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Canadian Society of Clinical Chemists (CSCC) consensus guidance for testing, selection and quality management of SARS-CoV-2 point-of-care tests

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ABSTRACT

Objectives: A consensus guidance is provided for testing, utility and verification of SARS-CoV-2 point-of-care test (POCT) performance and implementation of a quality management program, focusing on nucleic acid and antigen targeted technologies.

Design and Methods: The recommendations are based on current literature and expert opinion from the members of Canadian Society of Clinical Chemists (CSCC), and are intended for use inside or outside of healthcare settings that have varied levels of expertise and experience with POCT.

Results and Conclusions: Here we discuss sampling requirements, biosafety, SARS-CoV-2 point-of-care testing methodologies (with focus on Health Canada approved tests), test performance and limitations, test selection, testing utility, development and implementation of quality management systems, quality improvement, and medical and scientific oversight.

Abbreviations: CSCC, Canadian Society of Clinical Chemists; Ct, Cycle threshold; EQA, external quality assessment; LOD, limit of detection; LAMP, loop-mediated isothermal amplification; NAAT, Nucleic acid amplification assays; NPS, Nasopharyngeal swab; NS, Nasal swab; NWA, nasal wash aspirate; POC, point-of-care; POCT, point-of-care testing; PPE, personal protective equipment; QC, quality control; RT-PCR, reverse transcription polymerase chain reaction; SOP, standard operating procedure; TAT, turn-around time.

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1. Background and scope

The COVID-19 pandemic has presented significant challenges to healthcare systems across Canada, with clinical and public-health decisions heavily relying on laboratory testing for timely identification of cases, followed by contact tracing and isolation, aimed at limiting chains of transmission. Given their accuracy, laboratory-based molecular tests are widely accepted as the gold standard for diagnosis. However, delays in turn-around time (TAT) due to testing backlogs or logistical challenges (e.g. specimen transportation to centralized testing facilities, especially from remote collection sites), diminish their utility when immediate decision-making is required. The swift development, regulatory approval and dissemination of SARS-CoV-2 nucleic acid amplification tests (NAAT) and antigen point-of-care-tests (POCT) potentially addresses this concern, although not without limitations.

The rapid introduction of SARS-CoV-2 POCT places significant pressure on clinical laboratories and public healthcare systems to respond quickly to ensure appropriate deployment of these tests in different settings. The purpose of this document is to provide guidance on the considerations that should be made when selecting, verifying and using SARS-CoV-2 POCT, as well as on how to develop and implement an appropriate quality management system to ensure ongoing performance is fit for the intended use and setting.

2. Sample Collection, handling and biosafety

Depending on the test, acceptable specimens may include freshly collected nasopharyngeal swabs (NPS), throat swabs, nasal swabs (NS), or nasal wash/aspirate, with NPS widely accepted as providing the best sensitivity. Expansion to saliva and oral fluid specimens, which are easier to collect and more amenable to frequent testing, are under investigation but currently considered off-label given that they are not validated for this use by manufacturers. Specimens should be collected by trained operators [1] given that inadequate collection or improper technique may lead to false negative results or false positive results if contamination occurs [2]. However there are home-collection kits pending Health Canada approval, and in these cases, detailed instructions on collection must be provided to the end-users. Users are also advised to follow single patient processing procedures to mitigate the risk of sample mix-up or kit mislabeling.

Sampling and testing should be conducted in accordance with the approved manufacturer's instructions which usually entails testing patients within the first week following the onset of symptoms [3]. If POCT use is expanded beyond the manufacturer's instructions' approved patient population, POCT users must recognize the risk in doing so and should validate the use of the POCT in the off-label patient population prior to testing. Attention must be paid to the length of time between collection and testing, the swab type, the need for and type of transport media, the potential for buffers to inactivate SARS-CoV-2, and specific temperature requirements during storage and testing. Reagent inventory as well as storage and temperature monitoring procedures should be in place. Incorrect swabs and/or transport media may interfere with testing or result in specimen dilution thereby decreasing sensitivity. Any conditions or materials that differ from approved instructions for use (e.g. extended timeframe for storage or use of off-label swabs or buffers) must be validated. Most SARS-CoV-2 POCT, do not control for sampling quality [1], bringing into question the reliability of a negative result. Validation of more than one swab type may be required if swab availability is of concern due to high testing volumes and supply chain limitations, however this may not be feasible for all sites.

Precautionary use of appropriate personal protective equipment (PPE) when handling samples is required [4]. Inactivation of SARS-CoV-2 in the samples may be done using heat, chemicals, detergent or UV light in laboratory settings [5–7], however this is time consuming and not practical for POCT and a separate inactivation step is not included in most POCT manufacturers' instructions. Extraction buffer used in SARS-CoV-2 POCT may also inactivate the virus but inactivation is not instantaneous and all fluids must be assumed to be potentially infectious. Samples can be manipulated outside of a Biosafety Level 2 laboratory if local risks are assessed and specific criteria, such as the WHO criteria, are fulfilled [8]. WHO criteria include testing performed by trained staff, use of respiratory protection (based on risk assessment) and other PPE (full-length long (elastic) sleeved lab coat, safety goggles/glasses, disposable gloves), implementation of a validated infectious waste disposal process, use of absorbing material to cover workspace surfaces, and working in a well-ventilated, calm workspace, free of unnecessary materials and without TAT pressure. In the event of spillage, a decontamination protocol should be followed using appropriate disinfectant [9].

The most optimal assays for POCT are those that require minimal specimen manipulation, can be run outside of biosafety cabinets, are Health Canada approved and available to end-users. These details are discussed further in Box 1.0.

