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CLINICAL GUIDELINE

What Is the Antibody Response and Role in Conferring Natural Immunity After SARS-CoV-2 Infection? Rapid, Living Practice Points From the American College of Physicians (Version 2)

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Description: The Scientific Medical Policy Committee (SMPC) of the American College of Physicians (ACP) developed these living, rapid practice points to summarize the current best available evidence on the antibody response to SARS-CoV-2 infection and protection against reinfection with SARS-CoV-2. This is version 2 of the ACP practice points, which serves to update version 1, published on 16 March 2021. These practice points do not evaluate vaccine-acquired immunity or cellular immunity.

Methods: The SMPC developed this version of the living, rapid practice points based on an updated living, rapid, systematic review conducted by the Portland VA Research Foundation and funded by the Agency for Healthcare Research and Quality.

Practice Point 1: *Do not use SARS-CoV-2 antibody tests for the diagnosis of SARS-CoV-2 infection.*

Practice Point 2: *Do not use SARS-CoV-2 antibody tests to predict the degree or duration of natural immunity conferred by antibodies against reinfection, including natural immunity against different variants.*

Retirement From Living Status: Although natural immunity remains a topic of scientific interest, this topic is being retired from living status given the availability of effective vaccines for SARS-CoV-2 and widespread recommendations for and prevalence of their use. Currently, vaccination is the best clinical recommendation for preventing infection, reinfection, and serious illness from SARS-CoV-2 and its variants.

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The Scientific Medical Policy Committee (SMPC) of the American College of Physicians (ACP) has been maintaining these living, rapid practice points to summarize the current best available evidence on the antibody response to SARS-CoV-2 infection and protection against reinfection with SARS-CoV-2 (Table 1). This is version 2 of the ACP practice points, which serves to update version 1, published on 16 March 2021 (3, 4). It is based on a focused update of a living, rapid, systematic review conducted by the Portland VA Research Foundation and funded by the Agency for Healthcare Research and Quality (5, 6). The SMPC developed these practice points according to ACP's practice points development process, details of which can be found in ACP's methods paper (7).

The intended audience for these practice points includes clinicians, patients, the public, and public health officials. The population includes adults who have been previously infected with SARS-CoV-2.

This version was approved by the ACP Executive Committee of the Board of Regents on behalf of the Board of Regents on 9 August 2021 and was submitted to *Annals of Internal Medicine* on 6 August 2021.

Although vaccine-acquired immunity and cellular immunity are important areas of research, this article does not evaluate them.

Key Questions Addressed in the Living and Rapid Systematic Review

Key Question 1 (not updated): What are the prevalence, level, and duration of detectable anti–SARS-CoV-2 antibodies among patients infected with or recovered from reverse transcriptase polymerase chain reaction (RT-PCR)–diagnosed SARS-CoV-2 infection?

See also:

Editorial comment
Related article

* This paper, written by Amir Qaseem, MD, PhD, MHA; Jennifer Yost, RN, PhD; Itziar Etxeandia-Ikobaltzeta, PharmD, PhD; Mary Ann Forciea, MD; George M. Abraham, MD, MPH; Matthew C. Miller, MD; Adam J. Obley, MD; and Linda L. Humphrey, MD, MPH, was developed for the Scientific Medical Policy Committee of the American College of Physicians. Individuals who served on the Scientific Medical Policy Committee from initiation of the project until its approval were Linda L. Humphrey, MD, MPH† (*Chair*); Adam J. Obley, MD† (*Vice Chair*); Robert M. Centor, MD‡ (*Immediate Past Vice Chair*); Elie A. Akl, MD, MPH, PhD†; Rebecca Andrews, MS, MD†; Thomas A. Bledsoe, MD‡; Andrew Dunn, MD, MPH†; Mary Ann Forciea, MD†; Ray Haeme†§; Janet A. Jokela, MD, MPH‡; Devan L. Kansagara, MD, MCR†; Maura Marcucci, MD, MSc‡; Matthew C. Miller, MD†; and CDR Mark P. Tschanz, DO†. Kate Carroll, MPH, and Shannon Merillat, MPH, MLIS, were nonauthor contributors from ACP staff. Approved by the ACP Executive Committee of the Board of Regents on behalf of the Board of Regents on 9 August 2021.
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Update Alerts: The literature update end date is 22 September 2021. No further updates for this topic are planned at this time.

