Workforce Serosurveillance to Track Long-term Modifications to COVID-19 Exposure Due to Factors in the Built Environment NCT04542200	Observational Cohort United States	Working population of Northwell Health	COVID-19 antibodies via serology testing	Enrolling by invitation as of February 8, 2021	December 31, 2022
Pediatric SARS-CoV-2 and MIS-C Long-term Follow-up NCT04830852	Observational cohort United States	*Recovery*: Participants aged 21 years and younger and enrolled within 12 weeks after acute infection or positive test. *Convalescent:* Participants aged 21 years and younger and enrolled more than 12 weeks after acute infection or positive test. *Household contact of infected patients*: Household contacts of the infected patients will serve as a control group *Parents/guardians of participants:* Parents or guardians of participants in all cohorts will also be enrolled for limited participation to complete questionnaires about how the family is impacted by the participant's health and SARS-CoV-2.	Incidence and prevalence of medical sequelae among symptomatic SARS-CoV-2 infection survivors, asymptomatic SARS-CoV-2 infection survivors, and MIS-C survivors over 6 years. Risk factors for medical sequelae among symptomatic SARS-CoV-2 infection survivors, asymptomatic SARS-CoV-2 infection survivors, and MIS-C survivors over 6 years.	Recruiting as of July 19, 2021	July 1, 2027

Study Title ClinicalTrials.gov NCT Number	Study Design Country	Population Description	Expected Outcomes	Status per Last Update on Clinical Trials.gov	Anticipated Primary Completion Date
A Longitudinal Study of COVID-19 Sequelae and Immunity NCT04411147	Longitudinal, observational cohort United States	People age 18 and older who have recovered from documented COVID-19 or were in close contact with someone who had COVID-19 but did not get the infection *Group 1*: Close contacts—individuals without COVID-19 diagnosis, lived in same home as a survivor during illness, were within 6 feet of a COVID-19 case for a prolonged period of time or had direct contact with secretions *Group 2:* COVID-19 Survivor—individuals with documented prior COVID-19 infection and who have recovered	Medical Sequelae in COVID- 19 Survivors; Risk Factors for Medical Sequelae in COVID-19 Survivors; Antibody and cell-mediated immune responses to SARSCoV-2; Antibody and cell-mediated immune responses to SARSCoV-2 over time; Incidence of reinfection with COVID-19; Incidence of clinical silent infection; Mental health status in COVID-19 survivors and contacts	Recruiting as of May 28, 2021	December 31, 2027

Appendix E. Version History

Version 2 – Provides an update for findings on Key Questions 2 and 3.

Version 1 – Synthesizes available evidence (through December 2020) on prevalence of anti-SARS-CoV-2 antibodies following COVID-19.

Authors

Mark Helfand, M.D., M.P.H.[1]
Celia Fiordalisi, M.S.[1]
Jack Wiedrick, M.S.[2]
Katrina L. Ramsey, M.P.H.[2]
Charlotte Armstrong, B.A.[1]
Emily Gean, Ph.D.[1]
Kara Winchell, M.A.[1]
Irina Arkhipova-Jenkins, M.D.[1]

1. Scientific Resource Center to the AHRQ EPC Program
2. Oregon Health & Science University Biostatistics & Design Program

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Disclaimers

This report is based on research conducted by the Scientific Resource Center for the AHRQ Effective Health Care program under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2017-0003). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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This work was based on an evidence report, Risk of Reinfection From SARS-CoV-2 – An Update of an Antibody Response Following SARS-CoV-2 Infection and Implications for Immunity: A Living Rapid Review, by the Scientific Resource Center for the Evidence-based Practice Center Program at the Agency for Healthcare Research and Quality (AHRQ).

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Afterword

Recognized for excellence in conducting comprehensive systematic reviews, the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) program is developing a range of rapid evidence products to assist end-users in making specific decisions in a limited timeframe.

The AHRQ EPC Program recognizes that people are struggling with urgent questions on how to address the COVID-19 pandemic. To shorten timelines, reviewers make strategic choices about which review processes to abridge. The adaptations made for expediency may limit the certainty and generalizability of the findings from the review, particularly in areas with a large literature base. Transparent reporting of the methods used and the resulting limitations of the evidence synthesis are extremely important.

Given the rapidly evolving field, the AHRQ EPC Program will update this review to keep the medical community and public up to date as more studies are published through 2021. If you have comments or have unpublished data to share related to this report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov and will be considered in the next version of the report.

David Meyers, M.D.
Acting Director
Agency for Healthcare Research and Quality

Arlene Bierman, M.D., M.S.
Director
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Craig A. Umscheid M.D., M.S.
Director
Evidence-based Practice Center Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Christine Chang, M.D., M.P.H.
Task Order Officer
Evidence-based Practice Center Program
Center for Evidence and Practice Improvement

Report and Appendix References

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Abbreviations

ACP	American College of Physicians
AHRQ	Agency for Healthcare Research and Quality
CDC	Centers for Disease Control and Prevention
EHR	Electronic health records
HIPPA	Health Insurance Portability and Accountability Act
JBI	Joanna Briggs Institute
PCR	Polymerase chain reaction
RT-PCR	Reverse transcription polymerase chain reaction
SIREN	SARS-CoV-2 Immunity and Reinfection Evaluation
SoE	Strength of evidence
WHO	World Health Organization