3. Nucleic Acid-Targeted devices

3.1. Technology Overview

As of March 5th, 2021, Health Canada approved six POC NAAT assays for SARS-CoV-2 in the clinical setting (Table 1) [10]. All assays, except for the Abbott ID NOW, use RT-PCR technology for the identification of the SARS-CoV-2 virus. RT-PCR uses reverse transcription to transcribe complementary DNA from viral RNA, and then amplifies targeted gene(s) using polymerase chain reaction using primers to the viral spike (S) gene, nucleocapsid (N) gene, RNA-dependent RNA polymerase (RdRp) gene, membrane (M) gene, or envelope (E) gene. Samples are cycled through steps of denaturation, annealing and extension several times. Interpretation of RT-PCR is based on a cycle threshold (Ct) value cutoff where the Ct value is inversely proportional to the viral load in the sample [11].

The Abbott ID NOW, on the other hand, utilizes reverse transcription-loop-mediated isothermal amplification (RT-LAMP) for the qualitative detection of nucleic acid from SARS-CoV-2 using the RdRp gene as the target [11]. RT-LAMP uses reverse transcription followed by target gene amplification using strand displacing DNA polymerase together with 4–6 primers specific for the target gene [12].

NAAT may also be multiplexed to simultaneously detect SARS-CoV-2 as well as common respiratory viruses, such as influenza A and B and respiratory syncytial virus, all from a single swab. There are two Health Canada approved multiplexed assays approved for POCT use (Table 2). These devices amplify different viral target sequences using multiple specific probe and primer sets in the same reaction. Other multiplex assays such as the BioFire FilmArray RP2.1, are being used off-label in Canada in POCT settings.

3.2. Test performance

All Health Canada approved POC NAAT are intended for use in symptomatic individuals and performance in asymptomatic populations is under investigation. Performance of POC NAAT varies in comparison to laboratory-based tests [13–20]. Although many vendors claim clinical sensitivity and specificity of 100% (Table 1), real world data suggests otherwise. For example, published test performance characteristics suggest a sensitivity of 71.7–80.0%, and specificity of 99.6–100.0% for the Abbott ID NOW, and a sensitivity of 96.1–99.4% and specificity of 96.8–100.0% for the Cepheid Xpert Express in patients with confirmed COVID-19 as indicated by a positive RT-PCR laboratory–based testing result in symptomatic and asymptomatic individuals [17,18,21]. Sensitivity and specificity can vary based on the study design. It is most optimal to use the same sample set across multiple platforms for comparison of sensitivity and specificity.

Comparison of limits of detection (LODs) may provide a more robust approach to compare assay performance. However, independent studies

Table 1
Overview of Health Canada approved POC NAAT for detection of SARS-CoV-2 infection. All tests are Health Canada approved as of March 5, 2021. Data was obtained from manufacturer package inserts and published literature. Nasopharyngeal swab (NPS), nasal swab (NS), nasal wash aspirate, (NWA), Median Tissue Culture Infectious Dose (TCID50).

Format		SARS-CoV-2 NAAT				Multiplex NAAT	
Manufacturer		Abbott Diagnostics	Cepheid	Spartan Bioscience Inc.	Hyris	Cepheid	Roche
Assay		Abbott ID NOW	Xpert Xpress SARS-CoV-2	Spartan COVID-19	BKit Virus Finder Covid-19	Xpert Xpress SARS-CoV-2/Flu/RSV	Cobas Liat SARS-CoV-2 & Influenza A/B
Detection Platform		ID NOW device	GeneXpert System Xpress System	Spartan COVID-19 System Cube	bCube device & bApp software	GeneXpert System Xpress System	Cobas Liat
Technology		Isothermal amplification	rRT-PCR	rRT-PCR	rRT-PCR	rRT-PCR	rRT-PCR
Sample Type		NPS, NS, throat	NPS, NS, NWA	NPS	NPS, NS	NPS, NS, NWA	NPS, NS
SARS-CoV-2	Target region	RdRp gene	N2, E genes	N1, N2 genes	N gene	N2, E genes	RdRp, N genes
	LOD (vendor)	125 copies/mL	0.02 PFU/mL; 131 copies/mL	600 copies/reaction	10,000 copies/mL	131 copies/mL	12 copies/mL
	LOD (literature)	up to 20,000 copies/mL	100 copies/mL	n/a	n/a	100 copies/mL	0.012 $TCID_{50}$/mL
	Sensitivity* (vendor)	100% at 2–5 × LOD	97.8%	83.90%	100%	97.9%	100% at 1–2 × LOD
	Sensitivity (literature)	99%, 99.4% 96.1–100% 98.3% (Ct < 38.5)	99% 98.3 (Ct < 38.5)	n/a	n/a	99%	100% (Ct < 37.4)
	Specificity (vendor)	98.2%	95.6%	97.40%	100%	100%	100%
	Specificity (literature)	97–100% 96.8%, 100%	97–100%	n/a	n/a	97–100%	97%
TAT/Run time		5 min (pos), 13 min (neg)	30 min (pos) 45 min (neg)	60 mins	<60 min (pos), 90 min (neg)	36 min	20 min
Batch size		non-batch	non-batch	non-batch	6 samples	non-batch	non-batch
Other pathogens targeted		N/A	N/A	N/A	N/A	Influenza A, influenza B, RSV	Influenza A, influenza B
Health Canada approved		Yes (lab-based, POCT)	Yes (lab-based, POCT)	Yes (POCT)	Yes (POCT)	Yes (lab-based, POCT)	Yes (lab-based, POCT)
References		16–19	16–19	n/a	n/a	16–19	14

*In symptomatic individuals.

Table 2
Overview of Health Canada approved rapid antigen tests for detection of SARS-CoV-2 infection. All tests are Health Canada approved as of March 5, 2021. Data was obtained from manufacturer package inserts and published literature. Nasopharyngeal swab (NPS), nasal swab (NS), oropharyngeal (OP), viral transport media (VTM), Median Tissue Culture Infectious Dose (TCID50).