Table 1. Practice Points

Evidence is emerging about the antibody response after *initial infection* with SARS-CoV-2, as well as protection against future reinfection with SARS-CoV-2. These practice points do not evaluate vaccine-acquired immunity or cellular immunity. Vaccination is currently the best clinical recommendation for preventing SARS-CoV-2 infection or reinfection (1, 2). The following practice points are based on the current best available evidence.

Practice Point 1: Do not use SARS-CoV-2 antibody tests for the diagnosis of SARS-CoV-2 infection.

Practice Point 2: Do not use SARS-CoV-2 antibody tests to predict the degree or duration of natural immunity conferred by antibodies against reinfection, including natural immunity against different variants.

What has changed in the practice points since the last version?

- No changes to Practice Point 1.
- Retired Practice Point 2 from version 1, which stated, "Antibody tests can be useful for the purpose of estimating community prevalence of SARS-CoV-2 infection." This statement now has limited relevance in the United States because of widespread vaccine-associated antibodies and limitations in antibody testing to differentiate whether antibodies developed due to past infection with SARS-CoV-2 or vaccination.
- Modified the text of former Practice Point 3 (now Practice Point 2) with a more clear, actionable statement. This practice point previously stated, "Current evidence is uncertain to predict presence, level, or durability of natural immunity conferred by SARS-CoV-2 antibodies against reinfection (after SARS-CoV-2 infection)."

Key Question 1a (not updated): Do the levels and durability of detectable antibodies vary by patient characteristics (for example, age, sex, race/ethnicity, and comorbidities), COVID-19 severity (severity of the initial infection), presence of symptoms, time from symptom onset, or the characteristics of the immunoassay (sensitivity, specificity)?

Key Question 2 (updated): What is the risk for reinfection with SARS-CoV-2 among adults with prior SARS-CoV-2 infection?

Key Question 2a (updated): Does the risk for reinfection vary by patient characteristics (for example, age, sex, race/ethnicity, and comorbidities), severity of the initial infection, initial antibody levels, or SARS-CoV-2 variants?

Key Question 2b (updated): Is there a threshold level of detectable anti–SARS-CoV-2 antibodies necessary to confer natural immunity, and if so, does this threshold vary by patient characteristics (for example, age, sex, race/ethnicity, and comorbidities)?

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

Key Question 3a (updated): Does the duration of protection vary by patient characteristics (for example, age, sex, race/ethnicity, and comorbidities), severity of initial infection, initial antibody levels, SARS-CoV-2 variants, or case identification method (for example, surveillance, symptomatic testing only)?

Key Question 4 (not updated): What are the unintended consequences of antibody testing after SARS-CoV-2 infection?

Key Questions: Rationale for a Focused Update to the Living and Rapid Systematic Review

Updates to key questions in the living, rapid, systematic review are prioritized on the basis of identification of new evidence from literature surveillance that will likely substantially modify the conclusions or the certainty of evidence. Based on literature surveillance, the Portland VA Research Foundation and the SMPC determined that there was a signal to perform a focused update of key questions 2, 2a, 2b, 3, and 3a (large population-based studies that included uninfected comparison groups were published) and that the evidence for key questions 1, 1a, and 4 had not matured enough to evaluate the long-term persistence of antibodies, which would substantially modify the conclusions or certainty of evidence in the previous version. Consistent with methods for living systematic reviews and our living, rapid practice points (7), the inclusion criteria were modified to include large longitudinal studies with control groups to evaluate the risk for reinfection, and key questions were modified for clarity (**Appendix Table**, available at Annals.org).

