UK Health Security Agency

Antibody testing for SARS-CoV-2

Extended information for medical professionals and researchers on using and interpreting SARS-CoV-2 antibody tests

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Context

This document complements the existing Key Information and the UK Standards for Microbiology Investigations Serology Guidance. It provides additional information for medical professionals and researchers. It is not intended to direct clinical care but should provide guidance to professionals.

Indications for antibody testing

1. There are several possible indications for conducting an antibody test:

Population surveillance

Nationally, antibody testing is undertaken to understand vaccine effectiveness, monitor the impact of variants of concern (VOC) and estimate true prevalence. The Office for National Statistics (ONS) also regularly publishes the percentage of the population, by age groups, who have antibodies.

Inform use of monoclonal antibody treatments

For some antibody treatments antibody testing is recommended to determine treatment eligibility as they are most effective in individuals with no antibodies. Refer to the NICE COVID-19 rapid guideline on using monoclonal antibodies for further information.

Identifying response to vaccination and/or infection

Antibody testing may have a role where there is a clinical need to know whether an individual has had an antibody response to SARS-CoV-2 antigens. This testing may be necessary to inform clinical management or infection prevention and control (IPC) measures. Local laboratories and consultant virologists are best placed to advise on appropriate clinical needs for these antibody tests.

Natural history of antibody responses to SARS-CoV-2 infection and vaccination

Initial antibody responses

2. Seventy-five to 95% of previously healthy adults infected with SARS-CoV-2 produce anti-SARS-CoV-2 antibodies detectable using current assays. Non-seroconversion (failure to produce an antibody response) is less common following severe disease (less than 5%) than after mild or asymptomatic disease (2, 3, 4).

3. In immune naïve individuals, antibodies begin to be generated from 4 days post infection, and are reliably detectable within 20 days of symptom onset (5, 6). IgM is the first immunoglobulin class to be produced by the adaptive immune response, followed within a few days by the longer-lasting IgG immunoglobulin, which is most commonly detected in serological tests (7). A meta-analysis of antibody kinetics found that mean and median time to detection of IgM (4 to 14 days) was not significantly different to IgG (12 to 15 days) (8). IgM and IgG levels peak in weeks 3 to 7. IgM antibodies are usually undetectable beyond 7 weeks, although a subset of patients have much longer-lasting response (9). IgG antibodies persist for several months in most individuals, although can wane from as little as 56 days (see Figure 1) (10, 11). The magnitude of the peak antibody response does not appear to correlate with age or sex (12).

4. Some antibodies are known as neutralising antibodies. This means that they can restrict the replication of the virus in vitro, and so are believed to be important in antibody-mediated protection. Neutralising antibodies are usually detectable within 7 to 15 days of disease onset, and increase until 14 to 22 days before plateauing and then decreasing (8).

5. Antibody titres following infection vary. Antibody titres post-infection tend to be correlated with disease severity when infected: individuals that required hospitalisation tend to have higher antibody titres than those managed in the community, while asymptomatic infections induce even lower antibody titres (6, 13).

