Major Update 2: Antibody Response and Risk for Reinfection After SARS-CoV-2 Infection—Final Update of a Living, Rapid Review

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Background: The durability of the antibody response after SARS-CoV-2 infection and the role of antibodies in protection against reinfection are unclear.

Purpose: To synthesize evidence on the SARS-CoV-2 antibody response and reinfection risk with a focus on gaps identified in our prior reports.

Data Sources: MEDLINE (Ovid), EMBASE, CINAHL, World Health Organization Research Database, and reference lists from 16 December 2021 through 8 July 2022, with surveillance through 22 August 2022.

Study Selection: English-language, cohort studies evaluating IgG antibody duration at least 12 months after SARS-CoV-2 infection, the antibody response among immunocompromised adults, predictors of nonseroconversion, and reinfection risk.

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

Data Synthesis: Most adults had IgG antibodies after SARS-CoV-2 infection at time points greater than 12 months (low strength of evidence [SoE]). Although most immunocompromised adults develop antibodies, the overall proportion with antibodies is lower compared with immunocompetent adults (moderate SoE for organ transplant patients and low SoE for patients with cancer or HIV). Prior infection provided substantial, sustained protection against symptomatic reinfection with the Delta variant (high SoE) and reduced the risk for severe disease due to Omicron variants (moderate SoE). Prior infection was less protective against reinfection with Omicron overall (moderate SoE), but protection from earlier variants waned rapidly (low SoE).

Limitation: Single review for abstract screening and sequential review for study selection, data abstraction, and quality assessment.

Conclusion: Evidence for a sustained antibody response to SARS-CoV-2 infection is considerable for both Delta and Omicron variants. Prior infection protected against reinfection with both variants, but, for Omicron, protection was weaker and waned rapidly. This information may have limited clinical applicability as new variants emerge.

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In March 2021, we published the first version of a rapid, evolving, pragmatic review that described the antibody response in adults after an infection with SARS-CoV-2 (1, 2). In January 2022, we published a second review, meta-analysis, and data visualization (https://effectivehealthcare.ahrq.gov/products/immunity-after-covid/rapid-review) describing the risk for SARS-CoV-2 reinfection (3). Our objectives in conducting the original review were to assess the prevalence, level, and duration of the antibody response after infection; compare the risk for reinfection among those with a prior infection to persons who had never been infected; and examine the duration of protection against reinfection. We found that before the emergence of the Delta and Omicron variants, prior infection with the wild-type SARS-CoV-2 virus or the Alpha variant reduced the risk for reinfection by 80% to 97% (pooled estimate, 87% [95% CI, 84% to 90%]) compared with previously uninfected persons. Studies had a median follow-up of 8 months (range, 4 to 13 months), and protection remained above 80% for at least 7 months. There was sparse evidence on the duration of detectable antibodies beyond 6 months; whether the antibody response varied based on immunocompromised status or other factors, such as asymptomatic infection; and whether testing for SARS-CoV-2 antibodies provided clinically useful information about reinfection risk (that is, whether detectable antibodies correlated with protection).

This update examines evidence gaps identified in our previous 2 versions, with a focus on the persistence of IgG antibodies for longer than 12 months after infection, whether the antibody response varies in immunocompromised persons, and characteristics of those who do not seroconvert (key question [KQ] 1). We also evaluated available evidence regarding reinfection with Delta or Omicron variants after previous infection and the relation of antibody levels, symptoms status, and age to protection against reinfection (KQ2) as well as the duration of protection in the context of Delta and Omicron variants (KQ3).

Methods

Our protocol for this rapid, evolving, pragmatic review was developed with the American College of Physicians, registered at PROSPERO (CRD42020207098), and posted

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describe our confidence in effect estimates as high, moderate, low, or insufficient. The assessment is based on our analysis of the study limitations, directness, precision, consistency, plausible confounding, and strength of association.

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

RESULTS
This update adds 29 observational studies to the evidence base (Appendix Figure, available at Annals.org). Our main findings are shown in the Table.

