COVID-19: Guidance for professionals to support interpretation of antibody test results

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Background

People are increasingly accessing antibody testing, either through various different surveillance studies, private providers, or for diagnostic purposes. Certain countries allow antibody tests to permit entry. As more people access antibody tests there is an increasing chance that people approach primary care services for advice, particularly if seeking advice after vaccination.

Antibody response against SARS-CoV-2

Most people infected with SARS-CoV-2 generate antibodies against the structural proteins of the virus in the vast majority of cases. The most immunogenic antigens are located on the Spike (S) and Nucleocapsid (N) proteins. Tests available to NHS clinicians are lab-based and target either the anti-S or anti-N response. All SARS-CoV-2 vaccines currently licenced in the UK, USA and EU only contain the S protein/gene, therefore:

a. Anti-N positive confirms previous infection; and
b. Anti-S positive confirms previous infection and/or response to vaccination.

In immune naïve people, antibodies are made from 4 days post infection/immunisation (exposure) and become reliably detectable within 35 days of exposure. In people with prior exposure, antibodies are made from 4 days post infection and rise above existing titre rapidly, likely within 14 days. The titre of anti-S neutralising antibody to prevent viral infection (sterilising protection) for SARS-CoV-2 is unknown.

Antibody testing capability and uses

Testing for antibodies raised against SARS-CoV-2 can detect evidence of past infection and/or response to vaccination[1]; to monitor disease progression; or aid diagnosis of post-acute COVID-19, also known as 'Long-COVID'. Nationally,

[1] Detection of anti-N confirms past infection only; detection of anti-S suggest past infection or vaccination, or both. Currently all licenced vaccines only contain the S protein/gene allowing differentiation between response to vaccine and infection.

antibody testing is being used to understand vaccine effectiveness, monitor the impact of Variants of Concern (VOC), and estimate prevalence of infection. The ONS is also regularly publishing the percentage of the population, by age groups, who have antibodies.

UK residents may be offered an antibody test if they have tested positive by PCR as part of the Post Positive PCR Antibody Testing Initiative (PPPATI) run by Public Health England and operating across the UK. This will help to better understand the protection provided by antibodies, the levels associated with breakthrough infections and the impact of new variants.

Finally, it may be possible to provide confidence to an individual of their mitigated, but not eliminated, risk against disease based on past infection status or vaccination status, as identified by antibodies or medical records. Presence of detectable circulating antibodies will almost certainly result in a mitigation of severe disease on re-exposure but cannot at present be used to assure protection from infection. Confidence differs for each different VOC.

Immunity against SARS-CoV-2 - current understanding

Previous infection or partial course immunisation is highly likely to provide protection from severe symptoms in those who are subsequently infected, but less effective at preventing symptomatic disease when infected by variants of concern, such as Delta. This protection is highly likely to be similar across age groups. Full-course immunisation is more likely to protect against severe disease including after infection by new variants/variants of concern such as Delta.

It is almost certain that variants will continue to emerge and that the protective effect of prior exposure or vaccination will be reduced against at least some of these variants. For example, data suggest there is an approximate 10% reduction in protection from infection after full course immunisation for the Delta variant when compared to the Alpha variant[2]. PHE routinely publishes updates to the data on the real-world effectiveness and impact of the COVID-19 vaccines.

T-cell derived response is equally important in response to SARS-CoV-2, particularly for moderation, but is far more challenging to assess. A wholly T-cell driven

[2] COVID-19 vaccine surveillance report - week 30 (publishing.service.gov.uk) https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1007376/Vaccine_surveillance_report_-_week_30.pdf; page 7

response to SARS-CoV-2 is rare, and antibody testing remains the most accessible marker of immune response.

Result interpretation and SARS-CoV-2 antibody mechanics

Antibody (Ab) titres after vaccination or infection vary. People immunised with an mRNA vaccine are highly likely to follow a similar Ab titre curve to those infected with SARS-CoV-2. Patients immunised with viral vector vaccine are likely to have a slower Ab response after one dose. A negative result after one dose of vaccination should not be cause for concern, particularly if the vaccine was administered fewer than 56 days ago. Anti-S antibodies are present in the vast majority (>99%) of individuals[3] 28 days after a full SARS-CoV-2 vaccination schedule. A negative result after two doses of vaccine does not necessarily mean that the individual has no immune response. Immune responses are more complex than the measure of an antibody test which does not consider the role of T and B cell memory or that lower levels of antibodies may be present than can be measured by the test.

Although anti-S antibodies are present in the vast majority of individuals 28 days after a full SARS-CoV-2 vaccination schedule, waning of antibodies, even to levels below the detectable range, will likely not result in significant reduction in protection from severe disease, although mild or asymptomatic infections are likely to be possible.

At the present time there is no recommendation for administration of additional vaccination doses specifically for those with a negative serological test post-vaccination.

Anti-N response after infection, in general, decays faster than anti-S. It is highly likely that antibodies will be detectable for at least 10 months.

