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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 1)

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Description: The widespread availability of SARS-CoV-2 antibody tests raises important questions for clinicians, patients, and public health professionals related to the appropriate use and interpretation of these tests. The Scientific Medical Policy Committee (SMPC) of the American College of Physicians developed these rapid, living practice points to summarize the current and best available evidence on the antibody response to SARS-CoV-2 infection, antibody durability after initial infection with SARS-CoV-2, and antibody protection against reinfection with SARS-CoV-2.

Methods: The SMPC developed these rapid, living practice points based on a rapid and living systematic evidence review done by the Portland VA Research Foundation and funded by the Agency for Healthcare Research and Quality. Ongoing literature surveillance is planned through December 2021. When new studies are identified and a full update of the evidence review is published, the SMPC will assess the new evidence and any effect on the practice points.

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

Practice Point 2: *Antibody tests can be useful for the purpose of estimating community prevalence of SARS-CoV-2 infection.*

Practice Point 3: *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).*

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KEY QUESTION 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?

Key Question 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)?

KEY QUESTION 2

Do anti–SARS-CoV-2 antibodies confer natural immunity against reinfection?

Key Question 2a

Does natural immunity vary by such factors as initial antibody levels, patient characteristics, presence of symptoms, or severity of disease?

Key Question 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)?

See also:

Related article
Summary for Patients

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Update Alerts: The authors have specified in the Background section and the **Appendix** (available at Annals.org) the interval and stop date for updates to this Practice Points article. As *Annals* receives updates, they will appear in the Comments section of the article on Annals.org. Reader inquiries about updates that are not available at approximately the specified intervals should be submitted as comments to the article.

Table 1. Practice Points

Evidence is emerging about the antibody response to SARS-CoV-2 and its durability after initial infection with SARS-CoV-2 as well as protection against future reinfection with SARS-CoV-2. The following practice points are based on 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: Antibody tests can be useful for the purpose of estimating community prevalence of SARS-CoV-2 infection.

Practice Point 3: 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 3

If anti–SARS-CoV-2 antibodies confer natural immunity against reinfection, how long does this immunity last?

Key Question 3a

Does the duration of natural immunity vary by such factors as initial antibody levels, patient characteristics, presence of symptoms, or severity of disease?

KEY QUESTION 4

What are the unintended consequences of antibody testing after SARS-CoV-2 infection?

BACKGROUND

The widespread availability of SARS-CoV-2 antibody tests raises important questions for clinicians, patients, and public health professionals related to the appropriate use and interpretation of these tests. However, currently little is known about the relationship between SARS-CoV-2 antibodies and natural immunity. The potential for natural immunity to SARS-CoV-2 infection stems from the activation of B lymphocytes (humoral or antibody-mediated immunity) and T lymphocytes (cellular immunity). However, like with other viruses, the relationship between antibodies and natural immunity may vary on the basis of differences in the level and duration of antibodies produced as well as viral mutations of the infection. When persons are infected with SARS-CoV-2, uncertainty exists about whether the antibodies produced (IgM, IgG, IgA, or neutralizing) are protective against reinfection, and if so, for how long what levels of antibodies are needed for such protection (1). In addition, because antibodies to other coronaviruses have been shown to decline over time, how long such protection against reinfection may last also needs to be determined (2). As a step toward better understanding the immune response to SARS-CoV-2, the Scientific Medical Policy Committee (SMPC) of the American College of Physicians (ACP) developed these practice points on the basis of key questions related to the antibody-mediated natural immunity after SARS-CoV-2 infection. This article does not evaluate cellular immunity or artificial immunity conferred by vaccines, both of which are important areas of research.

The SMPC developed these rapid, living practice points (**Table 1**) on the basis of a rapid and living systematic evidence review done by the Portland VA Research Foundation and funded by the Agency for Healthcare Research and Quality (3, 4). The details of our process can be found in the **Appendix** (available at Annals.org). This version of the practice points is based on an initial search to 4 August 2020 that was subsequently revised and updated through 15 December 2020. It was approved by ACP's Executive Committee of the Board of Regents on behalf of the Board of Regents on 22 February 2021 and submitted to *Annals of Internal Medicine* on 22 February 2021. Ongoing literature surveillance is planned through December 2021. The target audience for these practice points includes clinicians, patients, the public, and public health officials. The target patient population includes adults who have been previously infected with SARS-CoV-2.

