Source: https://sacoronavirus.co.za/2020/08/24/guidance-on-the-use-of-sars-cov-2-antibody-tests/

RECOMMENDED USES OF SARS COV-2 ANTIBODY TESTS

Background

The diagnosis of acute COVID-19 relies on detection of SARS-CoV-2 RNA by real-time reverse transcription-polymerase chain reaction (PCR) from respiratory samples. Viral shedding from the upper respiratory tract is greatest between the presymptomatic period and within the first week of symptoms but drops off rapidly over time. Despite high specificity, the sensitivity of the SARS-CoV-2 RT-PCR from nasopharyngeal or midturbinate swabs is sub-optimal and may be influenced by timing of the swab, technique and limitations of the assay. Some patients present for testing late in their illness when viral titres in the upper airways are waning, and despite a clinical diagnosis of COVID-19 being made, may test negative by PCR, sometimes repeatedly1.

Serology tests to detect the presence of specific antibodies against infecting pathogens generally yield positive results from late in the course of acute illness (often >10 days after onset) or only during convalescence. Most but probably not all SARS-CoV-2 infected patients who recover clinically will seroconvert (i.e. form specific antibodies) against one or more SARS-CoV-2 antigens. A systematic review and meta-analysis of studies on the sensitivity and specificity of antibody tests for SARS-CoV-2 identified 38 studies that stratified results by time since symptom onset2. Pooled results for IgG/IgM had a sensitivity of 30.1% (95% ci 21.4 to 40.7) for 1 to 7 days, 72.2% (95% ci 63.5 to 79.5) for 8 to 14 days, 91.4% (95% ci 87.0 to 94.4) for 15 to 21 days after onset of illness. Between 21 to 35 days, pooled sensitivities for IgG/IgM were 96.0% (95% ci 90.6 to 98.3). Little data is available on antibody responses beyond 21 days from symptom onset. Some recovered COVID-19 patients were shown to sero-revert (i.e. had no detectable serum antibodies any longer) after several weeks to months. The available evidence suggests that the sensitivity of antibody tests (for any type of antibody, IgM, IgA or IgG) is too low in the first week since symptom onset (period of greatest infectiousness) to have a primary role for the diagnosis of COVID-19.

Local validation studies from NHLS and National Pathology Group cohorts confirms low sensitivity in PCR-positive symptomatic patients in the first 2 weeks after onset of symptoms across all 4 assays tested. In keeping with international experience, sensitivity increases with disease severity.

Small clusters of children and adolescents with COVID-19-associated multisystem inflammatory syndrome have been documented in Europe and North America. In these cases, PCR is commonly negative but serology for SARS-CoV-2 has been shown to be positive3. No studies have been performed to date in South African hospitals to investigate the utility of serology in patients admitted late in the course of disease (≥14 days) where PCR is negative.

Apart from laboratory based (“formal”) antibody tests, there are rapid diagnostic tests (RDT) for antibody testing at point-of-care. Most of these are based on the lateral flow principle. RDTs generally have lower sensitivities than laboratory-based antibody tests. Studies reporting validation results for RDTs have commonly been performed on small

numbers of samples. However, a recent country-wide seroprevalence study in Spain successfully used a point-of-care test (Orient Gene Biotech COVID-19 IgG/IgM Rapid Test Cassette)4.

The WHO has published draft COVID-19 Target Product Profiles for priority diagnostics to support response to the COVID-19 pandemic5. The WHO acknowledges that due to the urgency of the current situation, the proposed Target Product Profiles are focused on priority use case scenarios. This to address the greatest needs. This also should acknowledge that access to optimal tests may not be possible and in certain circumstances where RT-PCR testing cannot be undertaken, there may be a utility for point-of-care testing for either antibodies or antigens provided specimens are taken at the correct time after infection.

Thus, based on this context, the following recommendations on the use of both RDTs and laboratory-based antibody tests are made.

- All the results of all antibody testing conducted must be recorded and reported to the National Health Laboratory Service (NHLS), utilising the appropriate application (found at: https://csa.nhls.ac.za/).

- RDTs must be administered by suitably qualified and trained health professionals only.

