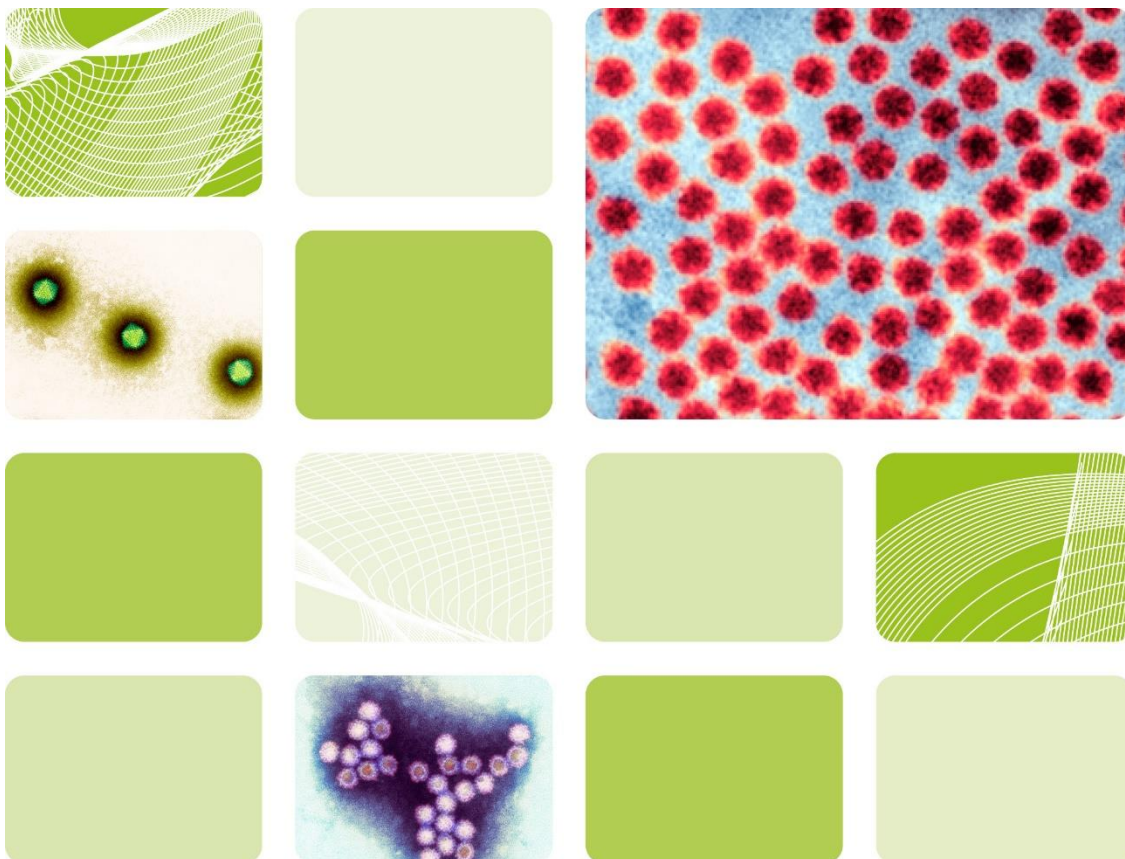




UK Health  
Security  
Agency

# UK Standards for Microbiology Investigations

## Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) serology



National Institute for Health and Care Excellence (NICE) has renewed accreditation of the process used by the **UK Health Security Agency** to produce **UK Standards for Microbiology Investigations (UK SMIs)**. The renewed accreditation is valid until **30 June 2026** and applies to guidance produced using the processes described in '**UK Standards for Microbiology Investigations Development Process**' (2021). The original accreditation term began on 1 July 2011.

## Acknowledgments

UK Standards for Microbiology Investigations (UK SMIs) are developed under the auspices of UKHSA working in partnership with the partner organisations whose logos are displayed below and listed on [the UK SMI website](#). UK SMIs are developed, reviewed and revised by various working groups which are overseen by a steering committee (see [the Steering Committee page on GOV.UK](#)).

The contributions of many individuals in clinical, specialist and reference laboratories who have provided information and comments during the development of this document are acknowledged. We are grateful to the medical editors for editing the medical content.