Table 2 presents clinical considerations, the **Figure** and **Table 3** summarize current evidence, and **Table 4** identifies additional evidence gaps. The **Appendix Table** (available at Annals.org) presents the data estimates supporting the practice points.

PRACTICE POINTS AND RATIONALE

Prevalence, Level, and Durability of Antibodies Among Patients Infected With or Recovered From SARS-CoV-2 Infection

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

Table 2. Clinical Considerations

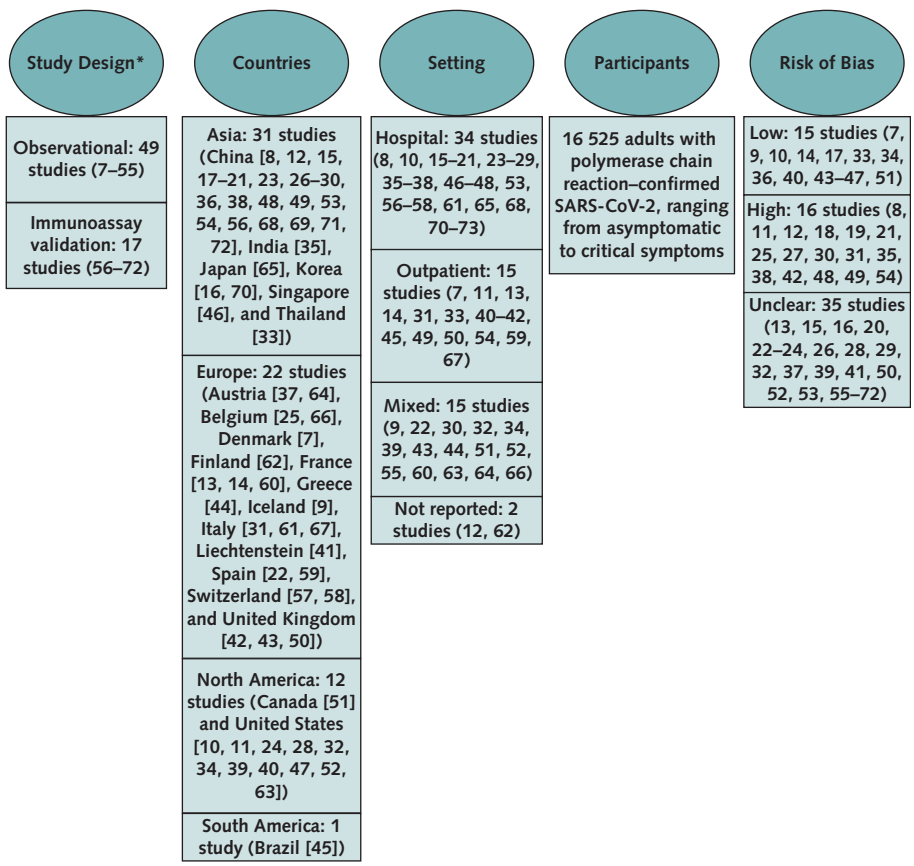
- In the face of uncertainty, patients with SARS-CoV-2 infection, those with a history of SARS-CoV-2 infection, and the public should follow infection prevention and control procedures to slow and reduce the transmission of SARS-CoV-2 (maintain physical distance; wear face coverings, such as surgical or cloth masks, in settings where physical distancing is not possible; use masks appropriately; self-isolate; quarantine; practice frequent hand hygiene [use soap and water or alcohol-based hand rub]; cover cough and sneezes using a bent elbow or paper tissue; refrain from touching the face; and regularly disinfect frequently touched surfaces) (5, 6).
- The relationship between the development of antibodies after SARS-CoV-2 infection and the risk for reinfection has not been established (3, 4).
- Although SARS-CoV-2 serologic tests detect IgM, IgG, and IgA immunoglobulins, the tests may also give a positive result due to cross-reactivity with antibodies to other coronaviruses (3, 4).
- Evidence considers serologic tests that were approved and for which emergency use authorization had not been revoked by the U.S. Food and Drug Administration as of 5 August 2020 (3, 4).
- SARS-CoV-2 serologic tests vary in accuracy, and there is insufficient evidence on the association between the use of different tests and the presence of detectable antibodies.
- These practice points evaluate only the antibody-mediated natural immunity response and do not address the role of other important natural immune responses, such cell-mediated immunity or artificial immunity conferred by vaccines.

