

Approaches to laboratory testing for Covid-19

Virologists working in large diagnostic laboratories in South Africa give insights into testing in a pandemic

Testing for SARS-CoV-2 is valuable for clinical and epidemiological reasons. Knowing if admitted patients have Covid-19 helps with clinical management and cohort nursing to limit spread to uninfected vulnerable patients and staff.

Testing health care workers who are symptomatic or have had high-risk exposures, helps to protect patients and colleagues. Epidemiological testing has been valuable in identifying hot spots and has been key to controlling the pandemic in several settings. However, limitations in laboratory facilities, expertise and access to test supplies pose major challenges for Africa. Even some industrialised countries have failed to respond promptly and sufficiently, which included failures to ramp-up testing. Delayed responses resulted in the rapid uncontrolled increase in hospitalisations and intensive care admissions; thus overwhelming the health care capacity in several countries.¹

There is a rapidly growing body of recommendations, reports and scientific papers about all aspects of the laboratory diagnosis of Coronavirus Disease 2019 (Covid-19).^{2,3} It is not easy to keep up with frequent updates and changes (and the often confusing way in which they are published on websites). While following the latest findings, we should keep in mind that the widespread use of pre-publication servers for manuscripts means that these studies have not yet been peer-reviewed; and are yet to undergo one of the most important steps in the scientific process.

Like for all viral infections of the respiratory tract, the diagnostic method of choice for Covid-19 is the detection of the aetiological agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in samples from the respiratory tract.^{5,6} The most commonly used, highly sensitive method is viral nucleic acid testing (NAT), mostly by reverse transcriptase polymerase chain reaction (RT-PCR), which is widely regarded as the gold standard.⁵

Within weeks of the discovery of SARS-CoV-2,

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several groups had developed, evaluated and published RT-PCR protocols.^{6,7} Many manufacturers adopted or adapted these protocols and a multitude of assays are now available commercially.⁸ While many of these commercial assays appear to perform well, choosing properly evaluated and, where applicable, officially authorised assays is of utmost importance to ensure reliable test results.⁹

Leveraging the substantial footprint in many African countries of high-throughput largely automated systems for HIV viral load testing and early infant diagnosis of HIV would be ideal, as long as this would not be at the expense of maintaining essential HIV services. Unfortunately again, test kit supplies for these platforms are too limited to allow efficient mass testing.¹⁰

As the Covid-19 pandemic unfolds, several factors have come to the fore as particularly relevant. Rather than give an overview of current testing guidelines and practices – which are prone to change over time, and in any case, for which good reviews are available¹¹ – we instead want to list some of the pertinent issues encountered in South Africa, the African country first and so far worst hit by the pandemic, and some proposed solutions.