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## Amendment table

Each UK SMI document has an individual record of amendments. The amendments are listed on this page. The amendment history is available from [standards@phe.gov.uk](mailto:standards@phe.gov.uk).

Any alterations to this document should be controlled in accordance with the local document control process.

|                               |   |
|-------------------------------|---|
| Amendment number/date         | 1/09 June 2022  |
| Issue number discarded        | 1   |
| Insert issue number           | 2   |
| Anticipated next review date* | 09 June 2025  |
| Section(s) involved           | Amendment   |
| Whole document                | Document presented in the new UK SMIs virology template.<br>Document amended with up-to-date information and references on SARS-CoV-2<br>Information on therapeutic neutralising monoclonal antibodies added to the document. |
| Section 7 and 7.1             | Flowchart and footnotes were updated  |
| Section 8                     | Interpreting and reporting laboratory results table updated   |

\*Reviews can be extended up to 5 years where appropriate

# 1 General information

[View general information](#) related to UK SMIs.

# 2 Scientific information

[View scientific information](#) related to UK SMIs.

# 3 Scope of document

Coronavirus disease (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), discovered in late 2019 (1). Most people infected with SARS-CoV-2 will experience mild to moderate respiratory illness and recover without requiring treatment (1). Black, Asian and Minority Ethnic (BAME) patients, older people, and those with underlying medical problems such as cardiovascular disease, diabetes, chronic respiratory disease and cancer are more likely to develop serious illness. See [COVID-19: the green book, chapter 14a](#) for a full list of people considered clinically extremely vulnerable from COVID-19.

COVID-19 vaccines have been widely available since December 2020 with all vaccines currently licensed in the UK using a form of the S protein as the main target for generation of neutralising antibodies.

SARS-CoV-2 seroprevalence testing programmes have been rolled out across all four nations of the UK with different approaches for testing certain key workers or patients. These antibody testing programmes have aimed to provide information on:

- the prevalence of SARS-CoV-2 infection in different regions of the country (2);
- how the disease spreads amongst symptomatic and asymptomatic individuals (3);
- the protective immunity against reinfection (4);
- the persistence of antibodies (5), and;
- trends in natural infection transmission and vaccine induced immunity (6).

SARS-CoV-2 serology may also be used in the clinical management of inflammatory diseases, including paediatric multisystem inflammatory syndrome (PIMS), when temporally associated with COVID-19 (7). Serology is utilised in conjunction with PCR testing to determine whether there is evidence of current infection, previous infection, and/or previous vaccination.

Therapeutic neutralising monoclonal antibodies (nMABs) bind to specific sites on the spike protein of the SARS-CoV-2 virus particle, blocking cell entry and inhibiting the progression of infection. Serological testing for the presence of detectable SARS-CoV-

2 anti-spike antibodies prior to treatment with neutralising monoclonal antibodies is advised where possible but is not necessarily a requirement for treatment with nMABs. Please refer to the latest guidance for nMABs treatment (8,9).

This UK SMI describes a diagnostic testing algorithm which supports and gives indications to the laboratories on how to interpret results from commercially available serological kits.

Refer to [Q1 – Evaluations, validations and verifications of diagnostic tests](#) and [Q 7 – Good practice when undertaking serology assays for infectious diseases](#) for information regarding good laboratory practice in serological testing.

In this rapidly evolving field, please consult [national sources](#) of up-to-date guidance and information about SARS-CoV-2 and COVID-19.

This UK SMI should be used in conjunction with other UK SMIs.

## 4 Background

Serological assays for SARS-CoV-2 may detect the humoral immune responses induced by the SARS-CoV-2 virus and/or SARS-CoV-2 vaccination. Unlike methods which detect the virus itself, antibody tests can demonstrate that an individual has been exposed to the virus or vaccine at some time prior to sampling, regardless of the current presentation. The detection of specific antibodies against different viral antigens, such as nucleocapsid or spike antigen, can differentiate vaccine response from natural exposure (assuming the vaccine antigen remains the spike protein alone).

A longitudinal study has reported that patients who recovered from mild SARS-CoV-2 infection developed SARS-CoV-2-specific IgG antibodies, a neutralising plasma response to the spike protein receptor binding domain RBD, and specific memory B and T cells, that were all detectable for at least 3 months (10). While there is an increase in evidence to demonstrate a multi-faceted cellular and humoral immune response following SARS-CoV-2 infection, correlates of immunity are not yet well defined (11). At present, serological assays cannot be used to infer the presence or absence of protective immunity against SARS-CoV-2, or as a sole method for the diagnosis of COVID-19 disease.