Practice Point 2: Antibody tests can be useful for the purpose of estimating community prevalence of SARS-CoV-2 infection.

Studies included in the evidence review focused on evaluating the trends in types of antibodies and their levels after symptom onset or confirmation of SARS-CoV-2 infection with a positive RT-PCR test result. Evidence from studies evaluating community prevalence in antibody response showed that patients develop an immune response after SARS-CoV-2 infection. This is evidenced by detectable IgA antibodies in most patients (low certainty), IgM in most patients (moderate certainty), IgG in nearly all patients (moderate certainty), and neutralizing antibodies in nearly all patients (low certainty). The antibody prevalence and levels may vary over time by certain patient characteristics (for example, age, sex, and race/ethnicity) and disease factors (for example, presence of symptoms and severity) (low certainty). The timing from symptom onset or PCR-confirmed infection of when antibodies first become detectable and the level at which they remain detectable vary depending on the type of antibody. At or around peak level, IgM, IgG, IgA, and neutralizing antibodies are estimated to be detectable in approximately 80%, 95%, 83%, and 99% of patients, respectively, after symptom onset or PCR-confirmed infection. Despite variation, each of these antibody types has its peak level on average between 20 and 31 days after symptom onset or PCR-confirmed infection. Evidence shows that antibodies may persist over time; IgM antibodies were detected up to 115 days (moderate certainty), IgG antibodies were detected up to 120 days (moderate certainty), IgA antibodies were detected up to 140 days (low certainty), and neutralizing antibodies were detected up to 152 days (low certainty).

Given that not all patients develop detectable antibodies early in the course of the infection and that the presence and levels may vary by patient and disease characteristics, antibody tests should not be used for the diagnosis of SARS-CoV-2 infection. It is also important for clinicians and patients to keep in mind that SARS-CoV-2 antibody test results may be falsely positive due to cross-reactivity with antibodies of other coronaviruses (74, 75). Furthermore, although a complete assessment of diagnostic accuracy of various antibody tests was beyond the scope of the evidence review, characteristics (for example, sensitivity, specificity, and accuracy) varied

Figure. Evidence description.



Evidence search and assessment done by the Portland VA Research Foundation (3, 4). Updated search for evidence updated through 15 December 2020.

* Observational studies include studies estimating seroprevalence among a given population that includes a small subpopulation known to have SARS-CoV-2 and cross-sectional or cohort studies characterizing the antibody response among adults with SARS-CoV-2 infection. Immunoassay validation studies include those validating the diagnostic performance of 1 or more immunoassays (3, 4).

