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Reliable detection of SARS-CoV-2 with patient-collected swabs and saline gargles: A three-headed comparison on multiple molecular platforms

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ABSTRACT

With increasing demands for SARS-CoV-2 testing, as well as the shortages for testing supplies, collection devices, and trained healthcare workers (HCWs) to collect specimens, self-collection is an attractive prospect to reduce the need for HCWs and expenditure of personal protective equipment. Apart from the traditional nasopharyngeal swab used for SARS-CoV-2 detection, alternative specimens have been validated such as a combined swabs of the oropharynx and anterior nares (OP/N), or throat samples using saline gargles. Both the alternative specimen types are amenable to self-collection. Objectives. This study aimed to compare the sensitivity of HCW-collected (OP/N) swabs, self-collected OP/N swabs, and self-collected saline gargles. Among 38 individuals previously testing positive for SARS-CoV-2 (or their close contacts), two self-collected specimen types (OP/N and saline gargles) were compared to HCW-collected OP/N swabs. SARS-CoV-2 testing was performed on three molecular assays: a laboratory-developed test (LDT), and two commercial assays on automated platforms: Cobas 6800 (Roche Diagnostics) and Panther (Hologic). The sensitivity of self-collected OP/N swabs was equivalent to healthcare worker (HCW)-collected OP/N swabs at 100.0 % [92.6%–100.0%] for all three molecular tests. The sensitivity of saline gargles was not significantly different than HCW-collected OP/N swabs, but varied slightly between instruments at 93.8 % [85.9%–93.8%] for the LDT, 96.8 % [88.6%–96.8%] for the Cobas assay, and 96.7 % [89.2%–96.9%] for the Panther assay. Overall, self-collection using OP/N swabs or saline gargles are reasonable alternatives to HCW-based collections for SARS-CoV-2 detection, and could facilitate broader surveillance strategies.

Since the onset of the COVID-19 pandemic, many strategies have been described to sustain diagnostic testing in times of specimen collection kit or testing reagent shortages (LeBlanc et al., 2020a; Patriquin et al., 2020; Becker et al., 2020; LeBlanc et al., 2020b). These include the use of specimens other than the traditional nasopharyngeal (NP) swabs in universal transport media (UTM) typically used for respiratory virus testing. For example, a combined oropharyngeal and nares (OP/N) swab collection was shown to be equivalent to NP swabs for SARS-CoV-2 detection using molecular methods (LeBlanc et al., 2020a; Patriquin et al., 2020; Kandel et al., 2021; Shakir et al., 2020; Desmet et al., 2021; Vlek et al., 2021). Other non-invasive collection

methods such as saliva and throat gargles have also gained much interest recently as they are amenable to self-collection (Goldfarb et al., 2021; Azzi et al., 2020; Kandel et al., 2021; Bennett et al., 2017; Iwasaki et al., 2020; Malecki et al., 2020; Miguères et al., 2020; To et al., 2020; Zhu et al., 2020; Pasomsub et al., 2021; Kam et al., 2020). Compared to healthcare workers (HCW)-based collection, self-collection reduces resources required for testing and offers opportunities for large scale population-based surveillance. Recently, the performance of saline gargles was shown to be superior to saliva specimens for the molecular detection of SARS-CoV-2, and were nearly-equivalent to HCW-collected NP swabs in adults and school-aged children (Goldfarb et al., 2021;

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Kandel et al., 2021). Here, a three-headed comparison of HCW-collected OP/N, self-collected OP/N, and self-collected saline gargles was conducted to compare their performance on three molecular assays.