- Laboratory-based serology testing should be conducted in ISO15189 accredited facilities only.

Recommendation for use

1. **Testing for SARS CoV-2-specific antibodies for the diagnosis of COVID-19**

The evidence suggests that the sensitivity of both laboratory-based and rapid, point-of-care antibody tests is too low within the 14 days since symptom onset to have a primary role for the clinical diagnosis of acute Covid-19. Hence, it is recommended that PCR testing remains the modality for acute clinical diagnosis of COVID-19, with laboratory-based and rapid point-of-care antibody tests possibly playing a very specific role in the following circumstances:

- To diagnose COVID-19 retrospectively in patients who have recovered from a COVID-19 compatible illness and are negative by SARS-CoV-2 PCR.

- To diagnose COVID-19 in patients in who are admitted with suspected SARS-CoV2 infection but who test negative for RT-PCR as an ancillary investigation. This will include children with suspected multisystem inflammatory syndrome who may test negative by SARS-CoV-2 PCR.

2. **Use of SARS CoV-2-specific antibodies for epidemiological purposes**

To identify **past exposure** to SARS-CoV2 in individuals optimally at 21-days post infection.

Evidence about the duration of antibody response ≥35 days is currently inconclusive and therefore there is no comment on the accuracy of antibody testing for population-based seroprevalence studies at this point. Potential uses include:

- Cohort surveillance e.g. targeted at healthcare and frail care institutions, prisons, workplaces and similar facilities where seroprevalence may be elevated

- **Population-level epidemiologic studies and surveillance programmes**, including community antibody surveillance in settings of recently suspected transmissions.

- To reconstruct of chains of transmission in outbreak settings.

3. **Use of SARS CoV-2-speficic IgG, IgM and/or IgA antibody testing as part of scientific research studies and clinical trials**

- Following appropriate institutional and other necessary approvals (e.g. HREC), the use of particular types of antibody tests (e.g. to measure neutralising antibodies) may include:

- To assess antibody reactivity as a prognostic marker.

- To assess SARS-CoV-2 vaccine responses.

- To identify potential convalescent plasma donors. While different antibody tests may be useful for screening potential convalescent plasma donors, neutralising antibody titres should subsequently be determined using a suitable assay such as plaque reduction neutralisation test.

Limitations of SARS-CoV-2 antibody testing

False negative test results

A negative antibody test result does NOT reliably rule out prior SARS-CoV-2 infection.

Possible causes would be:

- Insufficient sensitivity of antibody test.

- Acute phase testing (specifically within 14 days post-symptom onset).
- Some patients may not form detectable antibodies, especially following asymptomatic SARS-CoV-2 infection.
- Waning of antibodies over time, and as soon as 1-2 months in asymptomatic or mild cases.

False positive test results.

A positive antibody test result does NOT reliably prove prior SARS-CoV-2 infection.

Possible causes would be:

- Insufficient specificity of antibody test.
- Cross-reacting antibodies, e.g. those directed against other human coronaviruses.

The biological significance of specific anti-SARS-CoV-2 antibodies is uncertain because of the following factors:

- The detection of antibodies may not correlate with immune protection. A positive antibody test result therefore should not be regarded as proof of immunity and must not be used to reduce or abandon protective measures. The issuing of an "immunity passport" or "immunity certificate" based on a positive antibody test result is not recommended in South Africa or by the WHO.
- Antibodies detected by different assays do not necessarily represent neutralising antibodies that are assumed to be the best measure of humoral immunity and protection against infection and/or disease, the principal rationale behind using convalescent plasma as a possible treatment option.

Reporting requirements for all serology testing

It is important that **all serology test results** are recorded, to contribute to the national data base. All results must be reported to the National Health Laboratory Service (NHLS). For both rapid point-of-care and formal laboratory-based serology tests, the web-based application https://csa.nhls.ac.za must be utilised. The form and instructions

for using the COVID-19 RDT web application are available on the National Health Laboratory Service website at https://www.nhls.ac.za/sars-cov-2-antibody-reporting.

This guidance document will continuously be reviewed as more data becomes available, especially when more data on antigen tests emerge.

References

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