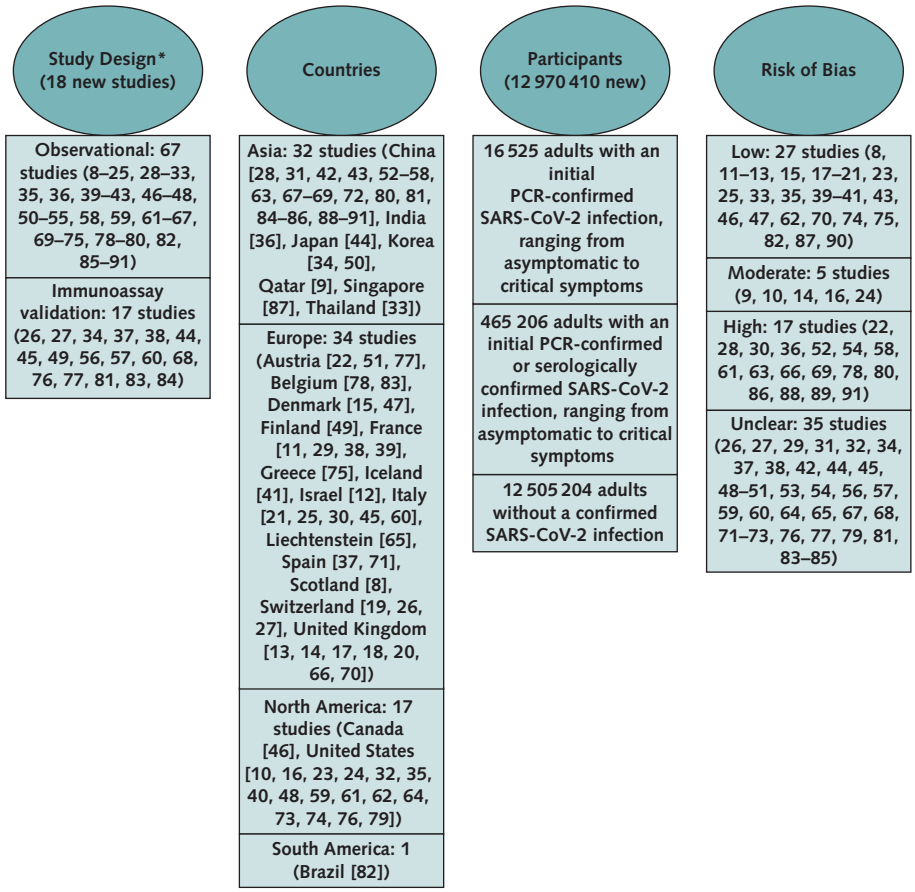
Overview of New Evidence

The evidence update (5, 6) identified 18 new studies (8–25) informing key questions 2, 2a, and 3, for which there were previously no studies that met the inclusion criteria in version 1 (3). These studies were initiated before the emergence of the Delta and Omicron variants and before the U.S. Food and Drug Administration's emergency use authorization of vaccines late in 2020 (5, 6). The new studies compared the risk for symptomatic reinfection (as a primary outcome) among adults with a recent SARS-CoV-2 infection with the risk for infection among adults without a recent infection, with "recent" defined as within 7 months of initial SARS-CoV-2 infection. These studies were designed to evaluate risk for symptomatic reinfection, with risk for asymptomatic reinfection as a secondary outcome. The new studies showed that patients with a recent SARS-CoV-2 infection have a substantially reduced risk for symptomatic reinfection (88% in the general population and 87% in health care workers) compared with those without a recent infection (key question 2) over follow-up of 4 to 13 months. There is also protection for asymptomatic reinfections, but the evidence is unclear about whether the degree of protection for asymptomatic reinfections is as high as it is for symptomatic reinfections. No evidence was identified on threshold levels of antibodies needed to confer protection from reinfection or the contribution of the antibody response to this protection (key question 2b). The systematic review update did not identify evidence from included studies on whether risk for reinfection varied by patient comorbidities (including immunosuppression) or by viral variants other than the Alpha variant (including the Delta and Omicron variants) (key question 2a), or whether the variation in the duration of protection varies by patient or clinical characteristics (key question 3a).

Updated Practice Points and Rationales (Version 2)

Evidence continues to emerge about the antibody response to SARS-CoV-2 infection and protection against

Figure. Evidence description.



The evidence search and assessment were conducted by the Portland VA Research Foundation (3, 5, 6). The evidence search was updated through 22 September 2021. PCR = polymerase chain reaction.