Table 3. Evidence Summary for Patients With PCR-Confirmed SARS-CoV-2 Infection

Outcome	Studies (Patients), *n*	Evidence	Certainty of Evidence*
Prevalence of SARS-CoV-2 antibodies based on timing since symptom onset or confirmatory PCR (key question 1)			
IgM	21 (6073)	Most† patients probably develop an IgM antibody response (7–9, 12, 14–19, 21–23, 27, 33, 35, 36, 39, 42, 46–48, 52, 61, 69)	Moderate
IgG	24 (9136)	Nearly all† patients probably develop an IgG antibody response (7–9, 12, 14–21, 23, 24, 27, 28, 31, 35, 39, 40, 42, 46–48, 52, 56, 63–67, 69)	Moderate
IgA	5 (747)	Most† patients may develop an IgA antibody response (9, 22, 31, 33, 41, 42, 44, 52, 62, 66)	Low
Neutralizing antibodies	8 (979)	Nearly all† patients may develop neutralizing antibodies (14, 16, 24, 29, 30, 34, 37, 45, 52)	Low
Levels of SARS-CoV-2 antibodies over time and durability (key question 1)			
IgM	22 (6704)	Antibodies probably peak at approximately 20 d after symptom onset or RT-PCR diagnosis and remain detectable for at least 115 d (8, 15, 18, 19, 21, 23, 26, 27, 29, 30, 33-36, 38, 42, 45, 46, 51, 56, 59, 61)	Moderate
IgG	25 (9269)	Antibodies probably peak at approximately 25 d after symptom onset or RT-PCR diagnosis and remain detectable for at least 120 d (9, 15, 17-21, 23, 25-27, 29, 30, 32, 35, 36, 38, 39, 42, 46, 49, 51, 52, 56, 62)	Moderate
IgA	6 (2234)	Antibodies may peak at approximately 16 to 30 d after symptom onset or RT-PCR diagnosis and may remain detectable for at least 140 d after symptom onset or RT-PCR diagnosis (9, 26, 33, 41, 42, 51, 62)	Low
Neutralizing antibodies	8 (997)	Antibodies may peak at approximately 31 d after symptom onset or RT-PCR diagnosis and may remain detectable for at least 152 d (14, 16, 24, 29, 30, 33, 34, 37, 42, 51)	Low
Variation in prevalence, levels, and duration of SARS-CoV-2 antibodies (key question 1a)			
Age	12 (9149)	Older age may be associated with higher antibody levels (9, 14, 20, 29, 32, 36, 37, 40, 43, 44, 56)	Low
Sex	12 (7577)	The antibody response to SARS-CoV-2 infection may not vary by sex (9, 14, 20, 29, 36, 37, 40, 43-45, 47, 56)	Low
Race/ethnicity	2 (2724)	Non-White race may be associated with higher antibody prevalence and levels (40, 43)	Low
Preexisting comorbid conditions	13 (7477)	Whether the antibody response to SARS-CoV-2 infection varies with preexisting comorbid conditions is very uncertain (28, 29, 32, 36, 39, 40, 43, 45)	Insufficient
Disease severity	30 (8900)	More severe COVID-19 illness may be associated with a more robust antibody response in terms of antibody levels (8, 9, 15, 18, 19, 22, 23, 25–29, 31–36, 38, 39, 42, 44, 46, 48, 56, 63, 64, 66, 71)	Low
Presence of symptoms	9 (4793)	The presence of symptoms may be associated with higher antibody prevalence and levels (8, 13, 31, 39, 42, 43, 64–66)	Low
Immunoassay tests	10 (1996)	Whether the presence of detectable antibodies varies on the basis of different immunoassay tests is very uncertain (9, 14, 16, 25, 29, 32, 35, 40, 43, 44, 57–59, 63, 64, 66)	Insufficient
Reinfection among patients with SARS-CoV-2 antibodies (key question 2)			
Incidence	NA	No studies addressed key question	Insufficient
Length of time between an initial PCR-confirmed SARS-CoV-2 infection and reinfection (key question 3)			
NA	NA	No studies addressed key question	Insufficient
Unintended consequences of antibody testing (key question 4)			
Physical distancing and behaviors	1 (84)	The effect of antibody testing on physical distancing behaviors is very uncertain (50)	Insufficient

NA = not applicable; PCR = polymerase chain reaction; RT-PCR = reverse transcriptase PCR.
* Insufficient certainty of evidence: confidence is inadequate to assess the likelihood of benefit (benefit minus harm) of an intervention or its effect on a health outcome. Low certainty of evidence: confidence in the effect is limited because the true effect may be substantially different from the estimated effect. Moderate certainty of evidence: confidence in the effect is moderate because the true effect is likely close to the estimated effect, but there is a sizable possibility that it is substantially different. High certainty of evidence: 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 on results from immunoassay validation studies (which provide less reliable estimates). For all other outcomes of interest, results from all studies were incorporated into strength of evidence assessments (3, 4).
† "Nearly all" refers to greater than 90% of the participants across studies, "most" refers to more than half of the participants across studies, and "some" refers to less than half of the participations across studies.

substantially among the antibody tests used in included studies (3, 4). Such variation can contribute to false-negative and false-positive test results and ultimately wrong conclusions (76, 77).