Serology is also useful in guiding epidemiological and public health control measures by providing information of the level and length of the immune response following SARS-CoV-2 viral infection. This information will help to determine the likelihood of reinfection and how rapidly new outbreaks may spread across the country, especially in health and social care workers and those at higher risk of clinical complications. Healthcare workers from all regions of the UK participated in a study called SIREN (Sarscov2 Immunity and Reinfection Evaluation) to determine the impact of detectable SARS-CoV-2 antibody on the incidence of COVID-19. The study showed that previous

SARS-CoV-2 infection protects most individuals against reinfection for a few months. Primary infection also reduces the risk of asymptomatic infection (12,13).

In symptomatic, immunocompetent individuals, SARS-CoV-2 infection will normally elicit the development of IgM and IgG antibodies. In the first 7 days of infection, the adaptive immune response begins to develop, and antibodies may not yet be detectable in peripheral blood. IgM and IgG antibodies are increasingly likely to be detected from 7 days after the onset of symptoms, at which time the majority of individuals will have a detectable antibody response (14). The detectable IgM response then begins to decline, reaching lower levels by week 5 and almost disappearing by week 7, while detectable circulating IgG normally persists beyond 7 weeks (15) (see Figure 1).

Asymptomatic and immunocompromised individuals may show a delayed or absent antibody response to SARS-CoV-2 infection (16). As more data becomes available, understanding of the antibody response will increase.

## 4.1 Antibody testing in the UK

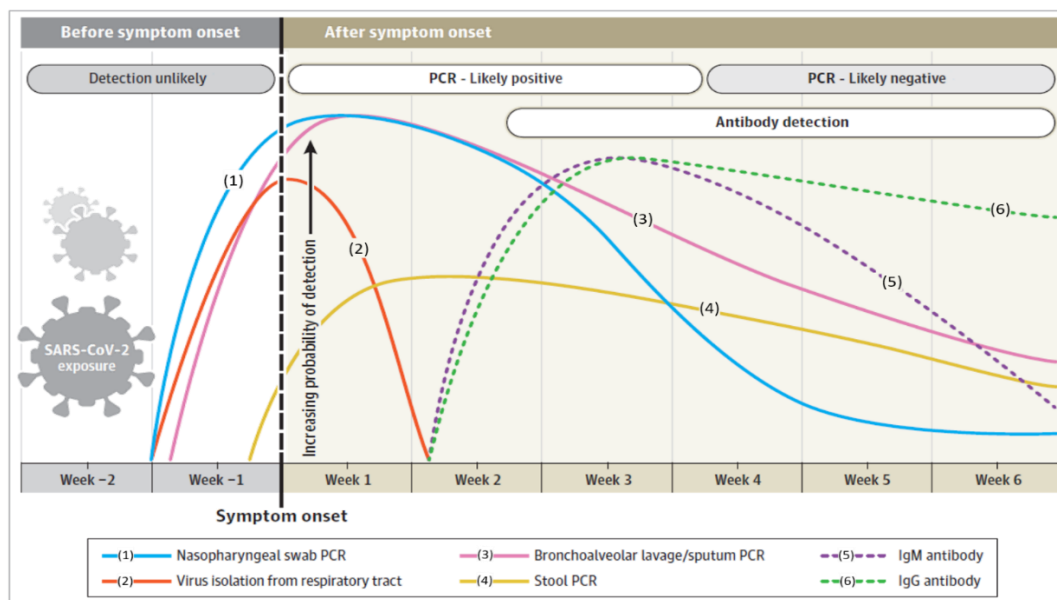
Coronaviruses have four structural proteins: the spike glycoprotein (S), nucleocapsid protein (N), envelope protein (E) and membrane protein (M). At the present time, some commercially-available antibody tests target the N protein, which is a relatively stable protein structurally associated with the viral genome, whereas others target the S protein, which contains some highly mutable regions and (along with the M and E proteins) is found on the surface of the virus. The nucleocapsid protein is highly immunogenic and induces an earlier antibody response than the spike protein during infection, making it an attractive protein for diagnostic assay design. The spike protein is also relatively immunodominant, consisting of 2 subunits: the S1 protein containing the receptor binding domain (RBD); and the S2 protein which mediates fusion of the virus particle to the cell membrane (17). To date, SARS-CoV-2 vaccines in the UK are based on the spike (S) protein thus detection of spike (S) antibody indicates past infection or past vaccination or both. SARS-CoV-2 spike protein is structurally similar to the SARS-CoV-1 spike protein, however cross-recognition of SARS-CoV-2 by SARS-CoV-1 monoclonal antibodies was not observed (18). See COVID-19: laboratory evaluations of serological assays for an evaluation of commercial kits in which cross-reactions to other *Betacoronavirus* also were not observed (19).