Manufacturer	Abbott Rapid Diagnostics	Becton Dickinson (BD)	Quidel Corporation	Assure Tech, (Hangzhaou) Co. Ltd.	BTNX Inc.	SD Biosensor Inc.
Assay	Panbio Covid-19 Ag Rapid Test Device	BD Veritor System For Rapid Detection Of SARS-CoV-2	Sofia 2 SARS Antigen FIA	COVID-19 Antigen Rapid Test	COVID-19 Antigen Rapid Test	Standard Q COVID-19 Ag Test
Detection Platform	n/a	BD Veritor Plus Analyzer	Sofia 2	n/a	n/a	n/a
Technology	Lateral flow assay - gold colloid	Chromatographic assay - detector particles	Lateral flow fluorescent immunoassay	Lateral flow assay	Immunochromatographic assay	Chromatographic assay
Portable Analyzer	No	Yes	Yes	No	No	No
Sample Type	NPS, NS	NS	NPS, NS	NPS, OP	NPS, NS	NPS
Target Antigen	Nucleocapsid	Nucleocapsid	Nucleocapsid	Nucleoprotein	Nucleoprotein	Nucleocapsid
LOD (vendor)	158 $TCID_{50}$/mL	140 $TCID_{50/}$mL	113 $TCID_{50}$/mL	n/a	502 $TCID_{50}$/mL	494 $TCID_{50}$/mL direct NP; 7924 $TCID_{50}$/mL NP stored in VTM
LOD (literature)	6.5×10^5 copies/reaction	n/a	n/a	n/a	n/a	n/a
Sensitivity[a] (vendor)	91.4% ($Ct \leq 33$)	84%	96.70%	94.3%	95.6% (NPS); 90.2% (NS)	97.1% ($Ct \leq 25$)
Sensitivity (literature)	98.2% ($Ct < 25$)[b] 95.2% ($Ct < 32$) 97.1%($Ct < 25$)[b] 94.9% ($Ct < 30$)[b] 77.8% ($Ct < 30$) [b] 73–98%	84–96% 76.3–96.4%	87.2% ($Ct \leq 35$) 76.8–93.8%	n/a	n/a	95.8% ($Ct < 30$) 100% ($Ct < 28$)
Specificity (vendor)	99.8%	100%	100%	99.1%	100% (NPS); 100% (NS)	98.9%
Specificity (literature)	100%	99–100% 98.7–100%	96.9% 96.4%	n/a	n/a	99.5% 100%
TAT/Run time	15 min	15 min	15 min	15 min	15 min	15 – 30 min
Health Canada approved	Yes (lab-based, POCT)	Yes (lab-based, POCT)	Yes (lab-based, POCT)	Yes (lab-based, POCT)	Yes (lab-based, POCT)	Yes (lab-based, POCT)
References	16,24–26	16,27	27–28	n/a	n/a	29–30

[a] in symptomatic individuals; [b] includes asymptomatic patients and healthcare workers.

often used different approaches to estimate LOD and different reporting units making it challenging to perform direct comparison based on published LOD.

One must also consider the sensitivity of POC tests truly depends on what is defined as the gold standard. When the Abbott ID NOW and Cepheid Xpert Xpress SARS-CoV-2 were compared against the Roche cobas SARS-CoV-2, overall sensitivity of 73.9% (95% confidence interval (CI) 63.2 – 82.3%) and 98.9% (95% CI 92.9 – 100%), respectively, were reported [22]. However, the positive agreement increased to 100% for both assays when medium and high viral concentrations, defined as Ct value < 30, were considered. For Ct value > 30, the ID NOW reported 34.3% (95% CI 19.7–52.2%) sensitivity while the Xpert reported 97.1% (95% CI 83.4 – 99.8%) [22]. When probable infectivity (Ct < 30) is used as a benchmark, the sensitivity of these tests shows significant improvement, however Ct results between methods are not always comparable.

The type of specimen used is also important to consider. In the study referenced above, nasopharyngeal swabs collected and placed in universal/viral transport media were used for both assays. The Abbott ID NOW's manufacturer's instruction now indicate to test dry swabs without the use of transport media in order to optimize sensitivity [22].

4. Antigen targeted devices

4.1. Technology Overview

As of March 5th, 2021, Health Canada has approved six POCT antigen tests for SARS-CoV-2 (Table 2) [23]. These devices use lateral flow immunoassay technology, similar to that used by POCT urine pregnancy screens, and provide a qualitative (positive/negative) result in approximately 15 min. The tests require a NPS or NS sample (dry or with universal/viral transport media) to be taken, mixed with extraction reagent, and applied to the testing device sample pad area. The sample migrates laterally and encounters labelled antibodies usually targeting the nucleocapsid protein of the virus due to its relatively high abundance [3]. The test line has immobilized anti-SARS-CoV-2 antibody that captures the target analyte bound to labelled antibody and results in a visual change. An internal control line is also present that will bind labelled antibody and appears regardless of whether target analyte is present. Interpretation of the test may be by visual detection or by use of a portable analyzer to reduce inter-user variability (Table 2). The result is valid if the internal control line is identified and if the test was read within the specified timeframe. Reading a test device too early or too late can cause inaccurate results.

4.2. Test performance

All Health Canada approved POCT antigen tests are intended for use in symptomatic individuals and performance in asymptomatic populations is under investigation. Reported clinical sensitivities for SARS-CoV-2 POC antigen tests (including non-Health Canada approved devices) range from 0 to 94%, with an average of 56.2% (95% CI 29.5 to 79.8%) when compared against laboratory-based RT-PCR tests in both symptomatic and asymptomatic individuals [18]. Differences between reported sensitivities may relate to device selection, sample integrity, sample type, sample size, sample collection time, antigen target, and/or end-user knowledge and capability to perform the test. Vendor claims for test sensitivity of Health Canada approved POCT antigen tests range from 84 to 96.7% although real-world data suggested sensitivity ranges from 73 to 100% (Table 2) [16,24–30]. The ability to detect SARS-CoV-2 antigens is thought to vary over the course of the infection, with the highest sensitivity achieved when viral loads are high during early infection [31]. A recent systematic review of rapid antigen tests showed sensitivities of 33% with low viral loads vs 93% with high viral loads ($\leq$30 Ct), highlighting the impact of the comparisons with the lab-based RT-PCR method on apparent sensitivity of antigen assays, and importance of considering probable infectivity [18].