Durability of the Antibody Response
Immunoglobulin G Duration Greater Than 12 Months
In our first report (2), we found that IgG may remain detectable for at least 120 days, based on the study with the longest follow-up at the time (37). For this update, 3 longitudinal studies completed during the first year of the pandemic before vaccine availability met inclusion criteria; these studies had a median follow-up of at least 12 months (range, 12.7 to 14 months) (7–9). Although a high proportion (83% to 97%) of adults had detectable IgG over the follow-up period in all 3 studies (Table 2 of Supplement 1), we have low confidence in this finding (low SoE) (Table). All studies were done early in the pandemic among adults who were mostly symptomatic during their primary infection, and we could not rule out the possibility that an asymptomatic or mild reinfection accounted for persistent antibodies. Results may not be generalizable to other settings or time periods or among adults with a mild or asymptomatic primary infection.

Immunocompromised Populations
In our original review, 3 observational studies provided insufficient evidence on the antibody response in immunocompromised populations. In this update, we identified 10 additional observational studies of the antibody response in immunocompromised patients compared with immunocompetent comparators: 3 studies in patients with cancer (16–18), 1 study in patients living with HIV (19), and 6 studies in patients who had undergone solid organ transplant (Table 3 of Supplement 1) (10–15). Immunoglobulin G antibodies were detected in most immunocompromised patients (≥65% at the first test after reverse transcriptase polymerase chain reaction diagnosis for all included studies, except for a single cohort study at just 15 days after infection, when IgG antibodies may not yet be detectable). However, IgG prevalence was consistently lower among immunocompromised patients compared with nonimmunocompromised control participants.

We are moderately confident that most adults who are immunocompromised due to solid organ transplant...
### Table. Summary of Findings

| Finding                                                                 | Studies (Total Cohort), n [Reference] | Study Limitations | Directness | Precision | Consistency | Plausible Confounding | Strength of Association | Strength of Evidence |
|------------------------------------------------------------------------|--------------------------------------|-------------------|------------|-----------|-------------|------------------------|------------------------|----------------------|
| A high proportion of adults maintained detectable levels of IgG antibodies >12 mo after SARS-CoV-2 infection confirmed by RT-PCR | 3 studies (445) [7-9]                 | Moderate           | Direct     | Imprecise | Consistent   | N/A                    | N/A                    | Low                  |
| Most immunocompromised adults develop IgG antibodies after solid organ transplant, but the overall proportion of those who develop antibodies is lower compared with immunocompetent adults | 6 studies (618) [10-15]               | Moderate           | Direct     | Imprecise | Consistent   | Present                | N/A                    | Moderate             |
| Most immunocompromised patients with cancer develop IgG antibodies, but the overall proportion of those who develop antibodies is lower compared with immunocompetent adults | 3 studies (464) [16-18]               | Moderate           | Direct     | Imprecise | Inconsistent | Present                | N/A                    | Low                  |
| Most immunocompromised adults living with HIV develop IgG antibodies, but the overall proportion of those who develop antibodies is lower compared with immunocompetent adults | 1 study (203) [19]                    | Moderate           | Direct     | Imprecise | Consistency unknown (single study) | Present                | N/A                    | Low                  |
| Nonseroconversion rates were low to moderate (2%–25%) and having had a mild or asymptomatic primary infection was associated with nonseroconversion | 6 studies (11 721) [20-25]           | Moderate           | Direct     | Imprecise | Inconsistent | Present                | Weak                   | Low                  |
| Prior infection with wild-type SARS-CoV-2 or the Alpha variant protected against reinfection with the Delta variant (80%–97%) | 6 populations (11 128 080) [26-31]   | Low                | Direct     | Precise   | Consistent   | Not present            | Strong                 | High                 |
| During the Delta wave, protection from prior infection with the wild-type virus or Alpha variant persisted for at least 13 mo, and up to 20 mo, in the general population, but waned after 13 mo in elderly persons | 3 populations (7 674 862) [26, 29, 30] | Moderate           | Direct     | Precise   | Inconsistent | Present                | Strong                 | Moderate             |
| For Omicron BA.1/BA.2, prior infection with the Delta variant reduced the risk for symptomatic reinfection by 50%–67%. Older variants were less protective (14%–32%). Any prior infection was highly protective against severe disease and death. | 5 populations (9 917 673) [28, 29, 31-33] | Low                | Direct     | Imprecise | Consistent   | Not present            | Strong                 | Moderate             |