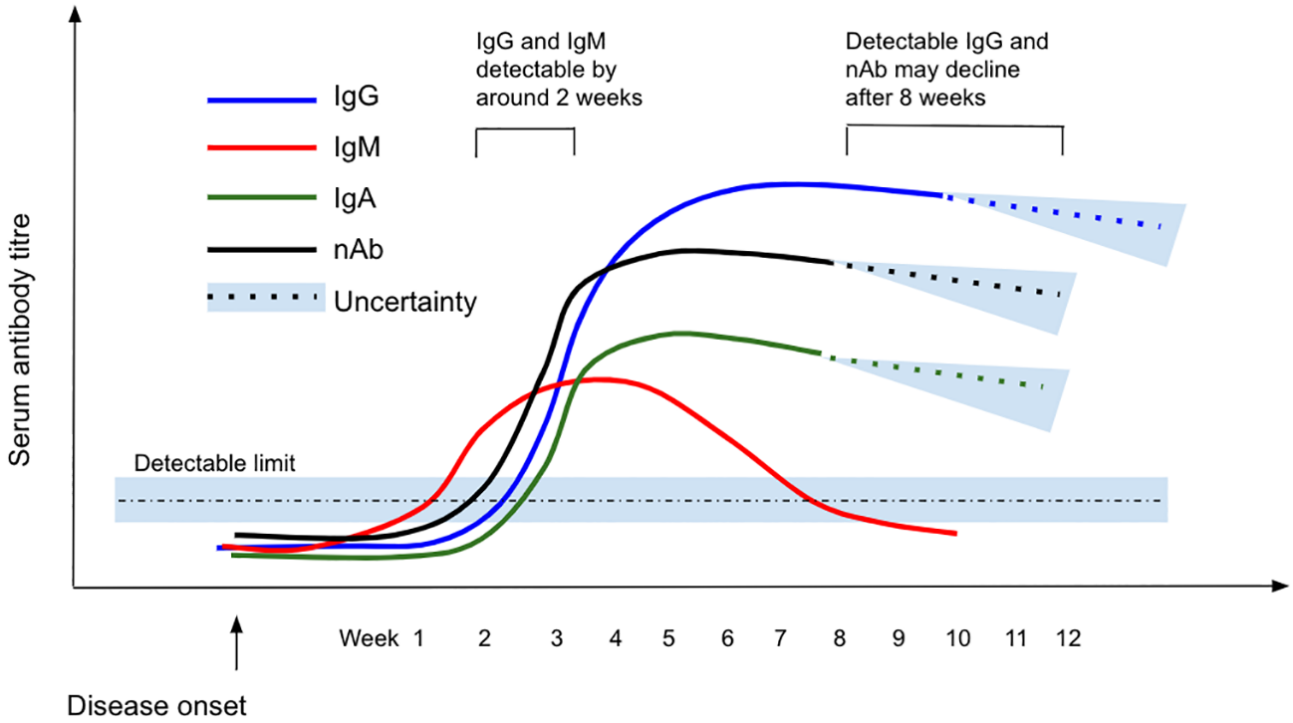
6. There are 29 potential SARS-CoV-2 antigens to which an antibody response (IgM and IgG) could have been elicited following infection (14). Antibody tests available to NHS clinicians are lab-based and target 2 of these:

- the nucleocapsid (‘N’) protein, which is found within the virus and protects its genome from environmental damage
- the spike (‘S’) protein, which is found on the surface of the virus. This contains several regions, such as the Receptor-Binding Domain (‘RBD’) which enables the virus to enter human cells. Anti-S antibody tests may target the entire S protein, or only certain regions (for example, RBD)

7. UK-approved vaccines (Pfizer BioNTech COVID-19 mRNA vaccine BNT162b2 or (Comirnaty®), Moderna mRNA-1273 COVID-19 vaccine (Spikevax®), AstraZeneca COVID-19 vaccine (Vaxzevria®), COVID-19 vaccine Janssen Ad26 COV2-S (recombinant) and Novavax COVID-19 vaccine (Nuvaxovid)) target only the S-protein and so only anti-S antibodies are produced following vaccination. Details of other vaccines can be found on the World Health Organization (WHO) website. Some of these internationally licenced vaccines include different proteins in addition to S, to which the following guidance will not apply. For interpretation of antibody responses following one of these vaccines please see the section Interpreting vaccines not approved in the UK.

8. A UK study of 8,800 vaccinated individuals found that over 96% of individuals had anti-S antibodies from 28 days after their first dose of Pfizer-BioNTech or Oxford-AstraZeneca vaccine, increasing to over 99% from 14 days after their second dose (15). Response to other UK-approved vaccines is likely to be similar.

Figure 1. Diagram suggesting the kinetics of IgG, IgM, IgA and neutralising antibody responses to infection with SARS-CoV-2. The y-axis is illustrative only and no scale is given (16)



Duration of antibody responses

9. Anti-S antibodies are detectable for at least 20 months following infection in most individuals, while anti-N antibodies tend to decline faster (5, 17). For individuals who have been infected, it is likely that those with a lower initial viral load have lower initial antibody levels and shorter-lived detectable antibody responses. Rapid recovery from mild illness is however associated with sustained antibody response (17, 18).

10. As vaccines have only been widely available since December 2020, less is known about the duration of antibody responses to vaccination. Anti-S antibodies are detectable for at least 6 months following vaccination with the Pfizer-BioNTech vaccine, and are expected to persist for considerably longer for all approved vaccines (19). UKHSA regularly publishes technical information on variant and vaccine surveillance.

11. Antibody titres are expected to decline over time, even in healthy individuals (see Figure 1). Protection against re-infection comes from circulating antibodies, T cells and memory B cells, which can rapidly produce antibodies following re-exposure. These cellular responses are more challenging to measure through standard serological testing. However, emerging data shows that cellular immunity is well established after vaccination and infection, and the large and rapid increase in antibody titres following a second vaccine dose strongly supports the presence of a good memory B cell response (20, 21, 22, 23).