Across studies, clinical specificity for rapid antigen tests is consistently high, with an average of 98.9% (95% CI 97.3% to 99.5%) [18]. It is possible that false positive results may result by antibodies, such as rheumatoid factor or other non-specific antibodies, or with viscous samples [32]. Cross-contamination or specimen mix-ups may also result in false positives. Early-stage evaluations of these performance characteristics have largely used remnant laboratory samples and thus further evaluations in a real-world setting are needed.

5. Test limitations

Test limitations due to analytical performance of individual POCT assays, as well as pre-test probability in the setting the test is applied, should be carefully considered. Laboratories, clinicians, infectious disease and public health experts, as well as end-users should be aware of these limitations.

A limiting factor of POC SARS-CoV-2 tests is the reduced clinical sensitivity (increased false negatives) compared to laboratory-based NAAT, specifically for antigen SARS-CoV-2 POCT. False negative results can occur when there are lower viral loads, hence the importance of the LOD, or when testing is done too soon after exposure in both POCT or laboratory-based methods. As a negative POCT may not rule-out SARS-CoV-2 infection [33], confirmation by laboratory-based testing may be required. The need for confirmatory testing largely depends on manufacturer recommendations as well as how the devices are being used and in which population. Confirmatory testing is particularly important in symptomatic individuals or other individuals with high pre-test probability of having COVID-19, such as patients with known exposures or in outbreak situations. It is recommended that confirmatory testing should occur within 24–48 h, otherwise the POC NAAT is considered a separate independent, non-confirmatory test [31,34]. Given the expected rise and fall of viral loads in COVID-19, modelling suggests surveillance using a test with a lower sensitivity may still be useful if it is used frequently (daily to every three days) and has an associated fast TAT [35]. POC NAAT and antigen assays are suitable for this purpose given that appropriate validation and verification studies are performed.

False positive results may also occur in POCT and laboratory-based methods. These can be minimized by following the manufacturer instructions for use, minimizing cross contamination by working in a clean environment, and confirming test results using laboratory-based NAAT [32]. Restricting testing to higher prevalence populations will also improve the positive predictive value by reducing the proportion of positive tests that are false positive. While positive results in high pre-test probability situations may not need confirmatory testing, given the potential for false positive results particularly for POC antigen testing, it would be prudent for patients with positives from low pre-test probability settings to receive confirmatory testing [23].

For each test, a risk assessment should be performed and entail 1) assessing the clinical performance of the test (part of test validation) 2) determining the rate and impact of false negatives and positives on the target population (e.g. in a long term care home vs. school vs. workplace) 3) deciding on whether the test is appropriate for use in this population based on the above and 4) deciding on whether confirmation testing is needed based on the performance.

6. Test selection

With the availability of multiple SARS-CoV-2 POCT technologies, careful consideration must be made regarding test selection and implementation. These considerations go beyond test performance alone and are highlighted in Box 1.

Box 1
Considerations to be made when selecting a SARS-CoV-2 POCT.

Consideration	Details
Regulatory approval	• Commercially available tests should be Health Canada approved prior to use for patient testing in Canada. Verification of Health Canada approved assays should be performed to confirm acceptable test performance in local settings prior to implementation; this is especially relevant for NAAT POCT which are more complex and have a higher risk of false positives from potential cross-contamination. Some provinces have been using POCT in off-label indications such as screening of asymptomatic population where positive results are followed up by lab-based molecular testing. Tests should be validated for the intended use before implementation.
Sample type and biosafety	• Availability of supplies (swabs), reagents and equipment should be considered. Tests validated for several different swab types or sample types are favourable. Redundancy in swab type is important to allow flexibility during supply chain shortages. Acceptance of alternate sample types permits potential future uses. • Assays with less stringent storage and usage conditions are preferred. • Availability of expertise/training and appropriate safety measures (i.e. PPE) required for collection of the sample and operation of the test should be considered.
Ease of use	• The complexity of operating instructions varies by device and is an important consideration for tests done by non-laboratory users. • Minimal sample processing and visual assessment of results is convenient at the point of care setting. • In some instances, availability of a test reader can simplify and standardize test interpretation. It may also facilitate interfacing with a laboratory information system. • Connectivity to a laboratory information system is ideal to enable electronic transition of results to the health care providers and public health portals, but may not be feasible if devices are used in a community setting
Quality of manufacturer's validation data	• The criteria used to evaluate assay performance by the manufacturer should be assessed, including the number of patients, number of days since symptom onset, severity of symptoms, choice and protocol of reference method, sample type, and sample preservation. These criteria should be compared against the intended test setting and use.
Manufacturing capacity	• Robust supply chain not only for reagents but also for other consumables (e.g. PPE, swabs) is ideal. • In some situations, selecting poorer performing tests may be appropriate when supplies for better performing tests are not available. Such approaches should be accompanied by risk mitigation efforts and may include increased testing frequency, confirmatory protocols, and modification of test interpretation and follow-up actions in recognition of test performance limitations.
Quality of manufacturers' technical and scientific support	• Having access to product information and technical support is important. Manufacturers with a strong customer support structure and a reputation for reliability would be favorable.
Quality management	• Having a robust quality management plan supported by laboratory professionals is ideal (see Sections 8.0 and 9.0)

7. Utility of Testing

SARS-CoV-2 NAAT and antigen POCT may be useful for preliminary diagnosis, outbreak screening, and surveillance as indicated in Box 2.

Box 2
Potential utility of SARS-CoV-2 NAAT and antigen POCT.

