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Clinical evaluation of nasopharyngeal, midturbinate nasal and oropharyngeal swabs for the detection of SARS-CoV-2

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ABSTRACT

In the setting of supply chain shortages of nasopharyngeal (NP) swabs, we sought to compare the ability of nasopharyngeal, midturbinate nasal, and oropharyngeal swabs (NPS, MTS, and OPS) to detect SARS-CoV-2. Community and hospitalized participants post-COVID-19 diagnosis were swabbed and tested for SARS-CoV-2 by PCR. Thirty-six participants had all 3 swabs collected. Using detection at any site as the standard, the percent positive agreements were 90% (95% CI 74.4–96.5), 80% (70.3–94.7) and 87% (62.7–90.5) for NPS, MTS, and OPS, respectively. Subsequently, 43 participants had OPS and NPS collected. Thirty-nine were positive with a percent positive agreement of 82.1% (95% CI 67.3–91.0) for OPS and 87.2% (73.3–94.4) for NPS. Combining all 79 patients tested, 67 were positive at either site with a positive agreement was 86.5% (76.4–92.7) for OPS and 91.1% (81.8–95.8) for NPS. OPS are an acceptable alternative to NPS for the detection of SARS-CoV-2 infections.

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1. Introduction

The ideal upper respiratory tract specimen type for respiratory virus detection is a nasopharyngeal (NP) specimen (Miller et al., 2018). Due to worldwide shortages of swabs and collection media arising from the coronavirus infectious disease-2019 (COVID-19) pandemic, it became necessary to identify alternatives to NP swabs (NPS) for COVID-19 testing sample collection. Furthermore, there are significant advantages to swabbing other sites such as anterior nares (or nares), midturbinate nares, the oropharynx, or a combination swab of nares and the oropharynx, including patient preference and potential for self-collection (Hanson et al., 2021; Lee et al., 2021). Saliva has also been investigated as an alternative specimen type for these purposes. Some assert that an anterior nasal or midturbinate swab can be equivalent, including the Infectious Disease Society of America guidelines but based on “very low certainty of evidence” (Hanson et al., 2021). However, a systematic review showed that they may be inferior to NPS (Lee et al., 2021). There is also

controversy regarding oropharyngeal swabs (OPS) where some including the IDSA suggest that oropharyngeal/throat swabs are inferior to NPS, but this swab type has been recommended widely as a suitable primary upper respiratory specimen type used initially in China and many other countries and is still recommended today by many agencies including the European Centre for Disease Control (Chinese Centre for Disease Control, 2020; 2021). In order to contribute to this debate, we present data comparing midturbinate nasal swabs (MTS) to OPS and NPS using a composite reference standard in known COVID-19 cases shortly after their diagnostic swab.

2. Methods

We identified COVID-19 cases using the Alberta Health Services Public Health or Alberta Public Health Laboratory (ProvLab) (Alberta, Canada) case line lists. Community patients were contacted and consented by the study investigators via phone for a health care worker to come to their home and collect additional samples. For hospitalized patients, in person oral consent was obtained by an infection control physician or designate physician. Whether patients were symptomatic and symptom onset date was determined based on the public health case investigation questionnaire or physician history. Symptom status was not recorded at the time of the study swab.

Abbreviations: NPS, nasopharyngeal Swab; OPS, oropharyngeal swab; MTS, midturbinate swab; UTM, Universal Transport Media; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; COVID-19, coronavirus disease-2019

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NPS were collected using the Flexible Mini Tip Flocked Swab (Copan S.P.A, Italy) in Universal Transport Media-RT (UTM; Copan), MTS using APTIMA Unisex Collection Kit (Hologic Inc, Marlborough, Mass), and OPS using the APTIMA Multitest Collection Kit or a polyester tipped nonflocked polyester swab (Puritan, Guilford, ME, USA or Copan) in UTM. Health care workers who received training and routinely collect specimens for diagnosing COVID-19 collected a NPS then the MTS followed by the OPS. The NPS was performed through 1 naris. For MTS collection, both nares were swabbed to a depth of at least 3 cm (or until resistance felt) and rotated 3 times. OPS collection involved swabbing of both sides of the oropharynx and the posterior pharyngeal wall under the uvula. Swabs were transported to the laboratory at room temperature and refrigerated until testing. The testers (laboratory technologists at ProvLab) were blinded to the initial results. The University of Calgary Research Ethics board approved this study (REB20-444).