However, for the purposes of estimating community prevalence of SARS-CoV-2 infection, antibody testing is a feasible option, keeping in mind that antibody levels peak roughly 3 to 5 weeks after symptom onset or PCR

Table 4. Evidence Gaps

- Research is needed to evaluate the degree of protection conferred by antibodies against reinfection and how long this protection may last
- Studies should be specifically designed to evaluate antibody-mediated natural immunity among patients who recovered from SARS-CoV-2 infection
- Research is needed to understand the associations of age, sex, race/ethnicity, preexisting comorbid conditions, presence of symptoms, and COVID-19 severity with antibody response, duration, and protection against reinfection.
- Studies are needed to understand why some patients with polymerase chain reaction–confirmed SARS-CoV-2 infection do not develop antibodies.
- Studies are needed to understand the downstream clinical consequences of antibody testing.

diagnosis. Also, the usability and interpretation of SARS-CoV-2 antibodies will need to be evaluated in persons vaccinated against COVID-19, as vaccination will also affect the development of SARS-CoV-2 antibodies.

Reinfection Among Patients With SARS-CoV-2 Antibodies and Unintended Consequences of Antibody Testing

Practice Point 3: 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).

Current evidence is limited about natural immunity conferred by SARS-CoV-2 antibodies. As discussed earlier, asymptomatic or symptomatic patients may develop an antibody response consistent with natural immunity after having SARS-CoV-2 infection, but key individual-level differences depend on such variables as COVID-19 disease severity, patient factors, types of antibodies and amount developed, and how long the antibodies last. This is an area of rapidly emerging new evidence. No identified evidence directly evaluates the association between antibodies and natural immunity, although 2 studies are in progress (7, 78). In the evidence review, a study (8) of hospitalized patients with COVID-19 (n = 47) reported a potential case of reinfection during the "convalescence stage" of the disease in 1 patient who did not have detectable IgM or IgG antibodies at 4-week follow-up. However, the study was not designed to determine whether antibodies confer immunity. Evidence does show that there are detectable levels of IgA antibodies in most patients (low certainty), IgM in most patients (moderate certainty), IgG in nearly all patients (moderate certainty), and neutralizing antibodies in nearly all patients (low certainty). Evidence also shows that IgG antibodies probably remain detectable for at least 120 days (moderate certainty) and neutralizing antibodies may remain detectable for at least 152 days (low certainty). The antibody prevalence and levels over time may vary by certain patient characteristics (for example, age, sex, and race/ethnicity) and disease factors (for example, presence of symptoms and severity) (low certainty). The evidence review also identified 3 longitudinal studies (indirect evidence) that used serologic rather than RT-PCR testing as the index test and, thus, did not meet the inclusion criteria. These studies suggest that antibody presence may be associated with natural immunity (78–81); however, the evidence review has not critically appraised them. Given that there is no direct evidence to inform the question of reinfection, we will consider modifying future searches to formally incorporate additional sources of indirect evidence, including these studies.

Evidence is uncertain (insufficient) about the unintended consequences of antibody testing.

Given limited knowledge about the association between antibody levels and natural immunity, patients with SARS-CoV-2 infection and those with a history of SARS-CoV-2 infection should follow recommended infection prevention and control procedures to slow and reduce the transmission of SARS-CoV-2 (5, 6).

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Note: The practice points are developed by the SMPC of the ACP. The practice points are guides only and may not apply to all patients and all clinical situations. 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: Practice Points Development Process