- Diagnostic – POC SARS-CoV-2 NAAT and antigen tests may be used in remote areas where geographical and other barriers prevent sufficient availability and TAT of laboratory based RT-PCR [3], such as assessment centers in rural communities, rural hospitals, or satellite hospitals. For antigen testing specifically, testing strategies involving serial testing can mitigate the effect of lower sensitivity and aid in timely case identifications that reduce transmission chains [23,36].
- Outbreak Screening - POC SARS-CoV-2 tests can be used to test clusters of symptomatic cases allowing for early identification of outbreaks. In addition, testing asymptomatic people exposed to areas in outbreak can be used for early identification of patients who require isolation to prevent further transmission [3,36,37].
- Surveillance - Test frequency and TAT are the most important variables in reducing SARS-CoV-2 spread when performing surveillance testing in asymptomatic individuals [35,38]. Rapid and frequent testing can lead to earlier identification and isolation of positive individuals and can overcome losses in test sensitivity. Asymptomatic individuals are more likely to spread the virus without realization, and infectivity is highest prior to or at symptom onset (~2 days) [39]. Repetitive testing may be helpful in semi-closed communities that allow interactions between individuals within and outside the facility [23], such as in hospitals, work-places, school dormitories, long-term care facilities, and/or correctional facilities [3]. However, SARS-CoV2 POCT devices currently authorized by Health Canada are approved for testing only in symptomatic patients [23]. Testing in off-label asymptomatic populations behooves users to recognize the risk of doing so and should only be done after validation of the POCT's performance in this patient population.

8. Quality management framework for SARS-CoV-2 POCT

To respond to the testing needs associated with the pandemic, POCT modalities have been rapidly deployed, often in the areas with scarce resources and laboratory expertise. This section highlights minimal requirements for a quality management framework to ensure testing is and will continue to remain fit for use in diagnosis or screening in different settings. The framework should include key components of process management (validation and/or verification of processes, internal quality control (QC), and external quality assessment), personnel training and ongoing competency assessment, document and records control (e.g. standard operating procedures (SOPs), protocols, and checklists), information management (e.g. result reporting and interpretation), investigation of nonconformities, ongoing assessment (e.g. quality indicators, internal audits and management review), continual improvement, and risk management[40].

For more comprehensive recommendations around quality assurance in POCT in general, please refer to a recently published guidance document by the Canadian Society of Clinical Chemists (CSCC) POCT Interest group [41].

8.1. Test verification

All POCTs for SARS-CoV-2 should be verified or validated before use. The principles for evaluation should be the same as those for central clinical laboratories and overseen by the POCT director or designate based on the institutional or regulatory/jurisdictional requirements.

Verification refers to the process of confirming the device or test meets the specifications as outlined by the manufacturer. Verification is required when the device and test will be used based on manufacturer instructions and according to the conditions of regulatory approval.

Verification should include, at minimum, evaluation of repeatability and concordance of POCT results to a validated laboratory RT-PCR SARS-CoV-2 method. Verification of the LOD should also ideally be included.

8.1.1. Samples for verification studies

Residual swab specimens (e.g. fresh or previously frozen), contrived dry swabs, or extraction buffer spiked with a known amount of viral material can be used in verification studies [42]. Samples may be selected based on days post-symptom onset, viral load Ct values from laboratory-based RT-PCR, or viral copy number. Manufacturer's instructions about sample handling and storage conditions should be followed to maintain sample integrity as much as possible. If residual swabs are used for verification of antigen methods, it must be ensured the samples are not heat-inactivated as this may denature antigen targets and impact detection.

For sites unable to obtain specimens from patients positive for SARS-CoV-2, or if the residual samples are stored in buffer/transport media that are not compatible with the method under evaluation, a prospective verification can be performed, where two respiratory swabs are collected per participant at the same time point: one for laboratory-based RT-PCR testing, and one for POCT. The need for additional swabs may require ethics approval. In Canada, many provincial pilot studies are adopting this approach. Another option would be to purchase third-party, commercially available SARS-CoV-2 positive quality control swabs. These however are limited in that they may not include the same variation in sequences found in all circulating SARS-CoV-2 found in the population, and the matrix may differ from human specimens. Please refer to Table 3 for additional method-specific guidance in selecting specimen types for verification studies.

8.1.2. Specific recommendations for verification studies

For qualitative tests with positive/negative readout, repeatability should be assessed by measuring, at minimum, a negative, a weak positive (close to the LOD), and a strong positive sample once a day/shift for three days/shifts [41] and include different operators (Table 3).

A concordance study with validated lab-based RT-PCR should, at minimum, comprise 20 patient samples (10 known positive and 10 known negative) (Table 3) [41]. For POC NAAT that can provide Ct information, the positive samples should cover the analytical measuring range of Ct values.

It is important that test providers consult with manufacturers to understand whether SARS-CoV-2 variants of concern affect performance of their methods. Manufacturers are responsible for ensuring manufacturer's instructions for assays are updated with this information as it becomes available.

There are several CLSI guidelines that can also be used as references for verification studies [43–45]. Please refer to Table 3 for additional guidance related to performing LOD, stability studies, and where possible parallel testing during initial implementation.

8.1.3. Additional resources with information about analytical and clinical performance of SARS-CoV-2 POCT

It is also important to validate tests when the intended use-case is outside the recommendations from the manufacturer. These studies will

Table 3
Guidance on Quality Assurance for POC SARS-CoV-2 tests.