* Observational studies include studies estimating seroprevalence among a given population that includes a small subpopulation known to have SARS-CoV-2 infection; cross-sectional or cohort studies characterizing the antibody response among adults with SARS-CoV-2 infection; and large, population-based observational (cohort, case–control) studies comparing risk for reinfection in adults with and without recent SARS-CoV-2 infection (3,5,6). Immunoassay validation studies include those validating the diagnostic performance of 1 or more immunoassays (3).

future reinfection. The following practice points are based on the current best available evidence. The Figure, Table 2, and the accompanying systematic review (5, 6) summarize changes in the findings. Table 3 presents clinical considerations, and Table 4 identifies evidence gaps.

We have retired Practice Point 2 from version 1, which stated, "Antibody tests can be useful for the purpose of estimating community prevalence of SARS-CoV-2 infection." The relevance of this statement is now limited given the increase in vaccinations in the United States and because antibody tests cannot differentiate antibodies that develop due to past SARS-CoV-2 infection from those that develop due to vaccination.

Practice Point 1: Do not use SARS-CoV-2 antibody tests for the diagnosis of SARS-CoV-2 infection

Reaffirmed Rationale

Studies included in the version 1 systematic review evaluated the prevalence, levels, and duration of different types of antibodies after symptom onset or confirmation of SARS-CoV-2 infection with a positive RT-PCR result (3). These studies showed that most patients develop detectable antibodies after SARS-CoV-2 infection; however, the timing of when different antibodies peak and how long they remain detectable may vary (low to moderate certainty). Furthermore, the antibody response may vary by age, sex, race/ethnicity, and the severity of the initial infection (low certainty), and the evidence is very uncertain (insufficient) as to whether the response varies by comorbidities or type of immunoassay. In addition, the diagnostic test characteristics (for example, sensitivity, specificity, and accuracy) vary substantially across the antibody tests used in the included studies (3–6), contributing to differing risks for false-negative and false-positive results (94, 95). For these reasons, based on the studies included in version 1, antibody tests should not be used for the diagnosis of SARS-CoV-2 infection.

Table 2. Evidence Summary

What has changed in the evidence since the last version?

- Risk for reinfection after initial SARS-CoV-2 infection: Added 18 new studies (previously no studies available)
- Variation in risk for reinfection after initial SARS-CoV-2 infection: Added 18 new studies (previously no studies available)
- Duration of protection against reinfection: Added 8 new studies (previously no studies available)