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Nonseroconversion

We identified 4 prospective cohort studies (20–23) comparing characteristics of patients who did not seroconvert 6 weeks after documented SARS-CoV-2 infection with those who did seroconvert, adding to the evidence from 2 cohort studies (24, 25) identified in our first report (2) (Table 4 of Supplement 1). Across these studies, the proportion of persons who did not develop antibodies ranged from 2% to 25%. Having no or few symptoms was the most consistent factor associated with nonseroconversion. Higher minimum cycle thresholds with polymerase chain reaction testing (indicating lower viral load) were associated with nonseroconversion in 2 studies (21, 23).

Study methodological limitations give us low confidence in these findings (low SoE) (Table). We do not know to what extent the use of different immunoassays accounts for study variation. Moreover, participants could have been misclassified as not seroconverting depending on the timing of testing. Finally, the clinical significance of nonseroconversion is unclear. Persons who do not seroconvert after infection may still have a robust humoral response with repeated virus exposure because of immune memory (38).

Magnitude and Duration of Protection From Previous Infection (KQs 2 and 3)

Updates of 4 controlled, longitudinal cohort studies (26, 27, 28, 32, 34, 35, 39, 40) included in our previous meta-analysis (3) and 2 new cohort studies (29, 30, 41) contributed to estimates of protection against reinfection in the Delta and Omicron eras (Table 5 of Supplement 1). For the Delta variant, there was consistent, high-quality evidence that prior infection reduced the risk for reinfection by 80% to 97% (high SoE) (Table 26–31). Longer follow-up for 3 of the cohorts suggested that, at least through the Delta wave, protection did not wane significantly for up to 13 months (moderate SoE) (Table 26, 27, 29, 39). In the population-based study done in Qatar, prior infection before the emergence of the Omicron variant protected against another pre-Omicron infection by 85.5%, waning to approximately 70% by the 16th month.

Compared with earlier waves, the Omicron waves were associated with an early, marked increase in the proportion of infections that were reinfections (40–43). Subsequently, cohort studies confirmed that prior infection was less protective against reinfection with the Omicron variants (BA.1, BA.2, BA.4, and BA.5) than against reinfection with Delta and older variants (moderate SoE) (Table 26, 28, 30, 32, 34, 39, 41).

Omicron BA.1 and BA.2

For Omicron BA.1 and BA.2, prior infection with the Delta variant reduced the risk for symptomatic infection by 50% to 67% (28, 31, 32, 39). Prior infection with older variants (for example, wild-type SARS-CoV-2 and the Alpha variant) was less protective against symptomatic infection (14% to 32%) and diminished more sharply over time. In the Qatar cohort, for example, protection against reinfection with Omicron BA.1 or BA.2 was higher among those with a recent Delta infection (approximately 60%) compared with all prior infections (39.8%) (39). In a Danish cohort study (28), protection against Omicron BA.1 or BA.2 was 43.1% if the previous infection occurred 3 to 6 months earlier and 22.2% if the previous infection had occurred at least 6 months earlier.

Omicron BA.4 and BA.5

Additional analyses in the Qatar population provided detailed information about protection against Omicron BA.4 and BA.5. Among unvaccinated persons, a previous infection with Omicron BA.1 or BA.2 reduced the risk for any infection with Omicron BA.4 or BA.5 by at least 68.7% (CI, 64.0% to 72.9%) compared with only 27.7% (CI,
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Severe Disease

