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MD006: Laboratory testing and use of COVID-19 serological test kits

BACKGROUND

1. On 30 January 2020, the World Health Organization (WHO) declared the COVID-19 (SARS-CoV-2) outbreak as a Public Health Emergency of International Concern (PHEIC), and shortly thereafter called for research on point of care (POC) diagnostics for use at the community level.

2. In response, numerous POC *in-vitro* diagnostics (IVDs) are in development or have entered the market in a number of countries. Most of them detect COVID-19 antigens or antibodies in a so-called "Rapid Diagnostic Test" (RDT) design.

TYPES OF COVID-19 RAPID DIAGNOSTIC TESTS

3. There are two types of COVID-19 serological RDTs, those that detect antigens and those that detect antibodies. COVID-19 antigen detection RDTs and COVID-19 antibody detection RDTs are different.
4. COVID-19 antigen detection RDTs diagnose the presence of a protein of the virus in body fluids, mostly in secretions of the upper respiratory tract.
5. COVID-19 antibody detection RDTs diagnose antibodies produced by white blood cells of the infected person during the infection. They are mostly detected in the blood. But it takes a few days after the onset of illness before the level of antibodies in the blood is high enough to be detected by the RDT. Further, antibodies remain in the body long after the infection has been cleared. Unlike other (laboratory-based) immunoassays, they do not provide quantitative information (information about the number of antibodies, expressed as dilution "titer").
6. COVID-19 antigen and antibody detection RDTs are "immunoassays" or "serological tests". They are based on interactions between antigens and antibodies. Other examples of immunoassays which are performed in the laboratory (mostly on batched samples) are Enzyme-Linked Immuno Sorbent Assays (ELISA) and Immuno Fluorescent Assays (IFA). Unlike ELISA and IFA tests, RDTs can be performed outside the laboratory.

CURRENT RECOMMENDATIONS FOR LABORATORY TESTING

7. The WHO has advised that molecular testing is the current recommended method for the identification of infectious cases of COVID-19.
8. The technical requirements for molecular testing are included in: Laboratory testing for COVID-19 in suspected human cases (https://apps.who.int/iris/bitstream/handle/10665/331509/WHO-COVID-19-lab_testing-2020.1-eng.pdf)
9. For the identification of COVID-19 infections:
    a) Nuclear acid amplification (NAAT) methods (molecular methods such as RT-PCR) are recommended. This comprises of the following applications:

- clinical diagnosis for patient care ("test and treat"),
- identification at triage and investigation of clusters ("test and isolate")
- confirmation of virus clearance after recovery

Respiratory tract specimens are recommended, other specimens are under investigation. These include:

- upper respiratory specimens (nasopharyngeal and oropharyngeal swab or wash)
- lower respiratory specimens (sputum and/or endotracheal aspirate or bronchoalveolar lavage).

b) Serology tests are currently not recommended for case detection. But they may play a role in research and surveillance.

c) Rapid Diagnostic Tests for antigen detection for COVID-19 need to be evaluated and are not currently recommended for clinical diagnosis pending more evidence on test performance and operational utility.

10. The WHO will update this guidance as more information becomes available.

VALIDATION STUDY RECOMMENDATIONS BASED ON THE TECHNOLOGICAL PRINCIPLES OF DIAGNOSTIC TESTS

11. SAHPRA has recommended the minimum testing that should be performed for SARS-CoV-2 diagnostics based upon the underlying technological principles of the test (Refer to MD007).

ANTIGEN DETECTION RDT

12. SAHPRA defines SARS-CoV-2 antigen diagnostic tests as those that detect SARS-CoV-2 antigens directly from clinical specimens.

13. SAHPRA recommends that the validation studies, including but not limited to the following, be conducted for a SARS-CoV-2 antigen detection RDT:

a) Limit of Detection/Analytical Sensitivity
b) Cross-reactivity/Analytical Specificity ·
c) Microbial Interference
d) Clinical Agreement Study

The clinical agreement study is intended to establish the performance characteristics (e.g., sensitivity/PPA, specificity/NPA) of the test. SAHPRA believes that clinical agreement should be established on human specimens, preferably leftover specimens from patients with or without SARS-CoV-2 infection. If SARS-CoV-2 positive clinical specimens cannot be obtained, it is acceptable to spike leftover specimens with SARS-CoV-2 materials. For devices claiming multiple clinical matrices, the most challenging matrix should be used in the validation studies.

ANTIBODY DETECTION RDT

14. SAHPRA defines SARS-CoV-2 antibody detection RDTs as tests that identify antibodies (e.g., IgM, IgG, IgA) to SARS-CoV-2 from clinical specimens.