Key Question	Studies (Participants), *n*	Design (Quality)*	Evidence	Certainty of Evidence†
Prevalence of SARS-CoV-2 antibodies based on timing since symptom onset or confirmatory PCR (key question 1) ***Not updated; based on search through 15 December 2020***				
IgM	21 (6073)	6 OBS (good) 8 OBS (poor) 7 OBS (unclear)	>50% of patients probably develop an IgM antibody response (36, 39, 41–43, 47, 48, 50, 53, 58, 59, 63, 66, 69, 71, 72, 86–90)	Moderate
IgG	24 (9136)	6 OBS (good) 9 OBS (poor) 9 OBS (unclear)	>90% of patients probably develop an IgG antibody response (30, 36, 39, 41, 42, 47, 48, 50, 53, 58, 59, 62, 63, 66, 67, 69, 72, 73, 79, 86–90)	Moderate
IgA	5 (747)	1 OBS (good) 2 OBS (poor) 2 OBS (unclear)	>50% of patients may develop an IgA antibody response (30, 33, 48, 65, 66)	Low
Neutralizing antibodies	8 (979)	3 OBS (good) 1 OBS (poor) 4 OBS (unclear)	>90% of patients may develop neutralizing antibodies (35, 39, 48, 50, 51, 73, 79, 82)	Low
Levels of SARS-CoV-2 antibodies over time and duration (key question 1) ***Not updated; based on search through 15 December 2020***				
IgM	22 (6704)	7 OBS (good) 8 OBS (poor) 5 OBS (unclear) 2 IV (unclear)	Antibodies probably peak at approximately 10 days after symptom onset or RT-PCR diagnosis and remain detectable for ≥115 days (28, 32, 33, 35–37, 42, 43, 45, 46, 52, 53, 58, 63, 66, 69, 72, 82, 85, 87, 88, 90)	Moderate
IgG	25 (9269)	5 OBS (good) 10 OBS (poor) 9 OBS (unclear) 1 IV (unclear)	Antibodies probably peak at approximately 25 days after symptom onset or RT-PCR diagnosis and remain detectable for ≥120 days (28, 31, 32, 36, 41–43, 46, 48, 49, 52–54, 58, 59, 63, 66, 67, 69, 72, 78, 85, 87, 88, 90)	Moderate
IgA	6 (2234)	3 OBS (good) 1 OBS (poor) 1 OBS (unclear) 1 IV (unclear)	Antibodies may peak at approximately 16 to 20 days after symptom onset or RT-PCR diagnosis and may remain detectable for ≥140 days (33, 41, 46, 49, 65, 66)	Low
Neutralizing antibodies	8 (997)	3 OBS (good) 2 OBS (poor) 3 OBS (unclear)	Antibodies may peak at approximately 31 days after symptom onset or RT-PCR diagnosis and may remain detectable for ≥152 days (35, 39, 46, 50, 51, 66, 73, 80)	Low
Variation in prevalence, levels, and duration of SARS-CoV-2 antibodies (key question 1a) ***Not updated; based on search through 15 December 2020***				
Age	12 (9149)	6 OBS (good) 5 OBS (unclear) 1 IV (unclear)	Older age may be associated with higher antibody levels (31, 32, 39, 41, 43, 51, 53, 62, 67, 68, 70, 75)	Low
Sex	12 (7577)	8 OBS (good) 3 OBS (unclear) 1 IV (unclear)	The antibody response to SARS-CoV-2 infection may not vary by sex (31, 39, 41, 43, 51, 62, 67, 68, 70, 74, 75, 82)	Low
Race/ethnicity	2 (2724)	2 OBS (good)	Non-White race may be associated with higher antibody prevalence and levels (62, 70)	Low
Comorbidities	13 (7477)	6 OBS (good) 6 OBS (unclear) 1 IV (unclear)	Very uncertain about whether the antibody response to SARS-CoV-2 infection varies with comorbidities (31, 32, 38, 39, 41, 43, 59, 62, 67, 70, 71, 79, 82)	Insufficient
Severity of initial infection	29 (8534)	6 OBS (good) 10 OBS (poor) 8 OBS (unclear) 5 IV (unclear)	More severe COVID-19 may be associated with a more robust antibody response in terms of antibody levels (30–33, 35, 36, 41–43, 52, 53, 57–59, 63, 66, 68, 71, 72, 75–78, 83, 85, 87–89, 91)	Low
Presence of symptoms	9 (4793)	5 OBS (good) 1 OBS (unclear) 3 IV (unclear)	The presence of symptoms may be associated with higher antibody prevalence and levels (32, 39, 41, 44, 60, 62, 70, 75, 83)	Low
Immunoassays	10 (1996)	2 OBS (good) 1 OBS (poor) 1 OBS (unclear) 6 IV (unclear)	Very uncertain about whether the presence of detectable antibodies varies on the basis of different immunoassays (26, 27, 37, 39, 41, 50, 76–78, 83)	Insufficient