Commercially available serological assays can detect IgG alone, or both IgG and IgM (total antibody) (20). An evaluation, using serum samples from PCR-positive individuals, showed no substantive differences in sensitivity of assays whether they test for IgG alone, or both IgG and IgM (19).

Antibodies detected in an assay which includes spike proteins as an antigen may have a closer correlation with the presence of neutralising antibodies against SARS-CoV-2 (21).

The impact of infection with variant SARS-CoV-2 strains on the performance of serology tests is uncertain at present, but may not affect those commercial test kits and assays which detect a broad antibody repertoire.

**Figure 1: Estimated variation over time in diagnostic tests for detection of SARS-CoV-2 infection relative to symptom onset (15).**



Note: the dominant (or specific) viral variant; immunological competence of the host (including any response to specific SARS-CoV-2 vaccination); and use of SARS-CoV-2 antiviral therapies may all alter the time course shown above, both at the individual level and within populations.

Therapeutic interventions could also impact further evolution of variants. Significant protective levels could vary depending on evolving data

All laboratories performing serology testing should participate in a national external quality assurance (EQA) scheme and be aware of any sensitivity variance between assays. Refer to local validation data and use validated kits. Also refer to [UK SMI Q 7: good practice when ordering and undertaking diagnostic tests for infectious disease serology](#) for information regarding good laboratory practice in serological testing.

## 5 Safety considerations

The section covers specific safety considerations related to this UK SMI, and should be read in conjunction with the general [safety considerations on GOV.UK](#) (22-41).

Refer to guidance on COVID-19: safe handling and processing for samples in laboratories (42) and [Annex 2 of The approved list of biological agents \(2021\)](#) (23).



This guidance should be supplemented with local COSHH and risk assessments. Refer to current guidance on the safe handling of all organisms documented in this UK SMI.

## 6 Specimen processing and procedure

### 6.1 Specimen type

Blood, serum or plasma (follow manufacturers' specifications).