The SMPC, in collaboration with staff from ACP's Department of Clinical Policy, developed these practice points on the basis of a rapid and living systematic evidence review done by the Portland VA Research Foundation and funded by the Agency for Healthcare Research and Quality (3, 4). The SMPC comprises 11 internal medicine physicians representing various clinical areas of expertise and 1 public (nonclinician) member and includes members with expertise in epidemiology, evidence synthesis, health policy, and guideline development. In addition to contributing clinical, scientific, and methodological expertise, Clinical Policy staff provided administrative support and liaised among the SMPC, the evidence review funding entity and evidence team, and the journal. Clinical Policy staff and the SMPC reviewed and prioritized potential topic suggestions from ACP members, SMPC members, and ACP governance. A committee subgroup, including the SMPC chair, worked with staff to draft the key questions and led the development of the practice points. Clinical Policy staff worked with the subgroup and an independent evidence review team to refine the key questions and determine appropriate evidence synthesis methods for each key question. Via conference calls and e-mail, Clinical Policy staff worked with the committee subgroup to draft the practice points on the basis of the results of the rapid and living systematic evidence review. The full SMPC reviewed and approved the final practice points. Before journal submission, ACP's Executive Committee of the Board of Regents also reviewed and approved the practice points on behalf of the ACP Board of Regents. The evidence review team is planning ongoing literature surveillance at least through December 2021. When no new studies are identified, the SMPC will publish a comment on the most recent version of the practice points that indicates the date of the last search and that no new studies were identified. When new studies are identified but previous conclusions remain unchanged, the SMPC will publish an update alert letter that briefly summarizes the new evidence and updates the rationale and evidence tables for the practice points. When new studies are identified and a full update of the evidence review is published, the SMPC will assess the new evidence and reaffirm (via update alert letter) or revise and modify (via new version) the practice points. The SMPC will continually evaluate the priority level of each living topic and may decide to retire a topic early from living status if it determines that the topic is no longer considered a priority for decision making, if there is confidence that the conclusions are not likely to change with the emergence of new evidence or affect practice, or when it is unlikely that new evidence will emerge (82).

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Appendix Table. Data Estimates

Outcome	Studies (Patients), *n*	Evidence	Certainty of Evidence*
Prevalence of anti–SARS-CoV-2 antibodies based on timing since symptom onset or confirmatory PCR			
IgM	21 (6073)	The median of prevalence estimates (7-9, 12, 14-19, 21-23, 27, 28, 35, 36, 39, 42, 46, 52): 80%† (range, 9% to 98%) when measured approximately 20 d after symptom onset or RT-PCR diagnosis	Moderate
IgG	24 (9136)	The median of prevalence estimates (7-9, 12, 14-21, 23, 24, 27, 28, 31, 35, 39, 40, 42, 46, 52, 55): 95%† (range, 15% to 100%) when measured approximately 25 d after symptom onset or RT-PCR diagnosis	Moderate
IgA	5 (747)	The median of prevalence estimates (31, 33, 41, 42, 52): 83%† (range, 75% to 89%) when measured from 2 to 122 d after symptom onset or RT-PCR diagnosis	Low
Neutralizing antibodies	8 (979)	The median of prevalence estimates (14, 16, 24, 30, 34, 37, 45, 52): 99%† (range, 76% to 100%) when measured approximately 30 d after symptom onset or RT-PCR diagnosis	Low
Levels of anti–SARS-CoV-2 antibodies over time and durability			
IgM	22 (6704)‡	Earliest detected (*n* = 1715) (15, 17-19, 21, 23, 26, 27, 30, 35, 46, 61): Median, 7 d (range, 3 to 14 d) Peak (*n* = 5474) (15, 18, 19, 21, 23, 27-30, 35, 36, 38, 42, 51, 59): Median, 20 d (range, 10 to 35 d) Starts to decline (*n* = 2413) (19, 23, 29, 30, 34, 35, 51): Median, 27 d (range, 14 to 35 d) Latest detected (*n* = 567) (51): 115 d	Moderate
IgG	25 (9269)§	Earliest detected (*n* = 4348) (17-21, 25-27, 29, 30, 35, 38, 39, 46, 49, 62): Median, 12 d (range, 3 to 41 d) Peak (*n* = 5032) (9, 18, 19, 21, 25, 27, 28, 30, 36, 51, 52): Median, 25 d (range, 14 to 42 d) Starts to decline (*n* = 3286) (20, 28, 32, 51): Median, 60 d (range, 30 to 100 d) Latest detected (9): 120 d	Moderate
IgA	6 (2234)	Earliest detected (*n* = 40) (62): 11 d Peak (*n* = 632) (42, 51): Range, 16 to 30 d Starts to decline (*n* = 1977) (9, 41, 42, 51): Median, 30 d (range, 28 to 48 d) Latest detected (*n* = 217) (33): 140 d	Low
Neutralizing antibodies	8 (997)	Earliest detected (*n* = 103) (24, 37, 54): Range, 6 to 7 d Peak (*n* = 921) (14, 16, 37, 42, 51, 54): Median, 31 d (range, 15 to 45 d) Starts to decline (*n* = 126) (34, 37, 42): Median, 30 d (range, 22 to 60 d) Latest detected (*n* = 32) (34): 152 d	Low
Variation in prevalence of anti–SARS-CoV-2 antibodies by patient characteristics			
Age	*Summary: Older age may be associated with higher antibody levels* 12 (9194)	Seroprevalence (*n* = 3759) No difference in IgG prevalence, levels, and kinetics (20) No difference for neutralizing antibody activity (14) Higher prevalence among older adults, but not statistically significant (56) No difference in IgG seronegative status (40) No difference in seroconversion rates by patient age (43) Antibody levels (*n* = 5567) Among recovered group, antibody levels were higher in older persons (9) No difference in IgM or IgG levels (29) Statistically significant correlation between IgG levels and age (32) Patients with older age had higher IgM and IgG antibody levels (36) No difference in the antibody response by age (37) IgG levels significantly higher in older patients (56) Age >70 y associated with higher IgG concentration (43) Age ≥50 y correlated with higher IgG titers (44)	Low