Continued on following page

Table 2–Continued

Key Question	Studies (Participants), *n*	Design (Quality)*	Evidence	Certainty of Evidence†
Risk for reinfection after initial SARS-CoV-2 infection (key question 2) ***New studies; updated through 22 September 2021***				
Risk for reinfection	18 (12 968 006)	12 OBS (good) 5 OBS (fair) 1 OBS (poor)	Recent SARS-CoV-2 infection in adults reduces risk for symptomatic reinfection by 84% to 90% compared with adults without a recent infection (8–25) *Note: Recent infection protects against asymptomatic reinfection; however, it is unclear whether the strength of protection from initial infection is as strong for asymptomatic reinfection as it is for symptomatic reinfection‡ (8–11, 13, 18–25)*	High
Variation in risk for reinfection after initial SARS-CoV-2 infection (key question 2a) ***New studies; updated through 22 September 2021***				
Age	5 (529 105)	5 OBS (good)	Risk for reinfection may not vary by age (12, 15, 17–19)	Low
Sex	18 (12 968 006)	12 OBS (good) 5 OBS (fair) 1 OBS (poor)	Risk for reinfection does not vary by sex (8–25)	High
Race/ethnicity	1 (4411)	1 OBS (fair)	Very uncertain about whether risk for reinfection varies by race/ethnicity (10)	Insufficient
Comorbidities	NA	NA	No evidence	NA
Initial antibody levels	11 (3 241 686)	7 OBS (good) 4 OBS (fair)	Very uncertain about how initial antibody levels affect risk for reinfection (8–11, 13, 14, 16–20)	Insufficient
Severity of initial infection	10 (12 345 502)	6 OBS (good) 3 OBS (fair) 1 OBS (poor)	Mild or asymptomatic initial infections may be associated with higher risk for reinfection (8, 11, 13, 14, 16, 19, 20, 22, 24, 25)	Low
SARS-CoV-2 variants	3 (27 772)	3 OBS (good)	The Alpha variant may not affect protection against reinfection (12, 13, 18)	Low
Threshold level of antibodies to confer natural immunity (key question 2b) ***Updated through 22 September 2021***				
NA	NA	NA	No evidence	NA
Duration of protection against reinfection (key question 3) ***New studies; updated through 22 September 2021***				
Duration of protection	8 (80 206)	5 OBS (good) 2 OBS (fair) 1 OBS (poor)	Protection against reinfection remains >80% for ≥7 months (8, 9, 11, 15, 18, 19, 22, 24) Protection against reinfection may remain >80% for 7 to 10 months (11, 15, 18, 19, 22, 24) Very uncertain about protection against reinfection beyond 10 months (11)	High Low Insufficient
Variation in duration of protection against reinfection (key question 3a) ***Updated through 22 September 2021***				
NA	NA	NA	No evidence	NA
Unintended consequences of antibody testing (key question 4) ***Not updated; based on search through 15 December 2020***				
Physical distancing behaviors	1 (84)	1 OBS (unclear)	Very uncertain about the effect of antibody testing on physical distancing behaviors (64)	Insufficient

IV = immunoassay validity study; NA = not available; OBS = observational study; PCR = polymerase chain reaction; RT-PCR = reverse transcriptase polymerase chain reaction.

* Good quality: methodologically sound study with low risk of bias. Fair quality: methodologically questionable study with moderate risk of bias. Poor quality: methodologically flawed study with high risk of bias. Unclear quality: methodological soundness could not be determined.

† "Insufficient" indicates that confidence is inadequate to assess the likelihood of benefit (benefit minus harm) of an intervention or its effect on a health outcome. "Low" indicates that confidence in the effect is limited, as the true effect may be substantially different from the estimated effect. "Moderate" indicates that confidence in the effect is moderate, as the true effect is likely close to the estimated effect, but there is a sizable possibility that it is substantially different. "High" indicates confidence that the true effect is close to the estimated effect. Assessments regarding antibody prevalence were focused on results from seroprevalence, cross-sectional, and cohort studies rather than results from immunoassay validation studies (which provide less reliable estimates). For all other outcomes of interest, results from all studies were incorporated into the assessments (3).

‡ The certainty of evidence was not assessed for these comparisons.

Table 3. Clinical Considerations

- *Updated:* These practice points only evaluate the antibody-mediated natural immune response and do not address the role of other important natural or acquired immune responses, such as cell-mediated immunity or artificial immunity conferred by vaccination.
- *New:* Given uncertainty about the level and duration of protection that natural immunity confers, vaccination is currently the best clinical recommendation for protection against SARS-CoV-2 infection or reinfection (1, 2).
- *Updated:* The public should continue to follow recommended infection prevention and control procedures to slow and reduce the transmission of SARS-CoV-2 infection (92, 93).