Recommended Minimal Initial Verification per Device	Antigen POCT	NAAT POCT
Specimen types for verification	• Do not use heat inactivated samples for verification of antigen tests • Contrived dry swabs can be created using residual swab specimens in universal transport media (e.g. fresh or previously frozen that have not been heat inactivated) following the method described by the FDA [41] or residual specimen transport media can be used to spike the POC extraction buffer NOTE: it is important to choose samples with Ct values that take into account the limit of detection of the POCT and the extra dilution step when adding the dry swab or transport buffer to the extraction buffer • Manufacturer QC or third-party, commercial material with known viral load may be used but is suboptimal compared to clinical samples	• Residual swab specimens in universal transport media (e.g. fresh or previously frozen) can be used when liquid transport media is acceptable to use with the POCT • For NAAT only accepting dry swabs, contrived dry swabs can be created using residual swab specimens in universal transport media (e.g. fresh or previously frozen) following the method described by the FDA [41] or residual specimen transport media can be used to spike the POC extraction buffer • NOTE: it is important to choose samples with Ct values that take into account the limit of detection of the POCT and the extra dilution step when adding the dry swab or transport buffer to the extraction buffer • Manufacturer QC or third-party, commercial material with known viral load may be used but is suboptimal compared to clinical samples
Specimen stability(if testing will not be completed immediately)	• Many manufacturers recommend to perform analysis within a set time after specimen collection or after adding specimen to the POCT extraction buffer • Verify time intervals expected with typical daily workflow and if delays in testing after specimen collection are expected, ensure results with delayed testing are comparable to testing fresh specimens	
Repeatability	• Patient samples or QC material • SARS-CoV-2 negative, strong positive, and moderate/weak positive (close to claimed positive/negative cut-off or LOD) • Run each level once a day/shift for at least 3 days/shifts • Preferably by different operators	• Patient samples or QC material • SARS-CoV-2 negative, strong positive, and moderate/weak positive (close to claimed cut-off or LOD) • Run each level once a day/shift for at least 3 days/shifts • Preferably by different operators • When Ct data are available, measure precision aiming for $\leq$ 5% CV • When more than one gene is targets, measure repeatability/precision for each gene target
Limit of detection verification	• Residual patient samples with moderate Ct • Perform a series of dilutions bracketing expected cut-off and LOD • For each dilution, run samples in replicates of 5–10 (all data should be Log10 transformed for analysis). • Cut-off/LOD: Equivalent to Ct value at which 95% of replicates remain positive.	• Residual patient samples with moderate Ct • Perform a series of dilutions bracketing expected cut-off and LOD • For each dilution, run samples in replicates of 5–10 (all data should be Log10 transformed for analysis). • Cut-off/LOD: Equivalent to Ct value at which 95% of replicates remain positive. • Verify cut-off and LOD for each gene target
Concordance with laboratory-based RT-PCR method	• 10 SARS-CoV-2 positive (range of strong and weak positives, and variants of concern if available) • 10 negative patient samples • It is important to be aware of the method's ability to detect different SARS-CoV-2 variants of concern. Query manufacturer about this.	• 10 SARS-CoV-2 positive samples (range of Ct values, including those close to the limit of detection, and including variants of concern if available) • 10 negative patient samples • Verify for each gene target • It is important to be aware of the method's ability to detect different SARS-CoV-2 variants of concern. Query manufacturer about this.
Note on optimal number of samples for method validation for off-label use	• Optimal number of samples will depend on expected clinical sensitivity or specificity e.g. for assays where clinical sensitivity is > 98%, >50 samples are needed to observe a false negative result. • This is difficult to accomplish using previously collected specimens. To address this, side-by-side comparisons between POC and lab-based PCR should be performed prospectively after initial implementation until users are confident in the real-world performance of the test, and better understand its benefits and limitations.	
Performance Equivalence Between Devices (for sites with more than one device)	Method Comparison (between two or more POCT devices, including antigen readers or NAAT devices) • 10 SARS-CoV-2 positive samples and 10 negative patient samples should be performed on all devices to ensure performance equivalence • (For single-use antigen tests with no reader device, no performance equivalence is possible)	
Minimal Requirements for New Reagent Lot Verification	QC material: • 1 SARS-CoV-2 strong positive • 1 close to LOD • 1 negative	
External Quality Assessment (EQA)	• Sites must participate in an EQA program Split sample testing with a laboratory-based RT-PCR method can also act as EQA minimum frequency: twice per year	
Routine Quality Control	• Run a positive and a negative QC • Ideally, include third party material rather than relying solely on the manufacturer-supplied material • Run at defined interval and with each shipment, new lot of reagent, and with each shipment, new lot of reagents. NOTE: POC method may not be compatible with third-party QC material. Important to consult with manufacturer and verify performance.	

Cycle threshold, Ct; External quality assurance, EQA; Limit of Detection, LOD; Nucleic acid amplification testing, NAAT; Point of care, POC; Reverse transcription – loop-mediated isothermal amplification; RT-LAMP, Reverse transcription – polymerase chain reaction, RT-PCR; Quality control, QC.

help better inform the use-case and aid in determining the associated risks. Validation studies require large numbers of participants (e.g. for assays with claimed clinical sensitivity of 98%, at least 50 samples would have to be tested to observe one false negative result), and are labour intensive, rendering them impractical when deployment of testing is required with urgency. However, it is important to understand, as much as possible, the expected performance of a test for a given use-case.

To learn more about analytical and clinical performance of specific SARS-CoV-2 POCTs, providers can refer to resources such as Foundation for Innovative New Diagnostics (FIND) that includes a repository of studies that describe analytical sensitivity (LOD) and clinical evaluation (sensitivity and specificity) of different antigen POCT based on a large number of samples (typically 100 SARS-CoV-2 positives and 300 negatives) and conducted following a standard validation protocol [46,47].

In addition, peer reviewed studies of various SARS-CoV-2 POCTs are excellent sources of information about analytical and clinical performance of these assays in different settings as described in Box. 2.0 [24,48].

Health Canada has approved SARS-CoV-2 POCTs for use in symptomatic individuals, with guidance on clinical test performance requirements for symptomatic testing [3,49]. Testing for different uses, such as frequent screening of asymptomatic individuals for example, will likely impact the quality of the estimates of the clinical sensitivity and specificity. In addition, the prevalence of SARS-CoV-2 infection will change depending on the testing cohort and within the same cohort over time. Changes in infection prevalence can affect positive and negative predictive values of a test. For this reason, frequent review of overall positivity, false positive and false negative results following initial implementation is important. This can help sites adjust testing algorithms in face of changing prevalence.