Patients who had tested positive for SARS-CoV-2 or their household contacts gave informed consent to participate in this investigation. Specimens were collected in the following order: self-collected OP/N swab, HCW-collected OP/N swab, and a self-collected saline gargle. OP/N swabs were collected as previously described (Patriquin et al., 2020), using a foam-tipped swab from the BD ProbeTec Qx Collection Kit for Endocervical or Lesion Specimens (Becton, Dickinson and Company, Sparks MD USA). Patients were instructed to rub a single swab on one side of the posterior oropharynx, followed by the anterior nares bilaterally, before placing it in 3 mL of 1× phosphate-buffered saline (PBS) pH 7.4 (Gibco, ThermoFisher Scientific). The same procedure was then repeated by a HCW. For throat gargles, patients were asked to abstain from eating, drinking, smoking, chewing gum, and brushing their teeth for at least one hour prior to collection. They emptied a 5 mL container of 0.9 % sterile saline (Addipak, Teleflex, Morrisville, North Carolina, USA) into their mouth, and performed three alternating cycles of swishing the saline in their cheeks (5 s each cycle) and gargling in the posterior oropharynx (5 s each cycle) (Goldfarb et al., 2021). The gargle was expelled into a 90 mL sterile specimen container (New Century Scientific Diagnostics Inc, Etobicoke, Ontario, Canada). All samples were refrigerated until processed. Testing was performed within 12 h of collection using: 1) a laboratory-developed test (LDT) using real-time RT-PCR targeting E and RdRp genes (LeBlanc et al., 2020a; Corman et al., 2020); 2) the SARS-CoV-2 Test on the Cobas 6800 System (Roche Diagnostics, Rotkreuz, Switzerland), and 3) the Aptima SARS-CoV-2 Assay on the Panther System (Hologic Inc., San Diego, CA). For the LDT or Cobas 6800 assay, single target detection was considered an indeterminate result. For the Panther assay, 500 µL of specimen was placed into 710 µL Specimen Lysis Tube prior to processing, according to the manufacturer's directions, and results were defined by the manufacturer software. Results from each assay were collated and compared to a consensus standard consisting of concordant results between two methods. Indeterminate results were considered positive for statistical analyses. Sensitivity, 95 % confidence intervals (CI), and significance were assessed using 2×2 contingency tables and online software (<https://statpages.info/ctab2x2.html> and <http://vassarstats.net/tab2x2.html>).

A total of 38 participants were enrolled in this validation; all of whom had previously been or were currently symptomatic. The range of time between the most recent clinical test and the specimens used in this study was 0–7 days (median = 2 days). Thirty-two were SARS-CoV-2 positive and six were negative at the time of specimen collection.

Of 36 participants (30 positive and 6 negative) who provided self-collected and HCW-collected OP/N swabs, the sensitivity was equivalent, regardless of the molecular method (Table 1). In one patient, SARS-CoV-2 was detected from the self-collected swab (on both the LDT and Panther assays), but not from the HCW-collected swab. For the 38 participants (32 positive, 6 negative) who provided a saline gargle and HCW-collected OP/N swab, the gargle sensitivity varied slightly between molecular methods, with the LDT and Panther performing at 96.9 % and 96.8 %, respectively, and slightly lower sensitivity of 93.8 % for the Cobas 6800 (Table 1). No significant differences were noted between

specimen types or methods used. Of note, threshold cycle (CT) values for the gargles increased across all targets for both the LDT or Cobas 6800 assays, as compared to the reference method (Fig. 1). The CT values for the LDT (RdRp and E gene) increased by 1.6 (standard deviation [SD] ± 6.1) and 1.5 (SD ± 6.0), and those of the Cobas 6800 assay (Orf1a and E gene targets) increased on average by 1.2 (SD ± 4.8) and 1.2 (SD ± 5.0), respectively. This increase was not evident with self-collected OP/N swabs (Fig. 1).

OP/N swabs have been shown to be an acceptable specimen type for the detection of SARS-CoV-2, (LeBlanc et al., 2020a; Patriquin et al., 2020; Kandel et al., 2021; Shakir et al., 2020; Desmet et al., 2021; Vlek et al., 2021) and are recognized by the Infectious Diseases Society of America (IDSA) (Hanson et al., 2020a) and World Health Organization (WHO) (World Health Organization, 2020) guidelines as an alternative for SARS-CoV-2 diagnostics. Similarly, saline gargles have been validated in both children and adults as alternatives to NP swabs (Goldfarb et al., 2021; Kandel et al., 2021). In this study, the value of self-collection using OP/N swabs or saline gargles was compared to HCW-collected OP/N swabs, and both showed acceptable sensitivity for routine testing. In contrast to a recent publication where self-collected oropharyngeal and mid-turbinate (OPMT) swabs sensitivity was inferior to HCW-collected OPMT swabs (Tan et al., 2020), this study was consistent with others (Kandel et al., 2021; Shakir et al., 2020; Wehrhahn et al., 2020) in showing HCW-supervised self-collected OP/N swabs sampling the posterior oropharynx and anterior nares is a suitable alternative to HCW-collected OP/N swabs, regardless of the molecular method used.