Practice Point 2: Do not use SARS-CoV-2 antibody tests to predict the degree or duration of natural immunity conferred by antibodies against reinfection, including natural immunity against different variants

Updated Rationale

Because measuring antibodies is an approach for evaluating the immune response, questions arise about the role of antibody testing in assessing natural immunity and protection from reinfection after SARS-CoV-2 infection. Although new evidence (18 new studies) has emerged addressing the risk for reinfection among adults with recent SARS-CoV-2 infection, several important evidence gaps remain in the new body of evidence that limit the clinical role of antibody testing (Table 4).

Low- to moderate-certainty evidence showed that patients with asymptomatic and symptomatic initial infections develop detectable antibodies (3), and high-certainty evidence from new studies showed that recent initial SARS-CoV-2 infection reduced the risk for symptomatic reinfection by 84% to 90% in adults over follow-up ranging from 4 to 13 months. This degree of protection may be similar across age groups (low certainty), with the Alpha variant (low certainty), in persons in the general population and health care workers, and does not vary according to sex (high certainty). However, these studies do not establish that antibodies are primarily responsible for the observed natural immunity because none of the new studies examined the relationship between antibody levels and degree of natural immunity, including threshold levels of detectable SARS-CoV-2 antibodies necessary to confer natural immunity. Furthermore, the included studies were conducted before the Delta and Omicron variants became the dominant circulating strains. However, the systematic review identified 3 studies that were not yet fully reported (96) or were longitudinal uncontrolled studies (97, 98) and thus did not meet the inclusion criteria; these studies suggest that recent SARS-CoV-2 infection reduced risk for reinfection in adults after the Delta variant became the dominant strain.

It is important to note that none of the new included studies reported on the variation in risk for reinfection in patients who are immunocompromised or have other comorbidities, and evidence is very uncertain (insufficient) about other factors that may modify risk for reinfection, including initial antibody levels and race/ethnicity. Evidence is also conflicting about risk for reinfection in patients who had an asymptomatic initial infection (5, 6); studies show that risk for reinfection may be higher for patients who had a mild or asymptomatic initial infection compared with those who had a symptomatic initial infection (low certainty). Although evidence suggests a high degree of protection (>80%) against symptomatic SARS-CoV-2 reinfection in the short term (high certainty for up to 7 months and low certainty for 7 to 10 months), the duration of protection beyond 10 months is very uncertain (insufficient), and follow-up in the included studies is constrained by time elapsed since the beginning of the pandemic. Finally, none of the included studies reported on how the duration of protection might vary by such factors as variant strains, initial antibody levels, and patient characteristics.

Despite evidence that patients develop detectable antibodies (3) and have reduced risk for reinfection after initial SARS-CoV-2 infection, knowledge about the direct association of the antibody response and the degree of natural immunity to SARS-CoV-2 is still limited. In light of these evidence gaps, and considering previously reported insufficient (very uncertain) evidence (3) about the unintended consequences of antibody testing, we advise against antibody testing to evaluate for natural immunity. Patients with current or previous SARS-CoV-2 infection should continue to follow recommended infection prevention and control procedures to slow and reduce transmission of the virus (92, 93, 99).

Table 4. Evidence Gaps

- Studies are needed to understand why some patients with PCR-confirmed SARS-CoV-2 infection do not develop antibodies.
- *New:* Research is needed to determine the threshold levels of detectable SARS-CoV-2 antibodies that are necessary to provide continued protection against reinfection (antibodies from prior infection or vaccination) and to identify the most valid and reliable tests to determine these levels.
- *Updated:* Research is needed to understand the associations between antibody response and patient characteristics (age, sex, race/ethnicity, comorbidities, immunocompromised status, presence of symptoms, and severity of initial infection).
- *Updated:* Research is needed to determine how long protection from reinfection is conferred by antibodies and whether this varies by clinical and patient characteristics.
- *New:* The included studies were not entirely representative of patients who may be disproportionately affected by COVID-19. Research is needed to determine whether there are differences in protection against reinfection based on patient characteristics (age, race/ethnicity, comorbidities, and immunocompromised status).
- *New:* Research is needed to determine whether there are differences in protection against reinfection based on initial antibody levels, severity of initial infection, and SARS-CoV-2 variants.

PCR = polymerase chain reaction.