### 6.2 Specimen transport and storage conditions

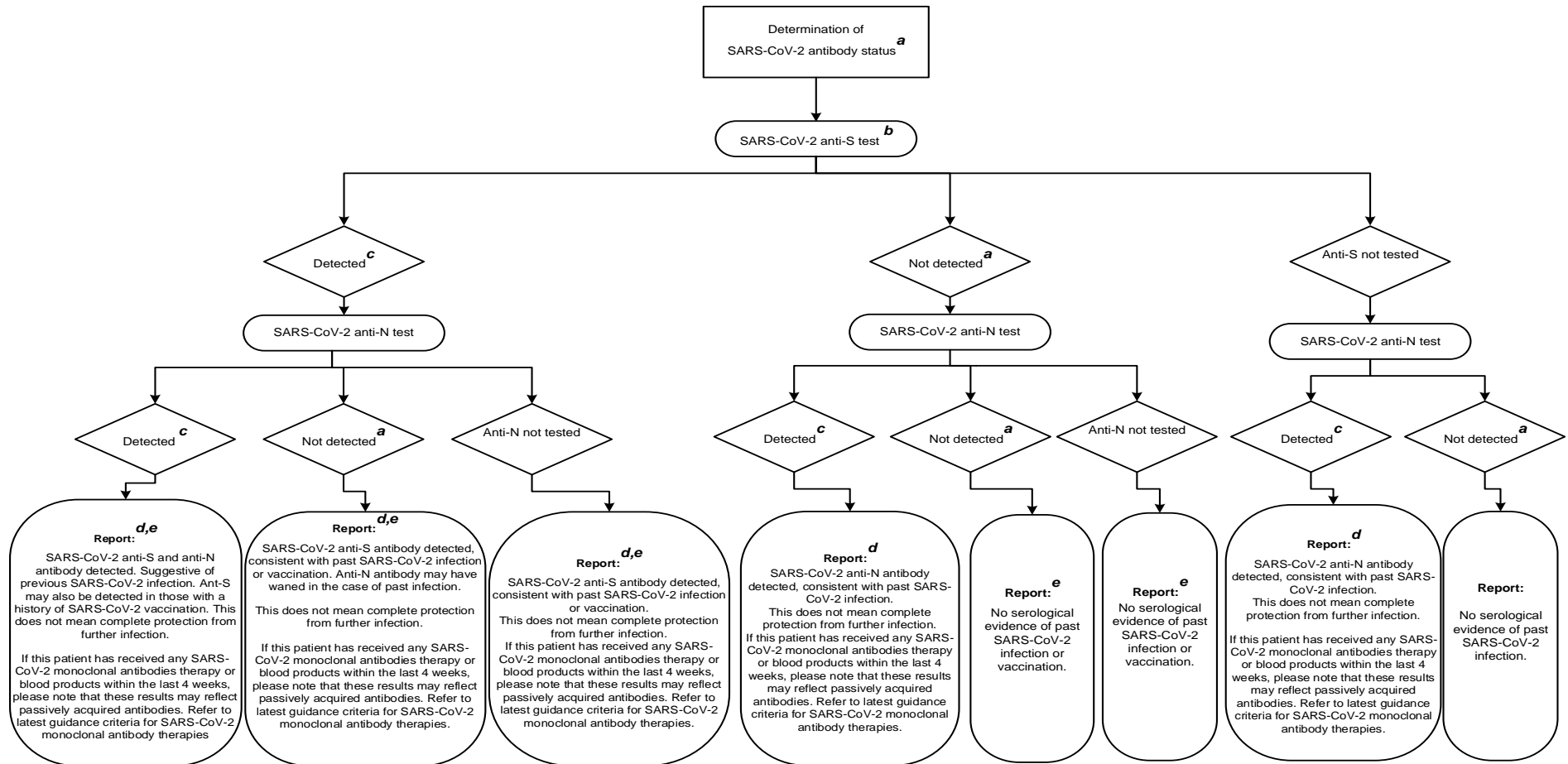
Specimens should be collected in appropriate CE or UKCA marked leak proof containers and transported in sealed plastic bags according to UK regulations.

Specimens should be transported and processed according to manufacturers' instructions or local validation data (43).

Samples should be retained in accordance with The Royal College of Pathologists guidelines 'The retention and storage of pathological records and specimens' (38).

# 7 Investigation of SARS-CoV-2 antibodies

An accessible text description of this flowchart is provided with this document



Note: It is important to follow current government guidelines for the latest advice on protection from SARS-CoV-2.

## 7.1 Footnotes relating to investigation of SARS-CoV-2 antibodies algorithm

- a) Immunocompromised individuals may not mount a detectable antibody response or may show a delayed humoral immune response to infection and/or vaccination. The timing of sampling, in relation to any potential or known infection or vaccination, should be considered for all individuals, as circulating antibodies may not yet have developed, or may have waned to undetectable levels. Serology tests are unsuitable for detecting current or recently-acquired infection. An appropriate respiratory tract sample should be tested for SARS-CoV-2 RNA if current infection is suspected.
- b) Anti-spike testing prior to treatment with nMABs is advised where possible but it is not a requirement for treatment with nMABs at the time of writing. Patients may be tested for anti-spike antibodies using any validated quantitative or qualitative anti-S assay that detects IgG alone, or both IgG and IgM (44).
- c) Consideration should be given to the possibility of a false positive result. The likelihood of false reactivity depends on local seroprevalence (45).
- d) Data is not currently available to understand how measurable circulating antibodies correlate to functional immunity, or the possibility of re-infection. Therefore, a reactive result cannot be interpreted to mean that the patient is immune, or that they are not currently infected or that they cannot transmit the virus to others.
- e) Inference of vaccination history by detection or absence of anti-S antibodies is only applicable to individuals who have received those vaccines which target the spike protein.