8.2. Subsequent device verification

Once initial verification is completed, additional instruments of the same platform can be verified with a protocol that includes a repeatability check using QC material and a patient specimen comparison (10 positive and 10 negative), half of which should also be tested on the original device to ensure performance equivalence between devices (Table 3). This largely applies to POC NAAT, which employ a separate analytical testing device. Being considered low complexity devices, POCT SARS-CoV-2 antigen tests do not require further evaluation once the initial full evaluation has been completed and accepted, unless there is a significant change to the manufacturing of the test or if this testing employs a reader device.

8.3. Routine QC

Regular QC testing must be performed to ensure ongoing accuracy of test performance (Table 3). The frequency for QC testing should be based on recommendations from the manufacturer, local regulatory bodies, or the laboratory overseeing testing. The laboratory overseeing testing can also provide guidance for the selection of QC material. Where possible, best practice is to use third party material rather than relying solely on the vendor-supplied material, especially when it does not reflect physiological matrix. When using third party material, both swab material and transport media must be compatible with the assay (e.g. PanBio is compatible only with certain swab types and no transport media). For SARS-CoV-2 POCTs, a QC close to the verified cut-off or LOD should be analyzed periodically. QC should be performed at defined intervals and with each shipment, new lot of reagents, and after new trainees have been trained before testing clinical samples is initiated.

8.4. Reagent lot validation

Recent studies of antigen detection POCT show evidence of reagent lot-to-lot and batch-to-batch variability that likely affect their analytical performance [50,51]. At minimum, validation of new test kit lots for NAAT and antigen detection should be performed using positive and negative QC ensuring that positive QC are close to the LOD in order to be able to detect a change in the LOD of the assay (Table 3).

8.5. External quality assessment (EQA) and internal audits

Sites should participate in a commercial EQA program with analyses performed twice a year, at minimum. Where possible, split sample testing with another laboratory, employing an RT-PCR method, can also act as EQA with comparison specimens analyzed at a minimum of twice per year (Table 3). Investigations of unacceptable EQA results that include root cause analysis should be performed, and corrective and preventative action reporting should be carried out. In addition to EQA, internal audits should also be performed at planned intervals to ensure operations meet accreditation requirements. Internal audits should be conducted by trained personnel to assess managerial and technical processes [40].

8.6. Training of end-users

Initial and ongoing training is critical to ensure optimal and consistent performance of POCT testing is maintained regardless of the expertise and skill level of the end-user. A study from the United Kingdom showed that test positivity decreased from 79% to 73% when SARS-CoV-2 antigen POCT was used by laboratory scientists versus trained healthcare-workers, respectively. The positivity dropped to 57.5% when self-trained members of the public were given a protocol to perform testing [51].

All staff who will perform POCT must receive training, ideally hands-on, which should be managed by the POCT director providing oversight of the program, preferably in consultation with a laboratory. Aspects to be included in training are outlined in the CSCC guidelines [41]. Staff performing POCT must demonstrate understanding of principles related to biosafety and the process for reporting to Public Health authorities in the respective jurisdiction. It is recommended to designate a small group of trained individuals (super-users) who will train others and ensure maintenance of competency. Initial and ongoing training checklists should be documented for each user. When POCT antigen tests are to be used in high-volume testing, training of users on batch processes should also be included to mitigate sample mix-ups and cross contamination.

8.7. Results reporting

Ideally devices will be interfaced with POCT data management software and/or a laboratory information system to facilitate transmission of patient results directly to the electronic medical record. If this is not possible, a process for manual entry of results into the patient record, whether paper or electronic, must be in place. A process documenting that results have been communicated to Public Health should also be in place. Where confirmatory laboratory-based testing will be performed, reports must specify the preliminary nature of the result obtained by POCT testing. For multiplex assays specifically, it is advised that each institution consults with all stakeholders to inform them that testing any respiratory virus will automatically translate to an order of all respiratory pathogens on the multiplex assay.

8.8. Document and record control

Documents for policies, processes, and SOPs related to POCT should be established alongside a document control system. These documents should be reviewed on an annual basis and can include: staff qualifications, inventory, equipment maintenance and repair, testing SOPs, verification of results, training records, competency assessments, QC results, quality indicator results, internal audit reports, corrective action reports and calibration tracking [52].

9. Quality improvement

9.1. Improving healthcare workflow

Increasing numbers of COVID-19 infections with mass utilization of laboratory-based RT-PCR tests can drain healthcare resources and increase costs. As increased laboratory testing volumes lead to longer TAT, there is continued risk for spread. With effective early public health measures including rapid POCT combined with laboratory-based testing, TAT can be decreased and institutions may obtain greater control over workflow and prevent outbreaks by isolating patients with COVID-19 sooner. POCT sites should strive to develop quality management dashboards through which operators can contact the POCT supervisor/coordinator with performance concerns or questions.

9.2. Quality indicators

Considering the constant pressure, the high workload as well as the high variability of staffing in the COVID-19 rapid testing environment, quality of processes is at higher risk. To monitor performance and allow for continuous quality improvement, quality indicators (QIs) can be put in place and should ideally cover the total testing process including the pre-analytical, analytical, and post-analytical phase [53].

Standardization of the use of QIs in the POCT field is still lacking. Readers can refer to the Working Group on Laboratory Errors and Patient Safety of the International Federation of Clinical Chemistry for a list of relevant QIs to be monitored (http://www.ifcc-mqi.com). Processes at higher risk of failure should be prioritized [54]. These include but are not limited to: result TAT, sample rejection rate, instrument/test errors and failures, end-user safety incidents, failed QC, incorrect result reporting, positivity rates and periodic cross-checks on patient specimens. Note that these quality indicators are not specific to SARS-CoV-2 POCT, but are commonly used for other routine tests as well.