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Appendix Table–Continued

Outcome	Studies (Patients), *n*	Evidence	Certainty of Evidence*
Sex	12 (7577)	*Summary: The antibody response to SARS-CoV-2 infection may not vary by sex* Seroprevalence (*n* = 3759) No statistical difference in antibody responses (20) No association with neutralizing antibody (14) Nonstatistically significant finding of higher prevalence among men (56) No difference (40) No difference (43) Antibody levels (*n* = 3995) Among recovered group, pan-Ig anti–S1-RBD and IgA anti-S1 levels were lower in female patients (9) IgM titers were higher in male patients than female patients; no difference was observed for IgG (29) No difference in IgG or IgM (36) No difference (37) No difference in antibody concentrations (43) No difference in IgG or IgM (47) No difference (44) No difference (45)	Low
Race/ethnicity	2 (2724)	*Summary: Non-White race may be associated with higher antibody prevalence or levels* Antibody prevalence (*n* = 2547) Non-Hispanic Whites were more than twice as likely as non-Hispanic Blacks to lack IgG antibodies (40) Antibody levels (*n* = 177) Higher IgG antibody concentrations were associated with non-White race (43)	Low
Preexisting comorbid conditions	10 (5553)	*Summary: Whether the antibody response to SARS-CoV-2 infection varies with preexisting comorbid conditions is very uncertain* Seroprevalence (*n* = 3860) Among patients with end-stage renal disease receiving hemodialysis, 13% had not developed antibodies at a mean of 13 d after having a positive PCR test result (22) Higher BMI is associated with high neutralizing antibody activity, whereas tobacco use, preexisting asthma, and hypertension had no association with high neutralizing antibody activity (14) Hypertension and BMI were associated with seroconversion (43) Prevalence of IgG was higher among patients without cancer (98% [95% CI, 96% to 99%]) than patients with cancer (65% [CI, 44% to 82%]; *P* = 0.001) (20) Among patients with multiple myeloma, 96% (22 of 23) had detectable IgG (28) No patients with cancer (*n* = 4) had detectable IgM or IgG (hematologic cancer [*n* = 2], metastatic lung carcinoma [*n* = 1], and glioblastoma [*n* = 1] under going chemotherapy or radiation) (60) Immunosuppressive therapy or medication was associated with seronegativity; no difference related to preexisting diabetes, hypertension, chronic heart disease, chronic kidney disease, chronic liver disease, or chronic obstructive pulmonary disease (40) Antibody levels (*n* = 3617) Among recovered group, BMI was associated with higher antibody levels; tobacco use was associated with lower antibody levels (9) IgG titers were significantly associated with diabetes (36) No significant differences in antibody concentrations when stratifying patients by comorbid conditions (hypertension, type 2 diabetes, obesity, and chronic kidney disease) (39) No significant difference in IgM or IgG titers by underlying disease (29) No correlations between initial virus-specific IgG level and BMI (32) Weight was positively correlated with IgM, IgG, and IgA titers (45)	Insufficient

