Guidance on the use of COVID-19 rapid diagnostic tests

ITM researchers wrote a position paper to guide the use of rapid diagnostic tests to test for COVID-19 infection.

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Dit is de omschrijving

These rapid tests are particularly interesting for low resource settings where lab tests are less obvious. The Institute has years of experience in developing and evaluating diagnostic tests for infectious diseases.

COVID-19 Rapid Diagnostic Tests: use in low resource settings

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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 diagnostics for use at the community level (1).

In response, numerous point-of-care *in-vitro* diagnostics (IVDs) are in development or have entered the market. The Foundation for Innovative New Diagnostics (FIND) collates a publicly available tracker list of COVID-19 IVDs comprising point-of-care IVDs (2). Most of them detect COVID-19 antigens or antibodies in a so-called "Rapid Diagnostic Test" (RDT) design.

COVID-19 antigen detection RDTs and COVID-19 antibody detection RDTs are different.

- 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.
- 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 and up to 10 days before the concentration of antibodies in the blood is high enough to be captured by the RDT. Further, antibodies persist 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").
- COVID-19 antigen and antibody detection RDTs are "immunoassays" or "serology 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.
- Rapid diagnostic tests (RDTs) are small stand-alone tests that are simple to use. They can be used at the point of care – i.e. at the site of triage and outside the hospital, by minimally trained staff, round the clock and on single samples. They provide test results within 15 minutes, conducive to a swift patient flow. In summary, they are attractive for decentralized testing particularly in low resource settings.

According to the European Centre for Disease Prevention and Control (1 April 2020) (3) and FIND (2), 10 COVID- 19 antigen detection RDTs and over 60 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.

To our knowledge and at time of writing (3rd April 2020), there are no validation reports of COVID-19 antigen- detection and COVID-19 antibody-detection

RDTs published in scientific literature (e.g. PubMed).

- The Belgium company CORIS Bioconcept has developed a COVID-19 antigen detection RDT (COVID-19 Ag Respi-Strip) for which reference validation (St Pierre Hospital Brussels and KU Leuven) is submitted for publications (4): among COVID-19 polymerase chain reaction (PCR) samples with high viral load (Ct value ≤ 25), sensitivity was 85% , but overall sensitivity was 60%; specificity was 100%. User- friendliness for low resource settings has not yet been assessed.
- There is one COVID-19 antibody detection RDT which received US FDA clearance (5) (in addition to CE mark), *i.e.* Cellex qSARS-CoV-2 IgG/IgM Rapid Test - the instructions for use of this product refer to one validation study (not published) conducted on stored samples with reverse transcriptase (RT)-PCR and clinical definitions as the reference method – of note, the day of sampling relative to the onset of symptoms was not documented.

What are the current recommendations for laboratory testing of COVID-19?

At time of writing, WHO recommends laboratory testing for COVID-19 as follows (6–8):

1. Identification of COVID-19 infections
   Nuclear acid amplification (NAAT) methods (molecular methods such as RT-PCR) are recommended.
   This comprises 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
   - Upper respiratory specimens (nasopharyngeal and oropharyngeal swab or wash)
   - Lower respiratory specimens (sputum and/or endotracheal aspirate or bronchoalveolar lavage).
2. Serology tests are currently not recommended for case detection. But they will play a role in research and surveillance (see below for example)
3. Rapid Diagnostic Tests for antigen detection for COVID-19 need to be evaluated and is not currently recommended for clinical diagnosis pending more evidence on test performance and operational utility.

What is the potential place of COVID-19 antigen detecting RDTs in the COVID-19 testing landscape?

The validation study of the Coris Bioconcept COVID-19 antigen detection RDT (COVID-19 Ag Respi-Strip) (4) is a step forward towards evidence for use of COVID-19 antigen detection RDTs. But how far are we? Table 1 below presents the performance needs in terms of accuracy of COVID-antigen detection RDT for different testing scenarios, assuming the products meet the requirements of operational utility (environmental stability and end- user friendliness). Pending further knowledge of virus dynamics and specimens suitable for testing, we limit the overview here to upper respiratory specimens. For more detailed scenarios, we refer to "Use Cases for SARS- CoV-2 Assays, prepared by Halteres Associates, March 25, 2020 (9). As can be read from the table, only RDTs with high sensitivity and specificity can be reasonably well used in the diagnostic algorithm. The sequential testing coined out for the Respi-Strip in the Epidemic Triage scenario (4) is a notable exception which potentially can alleviate pressure on frontline laboratory work (3) but, as stated above, has not yet been adopted by WHO.

What would be the application of COVID-19 antibody detection RDTs?

As mentioned above, 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 (10) and false positive reactions may occur. Whether exposure equals protection (immunity) also depends on which type of Ab used - IgG antibodies specific to nucleocapsid or spike protein confer immunity. 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. Based on general immunological knowledge, the co-presence of IgM and IgG (as detected by COVID-19 IgG + IgM antibody detection assays) might indicate a recent infection but this has not yet been demonstrated in this specific case. WHO mentions as well the need for validation of the serology tests.

Applications of COVID-19 antibody detection immunoassays serology tests are currently – and pending validation - limited to:

- Seroprevalence surveys *i.e.* 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.
- In NAAT-assay negative cases with strong epidemiological link to COVID-19 infection, paired serum samples (in the acute and convalescent phase) could support diagnosis (switch from negative to positive or ≥ 4-fold increase in titer). Of note this diagnosis is a diagnosis-in-retrospect and too late to impact patient care or isolation.

COVID-19 antibody detections RDTs have similar antibody/antigen reactions as their ELISA or IFA homologues but unlike them they

- Do not provide quantification of antibodies (precluding acute/convalescent testing), and
- 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.