Performance targets should be set for each of the indicators and monitored. Comparison between sites is highly recommended to provide benchmarks and promote quality improvement. Action plans should be put into place when targets are not achieved to allow for continuous improvement. Readers can refer to Sciacovelli et al. for guidance and benchmarks of multiple QIs applicable to COVID-19 POCT [55].

10. Medical and scientific oversight

Published POCT guidelines [53,56,57] outline the roles of a POCT committee including POCT director, POCT coordinator, site supervisor, and testing personnel, all of which apply to rapid SARS-CoV-2 testing performed within or outside the laboratory. Within the POCT committee, various members will fulfill specific roles. Medical or scientific representation on POCT committee should have sufficient breadth of knowledge to evaluate all modes of rapid testing. Where possible, laboratory personnel are ideally suited to be an integral part of POCT committees as outlined in Box 3.

Box 3
The role of laboratory professionals (e.g. laboratory director, pathologists, medical or clinical microbiologists, clinical biochemists, etc.) and supervisors in supporting SARS-CoV-2 POCT.

Position	Potential Responsibility
Laboratory professional	• Support the development of a robust quality management system. This includes providing guidance on test verification/validation, QC, end-user training and quality assurance requirements as outlined in Section 8. • Provide guidance on test selection, sample types, interpretation of results and test limitations. To the lay person, the difference between 95% or 99% sensitivity may not seem significant. It is the role of the laboratory professional to ensure that the potential consequences are understood. • Support the development of a risk analysis plan and mitigation strategies to ensure safety as outlined in Section 2. • Serve as a liaison between the laboratory and its clients which may include government personnel and policy makers. • Ensure that POCT meets regulatory, accreditation, national, local and organizational requirements [56]. Provision of SOPs, training, and competency assessments to non-laboratory and non-hospital staff may require new strategies for document control and learning management systems. • Where relevant, work with information technology personnel to ensure that test results are recorded in the health records promptly, accurately, and completely. They should ensure that results are reported with sufficient comments so that interpretation and clinical follow-up is accurate. • Assist with operationalizing testing and continually working with operations to identify and resolve performance issues as they arise, including false-positive/negative rates, failure rates and contamination occurrence. Quality targets should be set *a priori* based on verification studies. • Consider developing a generic change management process for the implementation of SARS-CoV-2 tests/rapid tests which can be applied to evaluate and implement various test proposals as they arise. This is important due to supply chain constraints, and thus laboratories may employ more than one SARS-CoV-2 rapid test.
Supervisor	• Technical and scientific oversight • Training and competency assessments of testing personnel • Available for day-to-day support of testing personnel by reviewing QC, corresponding with the manufacturer, and troubleshooting performance issues • Work with medical and scientific staff to select tests and verify performance

11. Conclusions and Summary of Recommendations

POCT has the potential to facilitate decentralized and frequent testing at scale. Rapid results mean fast initiation of contact tracing and isolation. SARS-CoV-2 POCT specifically are associated with tremendous urgency for implementation, and the release of tests with emergency use certification, some with limited validation studies. Laboratories therefore must sufficiently assess instrument and assay performance under compressed timelines, often with limited access to relevant clinical specimens and/or specimen types.

There must be a balancing of the needs for rapid test results, quality assurance, and resource availability. A major need of public health, especially during an outbreak is rapid information to understand the scope (for response planning) and initiating contact tracing and isolation/quarantining. In outbreaks where there is high prevalence of positive cases, even low sensitivity tests can provide useful information if the test specificity is high. To be effective, there must be rapid distribution of devices, but this means having a supporting quality infrastructure that is poised to rapidly train, and implement testing in a manner that optimizes effectiveness of the effort (despite limitations), and involving monitoring of performance to improve what can be. Traditional POCT quality frameworks are not feasible in such circumstances and cannot be implemented in a manner that meets the needs for quick setup and implementation. This does not mean there can be no quality framework, but rather one that still assures acceptable analytical performance of devices, effective pre-analytical and post-analytical processes to minimize potential for error, but is also adaptable to the wide variety of situations where devices are deployed. Ultimately, the degree of quality control/assurance will depend on available resources. But beneficial quality management frameworks that are developed collaboratively and involving stakeholders in the entire testing process, can still be constructed despite resource constraints.

Key recommendations and considerations are highlighted below:

1. For each SARS-CoV-2 POCT, refer to the manufacturer's procedure for sample collection and handling. Any deviation from the procedure must be validated.
2. All operators should be trained on proper sample handling and safety procedures prior to use of testing devices. SARS-CoV-2 POCT can be used outside a Level 2 Biosafety Cabinet when supported by local risk assessment and if appropriate PPE is worn.
3. SARS-CoV-2 POCT can be used diagnostically in symptomatic individuals, and for early outbreak investigations. Use of these tests for asymptomatic surveillance testing is currently not authorized by Health Canada although pilot studies are underway. Use for asymptomatic surveillance should be done only after validation has been performed and risks of this off-label use have been considered.
4. Risks of false negative and false positive results must be clearly communicated to individuals and the public. Laboratories should perform a risk assessment based on clinical performance of the test in the target population to determine the implications of false negative and false positive results.
5. When selecting a SARS-CoV-2 POCT device, the following aspects should be considered: regulatory approval, sample type and biosafety, ease-of-use, quality of validation data available, manufacturing capacity, quality of support and quality management.
6. Quality management systems should include process management, personnel training and ongoing competency assessment, document and records control, information management, investigation of nonconformities, continual improvement, and risk management.
7. A POCT committee should provide technical, scientific, operational and quality assurance oversight and each member should have defined roles.

Disclosures

JS has been a part of advisory panels for the following POCT Diagnostics companies: HLS Therapeutics, Roche and Abbott. SMP has been part of advisory panels for Verity, Cipher, Paladin Labs; has received honoraria for presentations from Merck; has received support for attending meetings from Copan; and has received financial support for research from bioMérieux; all outside the completed work.

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