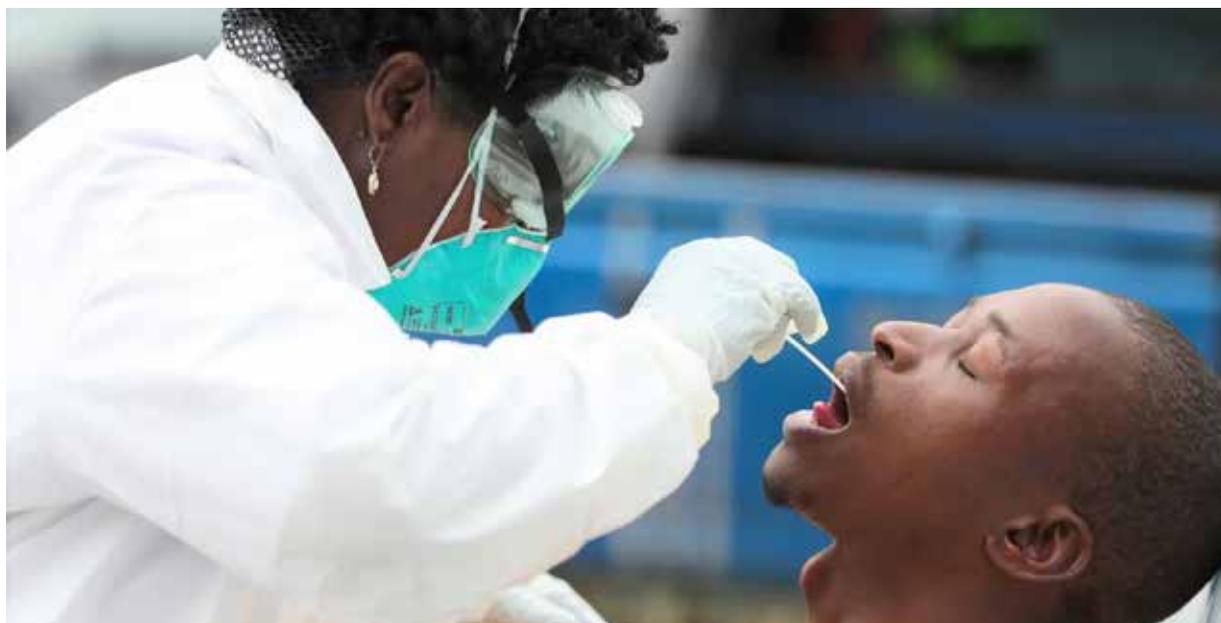
Sample types and specimen collection

A combination of nasopharyngeal and oropharyngeal swab samples has been recommended for ambulatory patients, and lower respiratory tract samples such as sputum and/or endotracheal aspirate or bronchoalveolar lavage from those with more severe respiratory disease. Specimen collection is uncomfortable to patients and exposes the healthcare worker. So this necessitates the use of adequate personal protective equipment (PPE). Alternatives such as self-administration of anterior nasal swabbing or collection of saliva appear promising,^{12,13,14} but definitive results of thorough comparative studies of saliva with other sample types are still in waiting. Although relatively easier to obtain, and resulting in less aerosol exposure of staff, saliva may contain inhibitory substances that may adversely affect NAT assays.

Point-of-care tests for SARS-CoV-2

For a disease that has a short incubation period and generation time, with those infected being potentially infectious two or even three days prior to onset of illness, a short turn-around time (TAT) from sampling to result is very important. Unfortunately, NAT usually requires specialised facilities and is not conducive to rapid TATs.

Some rapid tests for detecting SARS-CoV-2 RNA are



available commercially. Some require quite substantial manipulation by a skilled and experienced operator so are unsuitable for use outside specialised laboratories. The GeneXpert® system which is comparatively simple to use is widely used in Africa for the diagnosis of tuberculosis.¹⁵ While test cartridges for SARS-CoV-2 are available, the demand currently vastly outstrips supplies which seriously hampers realising the promise of this system for pandemic control.¹⁶

Assays to detect the presence of viral antigen in respiratory specimens have been developed.¹⁷ While evaluations are ongoing, so far, their sensitivity seems to be inferior to NAT. This is not surprising, given the experience with other viral respiratory tract infections. It remains to be seen whether even less sensitive tests may potentially play a role in pandemic management, if perhaps used for populations where utmost sensitivity is not essential. Antigen assays might be particularly attractive if they were in a point-of-care (PoC) or near-patient format.¹⁸

Innovations for laboratory-based NAT

Early institution of mass testing enabled settings such as mainland China, Hong Kong, Taiwan, Vietnam, Singapore, Korea and Germany to limit initial spread and enabled such settings to contain localised outbreaks through a combination of isolation and quarantine of infected and exposed individuals, respectively and population- and community level lockdown, hygiene and social distancing measures. However, many industrialised countries have failed to ramp up testing sufficiently and timely, missing the opportunity to limit Covid-19 transmission until it has become too widespread to contain.¹⁹ Leveraging the increasing footprint in many African countries of high-throughput largely automated systems for HIV viral load testing and early infant diagnosis of HIV would be ideal, as long as this would not be at the expense of maintaining essential HIV services. Unfortunately, again test kit supplies for these platforms are too limited to allow efficient mass

testing.²⁰

Even supplies of some components that received relatively little attention previously have become problematic in the pandemic situation; examples are swabs and nucleic acid extraction reagents. Sample preparation methods that do not make use of conventional nucleic acid extraction have therefore been developed and are being used by some laboratories.^{21,22} When doing so, one must consider the expected decrease in sensitivity and an increased frequency of inhibitory samples.²³

Another strategy to save test kits and reagents is pooled testing or 'pooling', i.e. testing several samples together in one test.²⁴ Pooled testing is useful when large numbers of specimens from populations with low prevalence of the condition to be diagnosed are to be tested. Pooling strategies should be evaluated carefully; potential pitfalls include a decrease in diagnostic sensitivity; the additional work effort required for pooling specimens and deconvoluting positive pools for re-testing of individual samples; an elevated risk for laboratory errors; and prolonged TATs for constituent samples in pools tested positive.^{25,26,27} Given the current shortages of extraction kits, pre-extraction pooling of samples may be the preferred option for SARS-CoV-2 testing.