In unvaccinated persons, protection against severe disease with Omicron BA.1 or BA.2 was 87.8% to 90% in the Qatari cohort (35, 39) and 69.8% in the Danish cohort (28). In a multivariable analysis of a large U.K. cohort, previous infection provided moderate protection against hospitalization (55%) and very high protection against death (>80%) (30). Severe disease and death from Omicron were rare in the U.K. nursing home setting, and previous infection seemed to provide some protection (33). However, in a Cleveland Clinic cohort, protection against hospitalization was lower than in other cohorts (44.4%) (32). After adjustment for age, sex, reason for testing, and vaccination status, protection against hospitalization and intensive care unit admission was reduced to 30%. The poorer results for the Cleveland Clinic cohort may be related to a lower proportion of recent (Delta or Omicron BA.1 or BA.2) infections and a higher prevalence of major comorbidities than the population-based studies.

Role of Antibodies in Protection

Our previous report found that seroconversion was associated with substantial protection against reinfection (3), but antibody testing to predict reinfection risk provided no additional information over the more widely used reverse transcriptase polymerase chain reaction test, and the role of antibody testing in clinical practice, if any, was uncertain. Although there is still no definitive evidence to guide practice decisions about antibody testing, studies are underway to delineate reinfection risk with infection-induced antibodies compared with vaccine-induced antibodies (44, 45). The U.K. SIREN (SARS-CoV-2 Immunity and Reinfection Evaluation) study is scheduled to complete data collection in March 2023 (46).

Discussion

A central question of this review has been whether a SARS-CoV-2 antibody test obtained in everyday clinical practice provides useful information about a person’s future risk for infection. In this update, we found that although the antibody response to SARS-CoV-2 infection in the Omicron era remains robust, protection against reinfection was lower.

The emergence of the Omicron variant, which evolved and spread despite high rates of vaccination and previous infection, has intensified interest in the capacity of SARS-CoV-2 variants to evade immune system protection. Recent infection with Delta or Omicron BA.1 or BA.2 seems to be protective against reinfection with Omicron for a few months but was lower than for previous variants and waned rapidly.

Although based on relatively few studies, our findings about protection against Omicron variants are likely to be robust. First, we prioritized large, well-conducted, controlled cohort studies, most of which used consistent methods throughout the entire pandemic. Second, our findings are concordant with those of test-negative case-control studies (47–50) as well as with recent cohort studies (51, 52) and preprints (53–57) identified by surveillance. In general, these studies confirm that protection against Omicron BA.1 or BA.2 from previous infection with the Delta or earlier variants was lower and waned more rapidly over time than for previous variants and that, whereas protection against BA.4 or BA.5 from BA.1 or BA.2 infection was robust for up to 4 months, this protection may wane rapidly (54). One preprint—a meta-analysis of cohort, case-negative case-control, and cross-sectional studies—confirmed that protection against death and severe infection was generally preserved (53).

The main implication of our findings about the antibody response and reinfection risk is that the presence of antibodies would be insufficient to estimate a person’s degree of protection against reinfection. Although understanding population seroprevalence has important public health implications, the value of antibody testing in clinical practice remains unclear.

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Appendix Figure. PRISMA Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram.

Records identified through database searching (n = 17,836) Version 1: 3937 Version 2: 635 Version 3: 13,264

Records identified through reference lists and gray literature searching (n = 161) Version 1: 87 Version 2: 32 Version 3: 42

Excluded at the title/abstract (n = 16,146) Version 1: 2,979 Version 2: 477 Version 3: 12,690

Excluded at full text (n = 984) Ineligible population: 209 Lack of comparator: 73 Ineligible outcome: 137 Ineligible study design: 279 Ineligible publication type: 140 Outdated or ineligible systematic review: 19 Ineligible language: 91 Unable to locate full text: 8 Not Delta or Omicron relevant: 28

Records remaining after title and abstract review (n = 1,100) Version 1: 536 Version 2: 40 Version 3: 524

Records remaining after removal of duplicates (n = 17,246) Version 1: 3,515 Version 2: 517 Version 3: 13,214

Records remaining after full-text review and included in synthesis (n = 113) Version 1: 66 Version 2: 18 Version 3: 29 KQ1: 19 KQ2–3: 10

KQ = key question.