Fluctuations in antibody level

12. A significant increase in antibody levels (boosting) may suggest re-exposure, particularly in patients with a recent positive SARS-CoV-2 PCR test or new symptoms suggestive of infection. Minor fluctuations (both up and down) in antibody levels are likely to have no clinical significance.

Effect of novel variants

13. Most of the published research into the natural history of antibody responses to primary infection was conducted in 2020, before the emergence of the major variants of concern. It is not yet clear whether the antibodies induced by these variants have altered antibody kinetics. It is likely that primary infection by one of these variants will induce antibodies with similar kinetics to those elicited by virus types common earlier in the pandemic.

Distinguishing natural infection from vaccination

14. Both natural infection and current vaccinations expose the immune system to the S-protein, therefore both can elicit anti-S antibodies. However, only natural infection exposes the immune system to the N-protein, so anti-N antibodies should only be detected in individuals that have been infected or, rarely, acquired antibodies passively such as through intravenous immunoglobulin treatment. Therefore, in most cases:

- anti-N antibodies indicate prior infection, and
- anti-S antibodies indicate prior infection or vaccination

Atypical antibody responses

15. The initial point of reference for clinicians managing a patient with atypical antibody responses should be their local laboratory and consultant virologist or microbiologist. The tests used to measure antibody levels will vary between laboratories and local experts will be best placed to contextualise the results.

16. Interpretation should be made in the clinical context. For example, an individual with only anti-S antibodies but no history of vaccination would have developed these antibodies from natural infection but no longer have detectable anti-N antibodies, which can occur rapidly with some anti-N assays. Similarly, an individual with a history of vaccination and only anti-S antibodies, who also had a positive PCR test several months previously is most likely to have had their anti-N antibodies wane below the point of detection.

17. An individual with only anti-N antibodies, regardless of vaccination history, is most likely to have been infected in the past and lost their anti-S antibody response. It is also possible that this represents a false positive result and a repeat test on an alternative assay may be necessary, depending on the clinical need.

Table 1. Anti-N and anti-S antibody responses to natural infection and vaccination in a vaccinated immunocompetent individual

Antibody	Result	Interpretation
Anti-N Anti-S	Positive Positive	Past natural infection by SARS-CoV-2.
Anti-N Anti-S	Negative Positive	Not infected by SARS-CoV-2 OR naturally infected but anti-N antibodies have waned.
Anti-N Anti-S	Positive Negative	Past natural infection by SARS-CoV-2 AND Recent (<28 days) first dose vaccination OR no detectable antibody response to vaccination.
Anti-N Anti-S	Negative Negative	Unlikely to have been infected by SARS-CoV-2 or recent infection AND Recent (<28 days) first dose vaccination OR no detectable antibody response to vaccination.
Anti-N Anti-S	Indeterminate Indeterminate	Difficult to interpret. Please repeat the sample.

Table 2. Anti-N and anti-S antibody responses to natural infection and vaccination in an unvaccinated immunocompetent individual

Antibody	Result	Interpretation
Anti-N Anti-S	Positive Positive	Past natural infection by SARS-CoV-2.
Anti-N Anti-S	Positive Negative	Past natural infection by SARS-CoV-2 with waning of anti-S response OR false positive anti-N.
Anti-N Anti-S	Negative Positive	Past natural infection by SARS-CoV-2 with waning of anti-N response OR false positive anti-S.
Anti-N Anti-S	Negative Negative	Unlikely to have been infected by SARS-CoV-2.
Anti-N Anti-S	Indeterminate Indeterminate	Difficult to interpret. Please repeat the sample.

Interpreting vaccines not approved in the UK

18. Most vaccines currently in use around the world use only the S protein to elicit an immune response, and so antibody tests conducted on individuals who have received these vaccines can be interpreted in the same way as for UK-approved vaccines.

19. Some vaccines (notably those developed by Sinopharm and Sinovac) use an inactivated form of the SARS-CoV-2 virus to elicit an antibody response. As this inactivated virus contains both N and S proteins it is expected to produce anti-N and anti-S antibodies. This means that the presence of anti-N antibodies cannot be used to distinguish vaccination from natural infection in individuals vaccinated with one of these vaccines. Patient history will therefore be important to accurately interpret serology results.

20. More information on vaccines not approved in the UK can be found at COVID-19 vaccinations received overseas – GOV.UK (www.gov.uk).

