Health Canada
Health Products and Food Branch
Medical Devices Directorate

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***IN VITRO* SEROLOGICAL DIAGNOSTIC DEVICES FOR COVID-19**

BACKGROUND

In the context of the COVID-19 pandemic, Health Canada received submissions for two types of *in vitro* diagnostic testing devices: nucleic acid-based tests and serological-based tests.

Nucleic Acid Technology

Nucleic acid amplification testing (based on Reverse Transcriptase - Polymerase Chain Reaction (RT-PCR) is the technology used by the National Microbiology Laboratory (NML) and other public health laboratories across Canada and around the world for determination of COVID-19 infection by detecting the presence of the virus itself. All diagnostic devices authorized for COVID-19 in Canada to date are of this type.

Swabs are used to take samples of mucus from far back in the nasal and throat cavities (nasopharyngeal and oropharyngeal samples). These mucus samples are most likely to contain the virus if the patient is infected. The technology then detects the presence of the virus by copying pieces of the viral ribonucleic acid (RNA) to a detectable volume. The process of RNA amplification can be time consuming in some systems, but has been minimized by others. An active infection must be present for there to be a sufficient amount of viral RNA to be detected by this technology.

The technology requires buffer solutions and enzymes, which are complex active proteins. Due to increased demand, both buffer solutions and enzymes are in short supply globally at this time and enzymes are difficult, time-consuming and expensive to produce. The technology can be carried out in a laboratory or by a portable machine. If being carried out by a laboratory, transport media is further required to stabilize the sample for transport from the collection centre to the laboratory.

Serological Technology

Serological tests are based on detection of antibodies developed by a patient's immune system in response to infection with SARS-CoV-2. No devices of this type have been approved for COVID-19 in Canada to date.

These technologies are often more rapid than nucleic acid technologies, and can be delivered in a lateral flow format which facilitates use at point of care, for example in a doctor's office, or in remote locations. However, other applications of this technology have to be carried out in laboratories, which could include hospital laboratories. Serological tests do not require swabs, for which shortages are of concern. Instead they use whole blood (finger-prick), serum, or plasma.

This type of test doesn't detect the virus itself, but rather the body's reaction to an infection. It can take time (days to weeks) after an initial infection for antibodies to be produced. Further, the antibodies remain present for variable amounts of time after a viral infection is over. This technology can therefore determine whether a patient has had an infection even if they are no longer infected. This type of test may not work for an immune-compromised individual.

CONSIDERATIONS

Accurate diagnosis of active infections is critical in the context of the pandemic because it enables patients to be directed to self-isolate, and guides public health agencies to trace an infected patients' contacts and direct them to self-isolate as well. Health Canada has specific concerns about serological technologies as relates to the time required for antibody development (the seroconversion process) and the potential for cross-reactivity with other viruses. If a patient is tested before their immune system has created antibodies, they can be misdiagnosed as falsely negative because they have not yet produced detectable antibodies. The time required for a sufficient immune reaction against SARS-CoV-2 to create detectable antibodies is not yet well understood, but is generally assumed to take about one week. Additionally, a patient can be misdiagnosed as falsely positive due to antibody "cross-reactivity" between antibodies and immunologically related viruses. In the context of a pandemic, such errors could have important impacts.

INTERNATIONAL CONTEXT

International partner regulatory organizations, including the US, Australia, UK, Ireland and Singapore have taken similar approaches in regulating these technologies and most agree that serological diagnostic tests are not appropriate for use in diagnosis at this time. Some allow the use of such tests for follow-up of patients who previously received a positive diagnosis, or under the jurisdiction of their public health authorities. Some discourage the use of these tests altogether.

On March 22, the World Health Organization published interim guidance[1] which states that "serological assays will play an important role in research and surveillance but are not currently recommended for case detection." They indicate that further evidence on test performance and operational utility are necessary before these tests can be recommended for clinical diagnosis.

The US has made a distinction between the use of serological tests for diagnosis purposes and for research/follow-up purposes. With respect to diagnosis, the US FDA is accepting submissions for serological testing to be used as the sole basis to diagnose or inform infection status, but as of March 27, 2020, had not authorized any such test for that purpose. With regards to the use of serological testing in laboratories or by healthcare workers at the point-of-care for other purposes, the US FDA states in their guidance[2]:

> Considering that serology tests are less complex than molecular tests and are solely used to identify antibodies to the virus, FDA does not intend to object to the development and distribution by commercial manufacturers or development and use by laboratories of serology tests to identify antibodies to SARS-CoV-2, where the test has been validated, notification is provided to FDA, and information along the lines of the following is included in the test reports:
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> - This test has not been reviewed by the FDA.
> - Negative results do not rule out SARS-CoV-2 infection, particularly in those who have been in contact with the virus. Follow-up testing with a molecular diagnostic should be considered to rule out infection in these individuals.
> - Results from antibody testing should not be used as the sole basis to diagnose or exclude SARS-CoV-2 infection or to inform infection status.
> - 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.