SARS-CoV-2 antibody testing

SARS-CoV-2 antibodies are not detectable during the stage of maximum infectiousness (two days prior to and up to one week after onset of illness) and cannot be used to diagnose patients in the early stage of disease. Antibody tests may, however, be used in a manner complementary to respiratory sampling for virus detection because of the reciprocal sensitivities of antibody tests compared to NAT testing for SARS-CoV-2.²⁸ NAT testing has high sensitivity during early infection, sometimes even before symptom onset, but detection of virus declines with the progression of the infection. The sensitivities of SARS-CoV-2 testing follow the converse pattern, being low early in infection but with both IgM and IgG increasing at day 14 and after

onset of symptoms.²⁹ The presence of specific IgG antibodies demonstrated using a validated test in a serum sample obtained no sooner than 14 days, and preferably between 14–21 days after onset of illness, indicates previous or recent SARS-CoV-2 infection.³⁰ Serological testing can be used to retrospectively assess whether an individual had been exposed to SARS-CoV-2, irrespective of being symptomatic or asymptomatic, although seroconversion may be delayed and antibody responses weaker and more short-lived in asymptomatic individuals.^{31,32} Patients identified as IgG-positive are likely to have been acutely infected two or more weeks ago and are likely no longer infectious.

Potential uses include testing of asymptomatic patients prior to admission to health care facilities; the evaluation of ‘hotspots’ of SARS-CoV-2 transmission; and outbreak investigations to reconstruct chains of transmission; targeted surveillance of communities or cohorts such as staff, patients, visitors and residents of frail care institutions, prisons and workplaces. Repeat antibody testing over time allows longitudinal epidemiological assessments.³⁴ Under defined circumstances, antibody testing can supplement NAT, e.g. for suspected Covid-19 associated multisystem inflammatory syndrome in children, testing of CSF in SARS-CoV-2 associated encephalitis.³⁵ or when a high index of clinical suspicion persists despite a negative PCR result. Finally, antibody testing may also be used for the identification of potential convalescent plasma donors.

Several limitations should be borne in mind. The performance of any antibody assays to be used needs to have been evaluated.^{36,37,38} A negative antibody test result does not reliably exclude prior SARS CoV-2 infection. Possible causes of false-negative test results could be insufficient test sensitivity or lack of detectable seroconversion following especially asymptomatic SARS-CoV-2 infection. False-positive antibody test results could be caused by insufficient test specificity or cross-reacting antibodies, e.g. following infection with other human coronaviruses. In addition, detectable antibodies may not indicate immune protection. A positive antibody test result must not be regarded as proof of immunity to reduce or abandon protective measures.

Numerous rapid / near-patient / point-of-care antibody tests are being marketed, sometimes without even acknowledging the fundamental limitations of antibody versus direct virological diagnosis (see above). Evaluation studies published so far often show that the performance of most rapid antibody assays is inferior to that of laboratory-based tests, which is not surprising given the experience with rapid tests for other conditions. Based on current evidence, WHO does not recommend the use of rapid antibody tests for clinical decision-making.³⁸ To facilitate serology-based surveillance, research should be conducted on the possible use of dried blood spots (DBS) for laboratory-based antibody testing.

Conclusions and outlook

The ongoing Covid-19 pandemic undoubtedly poses a major challenge for diagnostic laboratory services. In Africa, many improvements in laboratory capacity have been achieved over the past fifteen or so years,

from the massive scaling up of HIV services (early infant diagnosis, CD4 and HIV viral load testing), from intensified tuberculosis testing to the Ebola epidemic response in West Africa. However, Covid-19 is different in that it appeared ‘out of nowhere’ and poses similar challenges for all countries. The ensuing massive and rapid rise in demand for test kits and reagents caused supply scarcities globally, with Africa being outcompeted by more affluent countries.³⁹ As John Nkengasong writes, ‘Lack of access to diagnostics is Africa’s Achilles Heel’.⁴⁰

Going forward, the only way to manage this difficult situation is by striking a workable balance between making SARS-CoV-2 testing available for those patients and cases who most need it, while avoiding any unnecessary testing. It will be necessary to define and stick to a clear strategy, which will have to be adapted as the pandemic reaches a country and then spreads locally.^{41,42,43,44,45}

Clear and up-to-date guidance is needed and must be followed by all role players, including different spheres of government. In South Africa for example, some official governmental recommendations have not been aligned with national Department of Health guidance, and for example, required negative PCR test results before an individual who had Covid-19 was allowed back to their workplace.⁴⁶ Such unnecessary requirements serve no purpose but increase the burden on laboratories and interfere with testing of clinically and epidemiologically relevant samples. As the SARS-CoV-2 pandemic spreads, laboratory staff will become infected, too; their infection risk is not exposure to specimens (provided some simple precautions are being followed) but instead to the community and also colleagues.⁴⁷ Therefore, the same rules will have to be followed as in all workplaces, including universal wearing of non-medical (cloth) masks, physical distancing, improved hand hygiene, regular cleaning and disinfection of surfaces, etc.

If approached sensibly and supported adequately, one of the legacies of the Covid-19 pandemic hopefully will be stronger African healthcare laboratory systems.⁴⁸

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