Antibodies and protection against infection

21. It is not yet known what level of antibodies are protective against infection. It is highly likely that higher antibody levels are more protective than lower antibody levels. However, the 'correlate of antibody derived protection from infection', that is, the titre of anti-S neutralising antibody to prevent viral infection (sterilising protection), for SARS-CoV-2 is unknown (24, 25, 26). Therefore, it is not possible to give individuals a binary answer as to whether they are fully protected from COVID-19, merely that they are better protected than if they had no antibodies.

22. It is inevitable that variants will continue to emerge that can reduce the protective effect of prior exposure and cause infections. For example, neutralizing antibody titres induced following vaccination decline over time and this can be significant in the context of antigenically distant variants such as Beta or Omicron (27, 28). However, as long as antibodies are still detectable, individuals are highly likely to be protected at least from severe disease. The latest information on the protective effects of vaccination can be found in the COVID-19 vaccine weekly surveillance reports.

23. The rate of antibody waning will likely be different for different age groups and will depend on how high the initial antibody levels were, and which aspects of immunity are less robust. Data so far suggests that initial antibody levels are lower in older and immunocompromised people. Emerging evidence has shown that additional doses of vaccines will maintain robust immune responses in these individuals.

Undetectable antibody response following a positive PCR test or vaccination

24. Measured rates of seroconversion depend on the population being studied, how infection is defined, which antibody is being measured (as anti-N tends to decline faster than anti-S), when after the infection antibodies are measured and the assay being used (11). The ONS COVID-19 Infection Survey found that less than 25% of individuals will not produce an anti-S antibody response following a positive PCR test, falling to less than 10% if a stricter case definition of SARS-CoV-2 infection was used. Less than 5% failed to seroconvert following severe disease (2). This study and others suggest that non-seroconversion is more common following mild or asymptomatic disease, in elderly individuals and in the immunocompromised.

25. Over 99% of individuals have a detectable antibody response 14 days after their second dose of Pfizer or Oxford-AstraZeneca vaccines. Response to other UK-approved vaccines is likely to be similar. Non-seroconversion following vaccination is more common in immunocompromised populations (15).

26. Otherwise healthy adults that do not produce an antibody response following mild infection are unlikely to require detailed follow-up. Individuals that do not produce an antibody response following severe disease or a full course of vaccination are likely to be immunocompromised and already managed for this in primary or secondary care, and should be aware of their risk of infection not just from COVID-19 but from other infections. The health care professionals helping these individuals to manage their underlying medical conditions are likely to be best placed to advise on appropriate follow-up.

27. At present there is no defined clinical pathway for individuals based solely on serology status. However, individuals with COVID-19 may be eligible for treatment with monoclonal antibodies only if they do not have detectable antibodies, regardless of prior infection status. Refer to the NICE COVID-19 rapid guideline on using monoclonal antibodies for further information.

28. The Joint Committee on Vaccination and Immunisation (JCVI) has provided advice on patient groups who would be eligible for a third primary dose of vaccination (fourth dose); information on the eligible groups can be found in the COVID-19 Greenbook chapter 14a.

Equivocal antibody results

29. Serological assays rely on antibodies binding to an antigen target, and then measuring the degree of binding through a variety of methods. Most serological assays have an equivocal zone as sometimes it is not possible to clearly ascertain whether specific antibody is present in the sample being tested. There are several possible interpretations for this:

a) The patient is seroconverting

At the start of the antibody response there will be a period where there are insufficient antibodies to produce a clear result. Similarly, a patient whose antibodies are waning will also pass through a period where antibodies are still present, but only in sufficient quantities to produce an equivocal result.

b) The patient has reactivity not due to anti-SARS-CoV-2 antibodies

This cross-reactivity may be transient and associated with one blood sample or assay, or it may be persistent.

30. Most equivocal results can be confirmed as positive or negative by testing the blood sample with a different assay or repeating the assay on a new blood sample obtained a week later.

31. A small proportion of patients will consistently have equivocal antibody results. It is most likely that these patients do not have anti-SARS-CoV-2 antibodies.

Antibody responses in special groups

Immunocompromised

32. The antibody response of immunocompromised individuals to infection and vaccination is heterogeneous, and likely to depend on the degree of immunodeficiency. In the OCTAVE study of 600 immunocompromised patients with weakened immune systems, the majority had antibody responses at 4 weeks post vaccination that were equivalent to those of healthy vaccine recipients. However, 11% failed to seroconvert, while a further 29% generated lower levels of antibodies than healthy controls. These reduced or absent antibody responses were more common in the most severely immunocompromised individuals (29).

33. Studies are ongoing to assess how effective a third vaccination dose is for individuals who fail to seroconvert from the first 2 doses. JCVI has provided advice on vaccination in the immunosuppressed (30).