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Appendix Table–Continued

Outcome	Studies (Patients), *n*	Evidence	Certainty of Evidence*
	Summary: More severe disease seems to be associated with a more robust antibody response in terms of antibody levels		Low
Disease severity	29 (8900)	Variation in antibody prevalence (*n* = 876): Association between disease severity and higher seroprevalence (18, 31, 33) Disease severity is associated with lower seroprevalence (22, 35) No difference (25, 63, 64, 66, 71) Variation in antibody kinetics (timing and duration [*n* = 2627]): Disease severity was associated with a delay in detectable antibodies compared with cases of less severe disease (8, 19, 28, 36, 56) Disease severity was associated with earlier seroconversion (46) Variation in antibody levels (*n* = 8228): Association between disease severity and higher antibody levels (9, 17, 19, 23, 27, 28, 32-34, 36, 38, 39, 42, 44, 46, 48, 63) Disease severity is associated with lower antibody levels (22, 29, 31); finding was specific to patients with critical illness (29, 31) Mixed findings (15) No difference (25, 26, 66, 71)	
	Summary: The presence or absence of symptoms may be associated with higher antibody prevalence and levels		Low
Symptoms	9 (4793)	Presence of symptoms associated with higher antibody prevalence and levels (*n* = 2155) (32, 40) Inconsistent results (*n* = 2638) (9, 14, 43, 44, 65-67)	
	Summary: How the antibody response to SARS-CoV-2 infection changes due to immunoassay test is inconsistent		Insufficient
Immunoassay tests	10 (1996)	For an overview of the immunoassay tests used in the included studies (i.e., immunoassay manufacturer information, performance characteristics, and authorization status in the United States and Europe), please see Supplement Table 4 in the accompanying evidence report (3, 4)	
Reinfection among patients with SARS-CoV-2 antibodies			
Incidence	NA	No studies addressed key question	Insufficient
Length of time between an initial PCR-confirmed SARS-CoV-2 infection and reinfection			
NA	NA	No studies addressed key question	Insufficient
Unintended consequences of antibody testing			
Physical distancing and behaviors	1 (84)	Among health care workers in the United Kingdom who had SARS-CoV-2 serologic testing answering how they would react to different test results (50) 11% said that positive antibody test results would mean "social distancing is less important" for them 30% said that they would be less likely to catch COVID-19 in the future 31% said that they would be happier to visit friends and relatives	Insufficient

BMI = body mass index; NA = not applicable; RBD = receptor-binding domain; RT-PCR = reverse transcriptase polymerase chain reaction.
* Insufficient certainty of evidence: confidence is inadequate to assess the likelihood of benefit (benefit minus harm) of an intervention or its effect on a health outcome. Low certainty of evidence: confidence in the effect is limited because the true effect may be substantially different from the estimated effect. Moderate certainty of evidence: confidence in the effect is moderate because the true effect is likely close to the estimated effect, but there is a sizable possibility that it is substantially different. High certainty of evidence: 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 on results from immunoassay validation studies (which provide less reliable estimates). For all other outcomes of interest, results from all studies were incorporated into strength of evidence assessments (3, 4).
† Calculation based on results of studies that evaluated antibody prevalence close to its estimated peak (20, 25, and 30 d after symptom onset or positive PCR test result for SARS-CoV-2 for IgM, IgG, and neutralizing antibodies, respectively), excluding studies that did not provide estimates within plus or minus 10 d of the peak. If studies reported antibody prevalence as measured by more than 1 immunoassay, the highest prevalence estimate was used. Calculations do not include results of total antibody immunoassays (IgM and IgG) (3, 4).
‡ The results of 2 studies (33, 45) were not reported in a way that could be synthesized with other studies.
§ The results of 3 studies (15, 23, 42) were not reported in a way that could be synthesized with other studies.