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SPECIAL INTEREST GROUP OF THE SOUTH AFRICAN MEDICAL ASSOCIATION

Guidance on the role of SARS-CoV-2 Rapid Antigen Tests

By the National Pathology Group 1 October 2020

The current gold standard method for the detection of SARS-CoV-2, the virus that causes COVID-19, is the reverse transcriptase polymerase chain reaction (RT-PCR) test, which is a type of nucleic acid amplification test (NAAT). Due to limitations related to complexity of performing these tests, global shortages in test kits and supplies, the requirement for laboratory equipment, high test cost and the potential for delayed turnaround times, there has been a drive towards the development of rapid point of care test methodologies for the detection of SARS-CoV-2. Immunoassay devices that detect SARS-CoV-2 antigen have been earmarked as a possible solution as a rapid near-patient testing device. Following their release to market though, SARS-CoV-2 antigen assays have shown variable performance during evaluations, with sensitivities ranging from 0 to 94%. Test specificity has at least been consistently high despite the wide variation in sensitivity. In an attempt to meet the unmet needs for testing globally, the Bill & Melinda Gates Foundation in partnership with the World Health Organization (WHO) and others have identified two recently released SARS-CoV-2 antigen assays for distribution to low and middle income countries. The producers of these tests, namely Abbott and SD Biosensor, claim sensitivity of 93% and 96% respectively. The SD Biosensor COVID-19 Ag assay was listed on 22 September 2020 as the first SARS-CoV-2 Antigen assay under the WHO Emergency Use Listing for In vitro diagnostics (IVDs) Detecting SARS-CoV-2. It should be noted that external evaluations for these two assays are still underway. While some of the SARS-CoV-2 antigen assays show promise as a rapid alternative to NAAT assays in the diagnosis of COVID-19, the NPG members would like to highlight the following issues which should be taken into consideration prior to implementation of these assays in practice:

- SARS-CoV-2 antigen tests are performed on respiratory specimens, particularly nasopharyngeal swabs, and therefore poor sample quality may produce false negative results. For this reason sample collection would still require staff trained in the methodology.
- Biosafety requirements need to be implemented when performing these tests, as operators would be processing potentially infectious specimens.
- Although these tests are easier to perform than NAAT tests, the requirements as per manufacturer's instruction still need to be followed precisely, documentation of results need to be done carefully, and factors such as storage and shelf-life need to be managed actively.

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- The sensitivity of the antigen tests are higher when viral loads are higher (low cycle threshold (Ct) in RT-PCR), which is usually within the first 5 days following symptom onset, therefore timing of testing is crucial.
- Manual interpretation of faint lines may be subjective.
- Low pre-test probability/low prevalence increase the likelihood of false positive results , which will limit the use of these tests for screening purposes, such as at points of entry, blood donation or elective surgery.
- There is still a lack of data re. performance of these tests in asymptomatic individuals.

The WHO have released an Interim Guidance document for Antigen-detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays on 11 September 2020, which offers recommendations for the appropriate use of these tests. The NPG wishes to highlight the following recommendations from this document in particular:

- The minimum performance characteristics required are a sensitivity of ≥ 80% and specificity of 97%.
- Clinical use should only be considered in settings where COVID NAAT is unavailable or where prolonged turnaround times preclude clinical utility of NAAT.
- Where possible, all samples giving positive Antigen results (or at least a subset) should be transported to laboratories with NAAT capability for confirmatory testing.
- A negative Antigen result cannot completely exclude an active COVID-19 infection, and, therefore, repeat testing or preferably confirmatory testing (NAAT) should be performed whenever possible, particularly in symptomatic patients.

The NPG members are of the opinion that further field evaluation data and more experience with these tests need to be gained before these assays can be safely and confidently used, particularly in settings where NAAT-based results are available within a reasonable amount of time. The WHO recommendation to confirm not only positive, but also some negative antigen results places a limitation on the clinical utility of these tests at present.

To date no SARS-CoV-2 antigen tests have been approved by South African Health Products Regulatory Authority (SAHPRA). Evaluations for the purpose of regulatory approval would need to take into account the complexities of sample collection (e.g. timing of sampling following the NAAT result), correlation with the NAAT result's Ct value/viral load, and if possible also symptomatic vs. asymptomatic individuals.