34. The timing of vaccination relative to immunosuppression is likely to be important in determining the level of antibody response. Individuals that have recently ceased immunosuppressive treatment are likely to have lower antibody responses compared to those with a longer interval between stopping immunosuppressive therapy and vaccination. Similarly, it is likely that the larger the gap between vaccination and the subsequent initiation of immunosuppressive treatment, the closer the antibody response will be to that which would have been expected in the absence of immunosuppression. JCVI has produced advice on when to offer a third primary vaccination to individuals commencing immunosuppressive treatment (31).

35. In immunocompromised groups, very low 'positive' levels of anti-S antibody on a quantitative assay (within the bottom 10% of the assay's positive range) should be interpreted in the context of clinical decision-making and laboratory advice. The multi-disciplinary team (MDT) should consider treatments for these patients on a case-by-case basis.

36. In immunocompromised patients on replacement immunoglobulin (intravenous or subcutaneous), the positive detection of anti-S antibodies should be regarded as a 'positive of unknown significance'. Patients on replacement immunoglobulin testing positive only for anti-S (and negative for anti-N antibodies) should therefore be considered to be seronegative for SARS-CoV-2. Should evidence for passive transmission of anti-N antibodies through replacement immunoglobulin emerge in the future, the detection of anti-N antibodies should also be regarded as a 'positive of unknown significance'.

37. Please refer to the COVID-19 Greenbook chapter 14a for the latest guidance on vaccination in the immunosuppressed and to the NICE COVID-19 rapid guideline for the latest guidance on

using antibody tests to determine eligibility for monoclonal antibody therapy in the immunosuppressed.

Elderly

38. Healthy elderly individuals are less likely to seroconvert than younger healthy adults, however those that do seroconvert are expected to produce comparable antibody responses to younger healthy adult (2, 32 to 35).

Pregnant

39. Healthy pregnant women are expected to have similar antibody responses from infection and vaccination to healthy non-pregnant women. It is likely there will be passive immunisation of the fetus through the placenta and the neonate through breastmilk. The protective effects of this passive immunisation are not yet known (36).

Children

40. Children have similar antibody responses to infection to young adults. Research studies have shown that antibody responses following Pfizer/BioNTech vaccination in children aged 5 to 11 and 12 to 15 years are similar to those found in young adults (37, 38, 39).

Assay types

41. Anti-SARS-CoV-2 can be detected using laboratory and point-of-care assays. Laboratory assays tend are the most sensitive and specific, and so are used for diagnostic purposes. As point of care assays are less sensitive and specific, they are not currently indicated for diagnostic purposes, but are a useful tool for surveillance and research studies. UKHSA regularly reviews the performance of antibody assays, refer to guidance on laboratory evaluations of serological assays for further information.

42. The performance of any antibody assay will depend on the quality of the sample, the antibody being measured (anti-S or anti-N), as well as the characteristics of the assay itself. For example, anti-S assays tend to be more sensitive to seroconversion after several months than anti-N antibodies, as anti-N antibodies decline more quickly. Local laboratories will be best placed to advise on the performance characteristics of the specific assays available to the clinician.

43. If there are concerns or questions around laboratory sensitivity or cut-offs these should be discussed in the first instance with local laboratory leads who will have access to comparative and performance data from the external quality assessment (EQA) scheme participation.

Probabilistic language

This scale refers to the probabilistic language used throughout the guidance, which indicates the likelihood of something occurring.

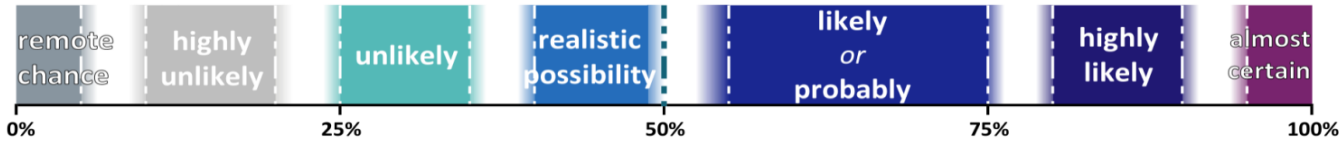


Table 3. Explanation of probabilistic language

Percentage	Probability
Approximately 0 to 8%	remote chance
Approximately 10 to 20%	highly unlikely
Approximately 25 to 35%	unlikely
Approximately 40 to 50%	realistic possibility
Approximately 55 to 75%	likely or probably
Approximately 80 to 90%	highly likely
Approximately 95 to 100%	almost certain

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About the UK Health Security Agency

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