health
Department:
Health
REPUBLIC OF SOUTH AFRICA

Enquiries: Prof S Abdool Karim
E-mail: salim.abdoolkarim@caprisa.org

INTERNAL MEMO

Date:	31 July 2020		
To:	**The Honorable Dr ZL Mkhize, Minister of Health**	From:	**Ministerial Advisory Committee (MAC) on COVID-19**

RECOMMENDATIONS FOR USE OF SARS-CoV-2 ANTIBODY TESTING

Request for Advisory sent to MAC/Problem/Concern

How should antibody tests (serology) for SARS-CoV-2 be used in South Africa in the management of COVID-19?

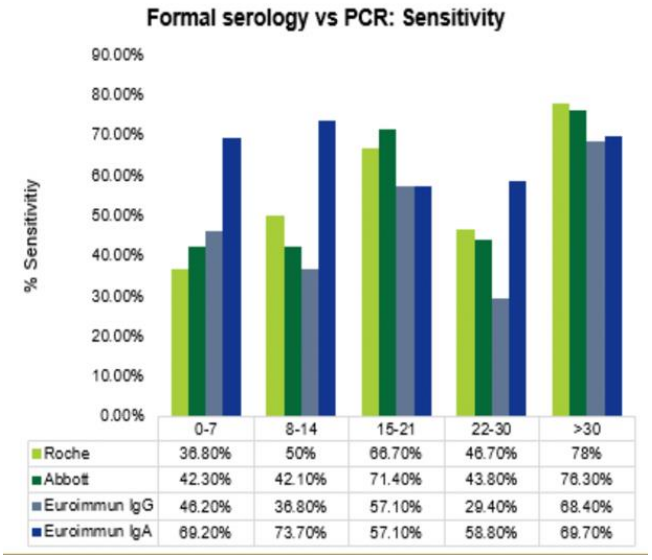
Points of consideration

- 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 PCR from nasopharyngeal or mid-turbinate swabs is sub-optimal and may be influenced by timing of the swab, technique, the assay itself etc.
- 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 repeatedly.
- 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).
- 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 onset[1]. 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). Very little data is available on antibody responses beyond 21 days from symptom onset. Some recovered COVID-19 patients were shown to sero-revert after several weeks to months, i.e. had no detectable antibodies any longer. The available evidence

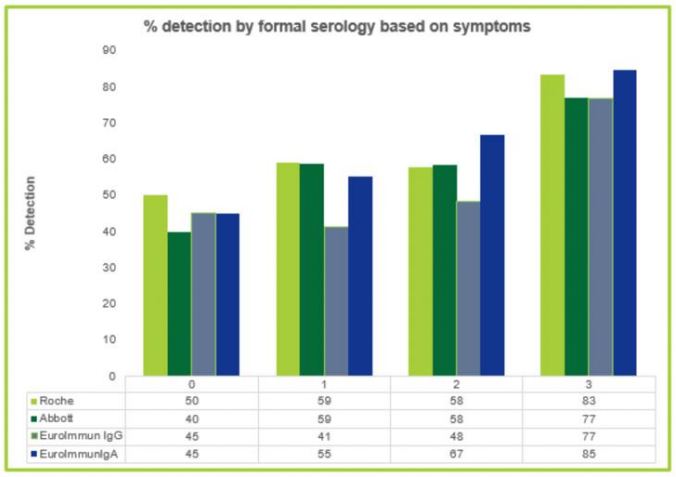
[1] *Cochrane Database Syst Rev.* 2020;6:CD013652. Published 2020 Jun 25. doi:10.1002/14651858.CD01365

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.

- 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 positive.[2]
- 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 (Figure – formal serology vs PCR: sensitivity). In keeping with international experience, sensitivity increases with disease severity (Figure - % detection by formal serology based on symptoms).