Concern about commercial promotion of COVID-19 antibody detection RDTs

The European Centre for Disease Prevention and Control (1 April 2020) (3) reports several COVID-19 RDT devices with fraudulent documentation, incomplete technical files and unsubstantiated claims, with some of them sold as alleged self-tests. As to regulation, "self-testing" is a more stringent regulated category of IVDs compared to the regular "for professional use". It is to be expected that in poorly regulated countries such practices will be more frequent.

In addition, we observed promotional product flyers and emails which were too optimistic and suggestive when advertising COVID-19 antibody detection RDTs. Intended use, performance data and interpretation are often not mentioned. The information given is sometimes incomplete (even misleading): as an example, the diagnostic sensitivity of the antibody test in NAAT-confirmed patients is given without mentioning the delay between NAAT and antibody testing. We recommend carefully reading the product's Instructions for Use. In the referred example (11) one can note (i) the absence of performance data and the (ii) incorrect mentioning of "anti-Dengue virus antibodies". Note that the Belgian health authorities have banned COVID-19 antibody detection RDTs from sale for a period of 6 months (12) in order to avoid misinterpretation of negative results.

Conclusion

- There is already a plethora of COVID-19 antigen and antibody detection kits on the market. Even when CE-marked, published data about diagnostic performance are scarce apart from a few exceptions.
- For identification of COVID-19 infected persons, WHO recommends NAAT testing on respiratory tract specimens. Antibody testing is not recommended. More evidence (performance, operational use) is awaited about COVID-19 antigen detection RDTs. Applications of COVID-19 antibody detection tests (including RDTs) are limited to seroprevalence studies and retrospective diagnosis in NAAT-negative patients.
- For one CE marked antigen-detection kit, a validation study is submitted for publication. Overall sensitivity is low (60%) and increased to 85% in samples with high viral load. At these values, the RDT can only be reliably used in an "epidemic triage of symptomatic patients" scenario in

conjunction with subsequent NAAT testing for the RDT-negative samples. Usability in low-resource settings has not yet been studied.
- We issue a concern about commercial promotion in particular for COVID-19 antibody detection RDTs.

References

- WHO. COVID 19 Public Health Emergency of International Concern (PHEIC): Global research and innovation forum: towards a research roadmap [Internet]. 2020.
- SARS-CoV-2 diagnostic pipeline [Internet]. [cited 2020 Apr 4].
- ECDC. An overview of the rapid test situation for COVID-19 diagnosis in the EU / EEA [Internet]. Stockholm; 2020.
- Mertens P, De Vos N, Martiny D, Jassoy C, Mirazimi A, Cuypers L, et al. Development and potential usefulness of the COVID-19 Ag Respi-Strip® diagnostic assay in a pandemic context. Submitt Publ. 2020;
- FDA Emergency Use Authorizations [Internet]. [cited 2020 Apr 4].
- WHO. Laboratory testing strategy recommendations for COVID-19: Interim guidance [Internet]. Geneva; 2020. Available from: WHO/2019-nCoV/lab_testing/2020.1
- WHO. Laboratory testing for coronavirus disease 2019 (COVID-19) in suspected human cases [Internet]. Geneva: World Health Organization; 2020.
- WHO Country & Technical Guidance - Coranavirus disease (COVID-19).
- Halteres Associates. Use Cases for SARS-CoV-2 Assays.
- Okba NMA, Muller MA, Li W, Wang C, GeurtsvanKessel CH, Corman VM, et al. SARS-CoV-2 specific antibody responses in COVID-19 patients. medRxiv [Internet]. 2020;2020.03.18.20038059.
- Liming Bio. COVID-19 IgG/IgM Combo Rapid Test Device: Instructions for Use [Internet]. [cited 2020 Apr 4].
- Federal Agency for Medicines and Health Products. Coronavirus: ban on the sale of rapid diagnostics tests due to risk of misinterpretation.

Table 1 Diagnostic performance requirements and place in diagnostic algorithm of COVID-19 antigen detection tests according to different COVID-19 decentralized testing scenarios. "Prevalence" refers to the proportion of COVID-19 positive individuals in the tested group. Abbreviations: NPV = negative predictive value (the probability that subjects with a negative screening test truly don't have the disease), PPV = positive predictive value (the probability that subjects with a positive screening test truly have the disease), Sn = sensitivity, Sp = specificity.

Testing scenario		Requirements diagnostic accuracy	Comments
1. Epidemic setting	Triage of symptomatic patients Moderate prevalence	High Sn to obtain high NPV Reasonable Sp to avoid unnecessary quarantine	Confirmatory NAAT testing at the central level to identify false positives
		Alternative: RDT with low sensitivity and high specific (such as the COVID-19 Ag Respi-Strip) can be used in a sequential testing algorithm: 1. high PPV 2. low NPV: negative tests are to be retested by NAAT methods	Retesting of RDT negative samples Ideally, sample of sample/buffer mixture used for RDT should be appropriate for subsequent NAAT testing: 1. sufficient volume 2. buffer compatible with NAAT-assay 3. sample stability preserved 4. leak-free tube or container
	Triage of contacts of COVID-19 persons Low Prevalence	Given the low prevalence: Very high Sn to increase NPV Very high Sp to increase PPV	Note 1: If COVID-19 infected, viral load will be low in these individuals – the Coris Ag Respi-Strip is not useful in this setting (sensitivity too low at low viral load). Note 2: targeted Sn and Sp are very high: > 99%
3. Endemic setting	Diagnosis of symptomatic persons Very low prevalence	Very high Sn and Sp needed	As above
4. Surveillance in sites with previous or potential outbreaks	Very low prevalence	Very high Sn and Sp needed	As above
5. Detection of previous exposure		COVID-19 antigen detection RDTs have no value See text for the value of COVID-19 antibody detection RDTs	