15. SAHPRA recommends that validation studies, including but not limited to, the following be conducted for a SARS-CoV-2 antibody detection RDT:

a) Cross-reactivity/Analytical Specificity
b) Class Specificity
c) Clinical Agreement Study

The clinical agreement study is intended to establish the performance characteristics (e.g., sensitivity/PPA, specificity/NPA) of the test. SAHPRA recommends that clinical accuracy should be established on human specimens from patients with microbiologically confirmed COVID-19 infection.

IDENTIFYING THE POTENTIAL APPLICATION OF COVID-19 ANTIGEN DETECTING RDTs IN THE COVID-19 TESTING LANDSCAPE

16. Only RDTs with high sensitivity (at least 85 %) and specificity (at least 98%) can be reasonably well used within the published national testing algorithm, assuming the RDTs meet the requirements of operational utility (environmental stability and end-user friendliness).
17. COVID-19 antigen detecting RDTs must undergo a performance evaluation, conducted by the national reference laboratory, in order to inform the decision by SAHPRA to authorise the RDT for use.

IDENTIFYING THE POTENTIAL APPLICATION OF COVID-19 ANTIBODY DETECTION RDTs IN THE COVID-19 TESTING LANDSCAPE

18. COVID-19 antibody detection immunoassays (serology tests) (ELISA, IFA and RDTs) are not recommended by WHO for identification of COVID-19 infections. They detect recent or previous exposure to COVID-19. Dynamics and specificity of the different Ig classes (IgM, IgG and IgA) are still under investigation and false positive reactions may occur. Whether exposure equals protection (immunity) also depends on which type of antibody is used. For example IgG antibodies specific to nucleocapsid or spike protein indicate immunity to COVID-19. Likewise, "immune" does not equal "non-infectivity" as it is not yet firmly known how long the virus is shed and the patient is thus still infective.
19. COVID-19 antibody detection RDTs must undergo a performance evaluation, conducted by the national reference laboratory, in order to inform the decision by SAHPRA to authorise the RDT for use.
20. Applications of COVID-19 antibody detection RDTs are currently - and pending the outcomes of performance evaluation - limited to use in the national testing algorithm. For example, these test kits may be used in seroprevalence surveys: studies which assess the proportion of individuals in a population who have had exposure to COVID-19. They can aid in investigations of ongoing outbreaks and in the (retrospective) assessment of attack rate and extent of an outbreak. The WHO guidance document for seroprevalence studies recommends the laboratory-based ELISA or IFA tests.
21. COVID-19 antibody detection RDTs have similar antibody/antigen reactions as their ELISA or IFA homologues but unlike them they:
    a) Do not provide quantification of antibodies (precluding acute/convalescent testing); and
    b) Are more vulnerable, subject to false-positive and false-negative reactions.

    The added value of an RDT over ELISA and IFA is in this case limited to its versatility (can be performed on site and on blood obtained on capillary finger prick).

CONCERNS ABOUT COMMERCIAL PROMOTION OF COVID-19 ANTIBODY DETECTION RDTs

22. According to the European Centre for Disease Prevention and Control (ECDC) (01 April 2020) and the Foundation for Innovative New Diagnostics (FIND), 10 COVID-19 antigen detection RDTs and over 90 COVID-19 antibody RDTs are Communauté Européenne (CE)-marked. However, they are CE-marked according to the "In Vitro Diagnostic Device Regulations" Directive 98/79/EC and not by the new Directive EU 2017/746 (which is more stringent and will be effective from 2022 onwards). According to the "old" 98/79/EC, manufacturers can obtain CE-mark by self-declaration and performance evaluation is therefore limited.
23. The ECDC reports several COVID-19 RDT devices with fraudulent documentation, incomplete technical files and unsubstantiated claims, with some of them sold as alleged self-tests.

SAHPRA'S POSITION ON COVID-19 ANTIBODY DETECTION RDTs

24. Antibody detection RDTs are for professional use only and must be used under the direct supervision of a healthcare professional only.
25. Negative results do not rule out SARS-CoV-2 infection, particularly in those who have been in contact with the virus.
26. Follow-up testing with a molecular diagnostic (NAAT methods such as RT-PCR) must be performed to rule out infection in these individuals.
27. Results from antibody testing should not be used as the sole basis to clinically diagnose or exclude SARS-CoV-2 infection or to inform infection status.
28. Positive results may be due to past or present infection with non-SARS-CoV-2 coronavirus strains, such as coronavirus HKU1, NL63, OC43, or 229E.
29. The authorisation for use of RDTs is limited to use in the national testing algorithm.
30. End-users, distributors and/or manufacturers must report any adverse event or product problem or suspected falsified product to SAHPRA.

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