	0-7	8-14	15-21	22-30	>30
Roche	36.80%	50%	66.70%	46.70%	78%
Abbott	42.30%	42.10%	71.40%	43.80%	76.30%
Euroimmun IgG	46.20%	36.80%	57.10%	29.40%	68.40%
Euroimmun IgA	69.20%	73.70%	57.10%	58.80%	69.70%



	0	1	2	3
Roche	50	59	58	83
Abbott	40	59	58	77
EuroImmun IgG	45	41	48	77
EuroImmunIgA	45	55	67	85

Number of patients

Roche	n
0	10
1	22
2	57
3	12
Abbott	n
0	20
1	29
2	65
3	13
EuroImmun IgG	n
0	20
1	29
2	66
3	13
EuroImmun IgA	n
0	20
1	29
2	66
3	13

0 - asymptomatic
1 – mild disease (upper respiratory tract symptoms)
2 – moderate disease (systemic symptoms, cough, gastrointestinal symptoms symptoms
3 – severe disease requiring hospital admission

- Rapid diagnostic tests (RDT) for antibody testing at point-of-care are based largely on the lateral flow principle. They 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).[3]

[2] *Lancet*. 2020;395(10237):1607-1608. doi:10.1016/S0140-6736(20)31094-1 and https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19
[3] Pollán M, Pérez-Gómez B, Pastor-Barriuso R, et al. Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study [published online ahead of print, 2020 Jul 3]. *Lancet*. 2020;S0140-6736(20)31483-5. doi:10.1016/S0140-6736(20)31483-5

- 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.

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 are:

- Insufficient sensitivity of antibody test.
- Some patients may not form detectable antibodies, especially following asymptomatic SARS-CoV-2 infection.
- Waning of antibody 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 are:

- 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 may be uncertain due to 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" 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.
- 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.

Recommendations

Testing for SARS-CoV-2-specific IgG antibodies for diagnosis of COVID-19

- The evidence suggests that the sensitivity of laboratory-based antibody tests is too low in the 14 days since symptom onset to have a primary role for the acute clinical diagnosis of COVID-19. Rapid, point-of-care antibody test sensitivities are generally worse still. Hence, the MAC recommends that PCR 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:
    - Diagnosis of COVID-19-associated multisystem inflammatory syndrome in children
    - To retrospectively diagnose COVID-19 in individuals with occupational exposure to SARS-CoV-2 who have recovered from a COVID-19 compatible illness.

Potential use of SARS-CoV-2-specific IgG antibodies for epidemiological purposes

Evidence about the duration of antibody response ≥35 days is currently inconclusive and therefore we are unable to comment on the accuracy of antibody testing for population-based seroprevalence studies at this point. However potential uses include:

- To perform cohort surveillance e.g. targeted at healthcare and frail care institutions, prisons, workplaces and similar facilities.
- To perform community antibody surveillance e.g. targeted at settings of recently suspected transmissions and for epidemiological assessments.
- To evaluate "hotspots" of SARS-CoV-2 transmission, at least in the 2-week period before sampling.
- To contribute to the reconstruction of chains of transmission.

Potential use of SARS-CoV-2-speficic IgG, IgM and/or IgA antibodies as part of scientific studies and clinical trials

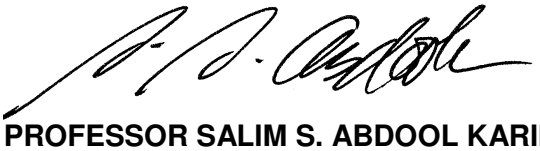
Following appropriate approvals, the use of particular types of antibody tests (e.g. to measure neutralising antibodies) may include

- To assess antibody reactivity as a prognostic marker
- To undertake population-level epidemiologic studies
- To assess SARS-CoV-2 vaccine responses
- To identify potential convalescent plasma donors

This advisory should be reviewed as more data becomes available, especially when more data on antigen tests emerge.

Thank you for consideration of this request.

Kind regards,



PROFESSOR SALIM S. ABDOOL KARIM
OVERARCHING CHAIRPERSON: MINISTERIAL ADVISORY COMMITTEE ON COVID-19
DATE: 31 July 2020

CC:

- **Dr S Buthelezi (Director-General: Health)**
- **Dr T Pillay (Deputy Director-General: National Health Insurance)**
- **Dr S Zungu (Project Lead: Sectoral Response to Covid-19)**
- **Incident Management Team**