Anti N	Anti S	Interpretative Comment
Positive	Positive	Suggestive of previous SARS-CoV-2 infection (anti-N). Antibodies found after SARS-CoV-2 vaccination present, but these are also present after infection.

[3] When lab-based quantitative assays are used.

Not assessed	Positive	Antibodies found after SARS-CoV-2 vaccination present, but these are also present after infection. Suggestive of response to SARS-CoV-2 vaccination or prior infection.
Positive	Negative	Suggestive of previous SARS-CoV-2 infection (anti-N). Antibodies that we would expect to see after vaccination were not identified; a negative result after one dose of vaccination should not be cause for concern, particularly if vaccine was administered fewer than 56 days ago.
Positive	Not tested	Suggestive of previous SARS-CoV-2 infection (anti-N).
Negative	Positive	Antibodies found after SARS-CoV-2 vaccination present, but these are also present after infection. Suggestive of response to SARS-CoV-2 vaccination or prior infection.
Negative	Negative	No serological evidence of past exposure; a negative result after one dose of vaccination should not be a cause for concern, particularly if vaccine was administered fewer than 56 days ago.
Indeterminate with other target Neg / Indeterminate	Indeterminate with other target Neg / Indeterminate	Difficult to interpret SARS-CoV-2 IgG. Please send a repeat sample in 2 weeks.

Assay types

Lab-based assays

Lab-based assays are considered "gold-standard". NHS labs and certain private providers offer lab-based assays of blood samples against the anti-S or anti-N response. Test performance varies, and PHE has evaluated various assays. NHS Test and Trace uses the Roche Elecsys® anti-N and anti-S platforms for the PPPATI study.

Point of care assays

Point of care (POC) assays are, generally, less sensitive than lab-based assays. Clinical specificity varies between assays. These tests are sometimes used in surveillance studies where results can be adjusted relative to performance of the assay of choice. POC assays are not recommended for individual use but are a useful tool for surveillance and research studies.

Evidence base

Longitudinal surveys of reinfections with SARS-CoV-2 and the antibody response over time are extensive in the UK. These include general population studies such as the ONS COVID-19 Infection Survey and priority cohort surveillances such as healthcare workers (SIREN) and care home staff and residents (Vivaldi).

These studies have contributed to an emerging research picture underpinning the key observations outlined above. Key data include:

a) Previous infection of SARS-CoV-2 (in presence of detectable circulating antibodies) was associated with an approximate 80% lower risk of infection for at least 7 months following the first infection[4] [5] [6] [7]. More recently the duration of protection has been shown to extend to 10 months amongst care home staff and residents[6].

[4] Hall, V. J., et. al.; 2021. SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: a large, multicentre, prospective cohort study (SIREN).

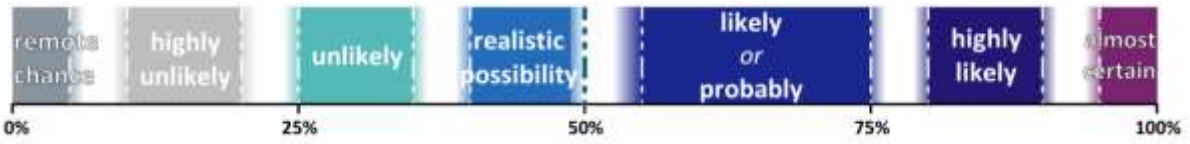
[5] Abu-Raddad, L. J., et. al.; 2021. SARS-CoV-2 antibody-positivity protects against reinfection for at least seven months with 95% efficacy.

[6] Hansen, C. H., et. al.; 2021. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study.

[7] Krutikov, M., et. al.; 2021. Incidence of SARS-CoV-2 infection according to baseline antibody status in staff and residents of 100 long-term care facilities (VIVALDI): a prospective cohort study.

b) Half-schedules of two-dose schedule vaccines against SARS-CoV-2 have been shown to be approximately 80% effective at preventing hospitalisation[8], although confidence differs for different VOCs and across different vaccines. Full-schedule immunisation[9] is reported to prevent 95-99% of deaths from infection and induces a stronger immune response than half course[10] [11], predominantly identified by antibody titre[12].

Probabilistic language



- ~0%-8%: Remote chance
- ~10%-20%: Highly unlikely
- ~25%-35%: Unlikely
- ~40%-50%: Realistic possibility
- ~55%-75%: Likely or Probably
- ~80%-90%: Highly likely
- ~95%-100%: Almost certain

[8] Lopez Bernal, Jamie, et al.; 2021. Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in England.

[9] Applicable for ChAdOx1 and BNT162b2.

[10] Hall, V. J.; et. al.; 2021. COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study.

[11] Shrotri, Madhumita, et al.; 2021. Vaccine effectiveness of the first dose of ChAdOx1 nCoV-19 and BNT162b2 against SARS-CoV-2 infection in residents of Long-Term Care Facilities (VIVALDI study).

[12] Shrotri, Madhumita, et. al.; 2021. Spike-antibody responses to ChAdOx1 and BNT162b2 vaccines by demographic and clinical factors (Virus Watch study).