Retirement From Living Status

The SMPC is retiring the ACP living, rapid practice points on the antibody response to SARS-CoV-2 infection and protection against reinfection with SARS-CoV-2 from living status (7), given the widespread availability and use of effective vaccines against SARS-CoV-2 infection in the United States. Vaccination is currently the best clinical recommendation for prevention of SARS-CoV-2 infection

and reinfection, including from currently circulating viral variants (1, 2).

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Note: The practice points are meant to guide care based on the best available evidence and may not apply to all patients or individual clinical situations. They should not be used as a replacement for a clinician's judgment. Any reference to a product or process contained in a practice point is not intended as an endorsement of any specific commercial product. All practice points are considered automatically withdrawn or invalid 5 years after publication or once an update has been issued.

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Appendix Table. Key Questions Version History

Key Question	Version 1	Version 2*
KQ 1	What are the prevalence, level, and durability of detectable anti–SARS-CoV-2 antibodies among patients infected with or recovered from reverse transcriptase polymerase chain reaction (RT-PCR)–diagnosed SARS-CoV-2 infection?	What are the prevalence, level, and **duration** of detectable anti–SARS-CoV-2 antibodies among patients infected with or recovered from reverse transcriptase polymerase chain reaction (RT-PCR)–diagnosed SARS-CoV-2 infection?
KQ 1a	Do the levels and durability of detectable antibodies vary by patient characteristics (for example, age, sex, race/ethnicity, and comorbidities), COVID-19 severity, presence of symptoms, time from symptom onset, or the characteristics of the immunoassay (sensitivity or specificity)?	Do the levels and durability of detectable antibodies vary by patient characteristics (for example, age, sex, race/ethnicity, and comorbidities), COVID-19 severity **(severity of the initial infection)**, presence of symptoms, time from symptom onset, or the characteristics of the immunoassay (sensitivity, specificity)?
KQ 2	Do anti–SARS-CoV-2 antibodies confer natural immunity against reinfection?	What is the **risk for reinfection** with SARS-CoV-2 among adults with prior SARS-CoV-2 infection? *Revised to include studies in which infection (cohort allocation) was documented by PCR (or by a combination of PCR and antibody testing) rather than by seroconversion or presumed seroconversion only, as well as to address magnitude of protection against future reinfection*
KQ 2a	Does natural immunity vary by such factors as initial antibody levels, patient characteristics, presence of symptoms, or severity of disease?	Does the **risk for reinfection** vary by patient characteristics **(for example, age, sex, race/ethnicity, and comorbidities)**, severity of the **initial infection**, initial antibody levels, **or SARS-CoV-2 variants**? *Revised to include studies in which infection (cohort allocation) was documented by PCR (or by a combination of PCR and antibody testing) rather than by seroconversion or presumed seroconversion only, as well as to address the magnitude of protection against future reinfection; modified to also assess variation by SARS-CoV-2 variants*
KQ 2b	Is there a threshold level of detectable anti–SARS-CoV-2 antibodies necessary to confer natural immunity, and if so, does this threshold vary by patient characteristics (for example, age, sex, race/ethnicity, and comorbidities)?	No changes
KQ 3	If anti–SARS-CoV-2 antibodies confer natural immunity against reinfection, how long does this immunity last?	What is the **duration of protection against reinfection** among adults with prior SARS-CoV-2 infection? *Revised to include studies in which infection (cohort allocation) was documented by PCR (or by a combination of PCR and antibody testing) rather than by seroconversion or presumed seroconversion only*
KQ 3a	Does the duration of natural immunity vary by such factors as initial antibody levels, patient characteristics, presence of symptoms, or severity of disease?	Does the duration of **protection** vary by patient characteristics **(for example, age, sex, race/ethnicity, and comorbidities)**, severity of **initial infection**, initial antibody levels, **SARS-CoV-2 variants**, **or case identification method (for example, surveillance, symptomatic testing only)**? *Rephrased for clarity; modified to also assess variation by SARS-CoV-2 variants and case identification method*
KQ 4	What are the unintended consequences of antibody testing after SARS-CoV-2 infection?	No changes

KQ = key question; PCR = polymerase chain reaction; RT-PCR = reverse transcriptase polymerase chain reaction.
* Language modifications are in boldface.