It should be noted that the reference method in this study is HCW-collected OP/N, as opposed to traditional NP swab (World Health Organization (2020)) used for respiratory viruses; however, OP/N was previously validated by our laboratory (LeBlanc et al., 2020a) and others, and shown to be non-inferior to NP in various settings (Kandel et al., 2021; Shakir et al., 2020; Desmet et al., 2021; Vlek et al., 2021). A possible limitation of this approach includes the biases inherent to the order of collection, which might have unintentionally favored the recovery of virus in the first specimen (i.e. self-collected OP/N); however, this order was deliberate, so as to acquire the self-collected OP/N more reflective of true self-collection, as opposed to being 'taught' where to place the swab based on their experience during HCW collection. The gargle was reserved for last, for the theoretical risk of washing and expelling a significant proportion of virial material from the oropharynx just prior to swabbing. Regardless of this potential bias in sample collection, no significant differences were noted between specimen types. Our study is limited by small numbers of positive participants and, as a consequence, patients with a lower viral load are not fully represented. This may have implications for result concordance among those samples with high CT values or asymptomatic patients.

Why should we use self-collected specimens for SARS-CoV-2 detection? In addition to reducing the need for skilled HCWs and personal protective equipment (PPE), self-collection methods are scalable and allow for timely mass surveillance – which is all the more important with the emergence and spread of SARS-CoV-2 variants of concern. Unsupervised home self-collection has been performed by both HCWs and the public at large, (McCulloch et al., 2020) with HCW volunteers largely

Table 1
Sensitivity comparison of HCW- and self-collected OP/N, and self-collected gargles.

Number of specimens	Collection	Specimen type	Sensitivity (% [95 %CI])		
			LDT	Cobas 6800	Panther
35	HCW-collected	OP/N	96.7 [88.9–96.7]	100.0 [92.6–100.0]	96.7 [88.9–96.7]
	Self-collected	OP/N	100.0 [92.6–100.0]	100.0 [92.6–100.0]	100.0 [92.6–100.0]
38	HCW-collected	OP/N	100.0 [92.8–100.0]	100.0 [92.3–100.0]	96.7 [89.2–96.9]
	Self-collected	SG	93.8 [85.9–93.8]	96.8 [88.6–96.8]	96.7 [89.2–96.9]

Abbreviations: Confidence intervals (CI); healthcare worker (HCW); laboratory-developed test (LDT); combined oropharyngeal and anterior nares swabs (OP/N); saline gargles (SG).