It should also be noted that, exceptionally, the US is reviewing all diagnostic tests for COVID-19 under a post-market model, authorizing them under their Emergency Use Authorization after receipt of a post-market submission.

Australia also published a statement on March 22, 2020[3], which reports that Australia has authorized 3 point-of-care serology tests, while requiring the submission of additional evidence to support performance within 12 months of approval. They state that, "antibodies will likely take 5 to 7 days to become detectable by these basic tests. Therefore, these tests are of limited use for the diagnosis of acute infection." They further indicate that

there are concerns about the quality and clinical utility of rapidly developed tests.

- There are significant limitations to the use of point-of-care serology tests and they are not recommended as first line tests for the diagnosis of acute viral infection
- If used properly by a trained medical professional, validated serological point of care tests have some utility in determining past infection for screening purposes e.g. return to work.

On March 26th, the UK and Ireland noted that they are discouraging the use of such tests. Singapore indicated that they have approved two tests, but would require confirmation of test results by nucleic acid-based diagnostic tests. On March 27, South Korea indicated that they have approved a serological test for export only – it is not for use in South Korea.

RECOMMENDED HEALTH CANADA POSITION

Canada has maintained a science-informed approach to managing the pandemic, including maintaining requirements for pre-market authorization of diagnostic technologies. Further, national and local restrictions and instructions relating to physical and social distancing are pro-active steps designed to reduce the spread of the virus even in the absence of perfect knowledge of active or previous infections. Providing the Canadian population and individuals with accurate information about appropriate public health measures and infection status is a pillar of the country's response to the pandemic.

Though international regulatory partners have taken different positions, there is currently general agreement about the inability of serological tests to be used as the sole basis for diagnosis. Research into serological testing is ongoing within Canada and worldwide and may soon reveal evidence of reliable information from the use of these tests under certain circumstances.

Pending further information, Health Canada will continue to prioritize the review of nucleic acid-based technologies to increase the number of tests able to detect active infections of COVID-19. Based on the currently available evidence, these tests are best placed to diagnose active infections and inform public health measures.

Applications for serological technologies will be screened to pro-actively request other outstanding pieces of information, and will be processed once a path forward has been determined for these technologies more generally. This may include eventually authorizing their use in limited circumstances or for limited purposes until further information becomes available.

NEXT STEPS

Health Canada will continue to seek expert advice and will work with partners to support further studies of the results that can be achieved with serological technology through the course of an active infection.

Health Canada will seek guidance and advice from Canadian serology experts. This will include leveraging the newly established COVID-19 Clinical Issues Team, led by Dr. Marina Salvadori, Senior Medical Advisor, to seek further support in its scientific review.

Health Canada will also follow the studies underway in Canada on these technologies. The NML will be undertaking validation studies of five different serological tests in the coming weeks and has offered to share the results of those studies with Health Canada. Additionally, SymThera Canada has indicated to Health Canada on March 26, 2020 that their company will be working with two hospitals to validate a serological test over the coming weeks.

Further, the NML has indicated that a national pandemic testing strategy is currently in development which may provide support to Health Canada's assessment of the technology. For example, the strategy might indicate that serological testing should be used only to track infection in patients who have been asked to self-isolate due to symptoms but in the absence of diagnostic evidence of infection. This would reduce the risk associated with a false-negative diagnosis, and would facilitate Health Canada requiring the technology's Indications for Use to reflect usage as advised by the testing strategy.

These various sources will be explored and monitored to inform Health Canada's assessment of serological technology for use in the context of the pandemic. It is expected that Health Canada's position will evolve as more information becomes available.

Approved by

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[1] https://apps.who.int/iris/bitstream/handle/10665/331509/WHO-COVID-19-lab_testing-2020.1-eng.pdf

[2] https://www.fda.gov/media/135659/download

[3] https://www.health.gov.au/resources/publications/phln-statement-on-point-of-care-serology-testing-for-sars-cov-2-the-virus-that-causes-covid-19