Note: interpretation of equivocal or indeterminate results will depend on the assay manufacturer's instructions and on local validation data.

## 8 Interpreting and reporting laboratory results

Interpretation and reporting table for SARS-CoV-2 anti-S and anti-N testing:

|   | Anti-S   | Anti-N       | Interpretative Comment  |
|---|----------|--------------|---|
| 1 | Detected | Detected     | <p>SARS-CoV-2 anti-S and anti-N antibody detected. Suggestive of previous SARS-CoV-2 infection. Anti-S may also be detected in those with a history of SARS-CoV-2 vaccination.</p> <p>This does not mean complete protection from further infection.</p> <p>It is important to follow current government guidelines for the latest advice on protection from SARS-CoV-2.</p> <p>If this patient has received any SARS-CoV-2 monoclonal antibodies therapy or blood products within the last 4 weeks, please note that these results may reflect passively acquired antibodies. Refer to latest guidance criteria for SARS-CoV-2 monoclonal antibody therapies</p> |
| 2 | Detected | Not detected | <p>SARS-CoV-2 anti-S antibody detected, consistent with past SARS-CoV-2 infection or vaccination. Anti-N antibody may have waned in the case of past infection.</p> <p>This does not mean complete protection from further infection.</p> <p>It is important to follow current government guidelines for the latest advice on protection from SARS-CoV-2.</p> <p>If this patient has received any SARS-CoV-2 monoclonal antibodies therapy or blood products within the last 4 weeks, please note that these results may reflect passively acquired antibodies. Refer to latest guidance criteria for SARS-CoV-2 monoclonal antibody therapies.</p>               |

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|   |              |              |   |
|---|--------------|--------------|---|
| 3 | Detected     | Not tested   | <p>SARS-CoV-2 anti-S antibody detected, consistent with past SARS-CoV-2 infection or vaccination.</p> <p>This does not mean complete protection from further infection.</p> <p>It is important to follow current government guidelines for the latest advice on protection from SARS-CoV-2.</p> <p>If this patient has received any SARS-CoV-2 monoclonal antibodies therapy or blood products within the last 4 weeks, please note that these results may reflect passively acquired antibodies. Refer to latest guidance criteria for SARS-CoV-2 monoclonal antibody therapies.</p> |
| 4 | Not detected | Detected     | <p>SARS-CoV-2 anti-N antibody detected, consistent with past SARS-CoV-2 infection.</p> <p>This does not mean complete protection from further infection.</p> <p>It is important to follow current government guidelines for the latest advice on protection from SARS-CoV-2.</p> <p>If this patient has received any SARS-CoV-2 monoclonal antibodies therapy or blood products within the last 4 weeks, please note that these results may reflect passively acquired antibodies. Refer to latest guidance criteria for SARS-CoV-2 monoclonal antibody therapies.</p>                |
| 5 | Not detected | Not detected | <p>No serological evidence of past SARS-CoV-2 infection or vaccination.</p> <p>It is important to follow current government guidelines for the latest advice on protection from SARS-CoV-2.</p>   |
| 6 | Not detected | Not tested   | <p>No serological evidence of past SARS-CoV-2 infection or vaccination.</p> <p>It is important to follow current government guidelines for the latest advice on protection from SARS-CoV-2.</p>   |

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Serology

|   |            |              |  |
|---|------------|--------------|--|
| 7 | Not tested | Detected     | <p>SARS-CoV-2 anti-N antibody detected, consistent with past SARS-CoV-2 infection.</p> <p>This does not mean complete protection from further infection.</p> <p>It is important to follow current government guidelines for the latest advice on protection from SARS-CoV-2.</p> <p>If this patient has received any SARS-CoV-2 monoclonal antibodies therapy or blood products within the last 4 weeks, please note that these results may reflect passively acquired antibodies. Refer to latest guidance criteria for SARS-CoV-2 monoclonal antibody therapies.</p> |
| 8 | Not tested | Not detected | <p>No serological evidence of past SARS-CoV-2 infection.</p> <p>It is important to follow current government guidelines for the latest advice on protection from SARS-CoV-2.</p>   |

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An explanation of the reference assessment used is available in the [scientific information section on the UK SMI website](#).

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