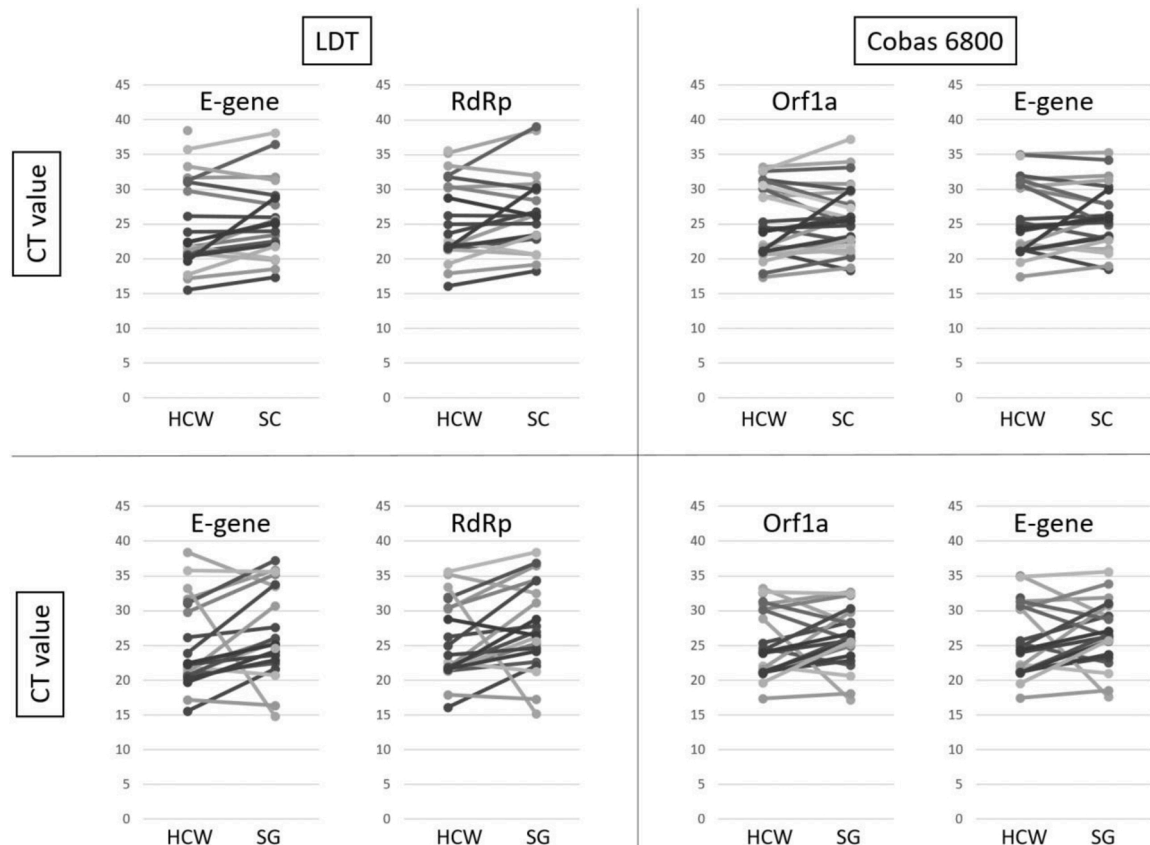


Fig. 1. Cycle threshold (CT) values comparison between healthcare worker and self-collected specimen types. Ct values are displayed for each target of two SARS-CoV-2 RT-PCR assays. Comparisons are made between the healthcare worker (HCW)-collected swabs and self-collected (SC) OP/N swabs or saline gargle (SG). Of note, relative light units (RLU) on the Panther do not follow a signal-dependent increase with concentration, and were therefore not presented.

agreeing to perform self-collected NP swabs for diagnosis or research purposes (Demmer et al., 2020), and a majority of community dwellers agreeing to self-collecting a throat swab sample at home (Hall et al., 2020). Self-collected swabs have a role in outbreak investigation and management (Knoll et al., 2020), and in target populations that require serial testing (O’Shea et al., 2020). Locally, regular interval asymptomatic voluntary testing by self-collected OP/N swabs has been implemented among HCWs in long term care facilities, and are being offered to asymptomatic inter-provincial trucking professionals, allowing them to conveniently deposit their specimens at defined locations.

In contrast to the growing literature of OP/N swabs and applications for self-collection, the literature on self-collected saline gargles have been scarce to date. Early in the pandemic, saline gargles had been suggested for use in hospitalized patients who could not generate sputum for lower respiratory tract investigations (Saito et al., 2020). More recently, saline gargles have been used as an alternative to NP collection, and found more acceptable to patients when compared to HCW-collected NP swabs (Goldfarb et al., 2021; Kandel et al., 2021; Malecki et al., 2020). In this study, a non-significant reduction in sensitivity was seen with gargles compared to HCW-collected OP/N swabs, and CT values obtained from gargles testing were higher than the comparator. This corroborates findings from prior studies (Goldfarb et al., 2021; Hanson et al., 2020b), and we suspect these relative differences are likely due to the specimen heterogeneity due to the dilution factor of using saline, the varying viscosity and mucous content, or potential inhibition from food particles in the gargle specimens. If the potential decrease in sensitivity of gargles was found to be real with further testing, a subtle decrease in sensitivity may be off-set by increasing the frequency of testing (Mina et al., 2020), though consideration has to be given to the many variables that can affect sensitivity

and the potential impacts for each setting where these would be implemented (Patriquin and LeBlanc, 2021). For now, like self-collected OP/N swabs, saline gargles could be considered for case-finding in large groups of people where individual HCW-operated sample collection is not feasible or is logistically difficult.

Overall, notwithstanding some limitations, self-collected specimens like OP/N swabs or gargles provide a simple, efficient, and less invasive form of testing for SARS-CoV-2 that could offer opportunities for broad surveillance approaches. While there are inadequate data to extrapolate results of this study to asymptomatic individuals and future studies should examine the wider applicability of these specimen types, we believe the ease of use of self-collected OP/N and gargles will be a welcomed solution for SARS-CoV-2 COVID-19 diagnostics.

Author statement

All authors contributed equally to the manuscript.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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