Throughout the course of the study, the Alberta Public Health Laboratory used different in-house SARS-CoV-2 reverse transcriptase real time-polymerase chain reaction (RT-PCR) assays: a singleplex assay (targeting areas in the E and RdRp genes, and MS2 phage internal control), a triplex assay (targeting the same areas as the singleplex assays but in 1 reaction), and a duplex assay (targeting only the E gene and MS2 targets in 1 reaction). The singleplex combination of assays and the triplex were considered positive if both SARS-CoV-2 targets were positive; if 1 was positive with a cycle threshold (Ct) value <35 or if the Ct of both targets was ≥ 35 , amplification from the same eluate was repeated in duplicate and was considered positive if at least 2/3 results had a Ct <41 for at least 1 target. The duplex was positive if the E gene Ct was <35 or if ≥ 35 and was repeated and 2/3 repeats had a Ct <41. Study samples collected from a participant were tested with the same assay (either singleplex, triplex, or duplex for all samples collected from that patient). These assays had equivalent performance with a limit of detection comparable to the commercial assays and the Corman et al. Sarbeco-E gene assay (Corman et al., 2020; Pabbaraju et al., 2021). Participants were initially diagnosed using the singleplex or triplex PCR in the MT vs OPS vs NPS comparison study. During the second study (OPS in UTM vs NP in UTM), the duplex PCR was implemented during the study, so diagnostic and study samples were tested using either the triplex or duplex PCR. In some cases for the second study, the AllplexTM-nCoV 2019 Assay (Seegene Inc, Seoul, South Korea) or the SimplexaTM COVID-19 Direct Kit (Diasorin Molecular LLC, Cypress, CA, USA) were used for diagnostic testing (Supplementary Table 2).

Positive agreement was determined by using a positive result at any site as the reference standard.

Graph Pad Prism v8.4.1 (Graphpad Prism Software L.L.C, San Diego, CA) was used for statistical analysis with the Wilson-Brown method for 95% confidence intervals (95% CI) and Wilcoxon matched-pairs signed rank test to compare Ct values.

3. Results

Thirty-six known SARS-CoV-2 positive outpatients (41% female; mean age 43.1, range 18–61) consented to a MTS, OPS and NPS using the APTIMA kits for the MTS and OPS. Thirty (86%) tested positive at 1 or more of the 3 sites. NPS had a positive agreement of 90% (95% CI 74.4–96.5), OPS 87% (95% CI 70.3–94.7) and MTS 80% (95% CI 62.7–90.5) ($P = 0.533$, Chi-squared test, Table 1). In only 2 cases was only 1 source positive (both MTS). Seven participants were positive from only 2 sources ($n = 2$ for NPS and MTS, $n = 5$ for NPS and OPS). The mean number of days from diagnostic swab to study swabs was 4.1 (range 1–6). All participants were symptomatic at the time of diagnostic swab sampling or before. The mean time from symptom onset to study swab was 10.5 days (range 4–23), for discrepant results the mean was 11.9 (Supplementary Table 1). The mean RdRp Ct value for NPS was 29.65 compared to 30.53 for MT ($P < 0.049$) and 31.59 for OPS ($P = 0.147$) (Supplementary Table 1). The initial

Table 1

COVID-19 PCR results for a nasopharyngeal swab (NPS) in UTM and midturbinate (MTS) or oropharyngeal swab (OPS) collected with APTIMA kits on the same person at the same time.

		OPS		MTS	
		Pos	Neg	Pos	Neg
NPS	Pos	25	2	22	5
	Neg	1	8	2	7
MTS	Pos	20	4	N/A	N/A
	Neg	6	6	N/A	N/A

Table 2

COVID-19 PCR results for nasopharyngeal (NPS) and oropharyngeal swabs (OPS) in UTM collected on the same person at the same time.

		OPS	
		Pos	Neg
NPS	Pos	27	7
	Neg	5	4

diagnostic test samples in this group were NPS ($n = 14$, 38.9%) or MTS ($n = 22$, 61.1%). The median time from collection to receipt in lab was 3 hours (range 1–24) and from collection to result was 35 hours (range 22–143).

Based on these findings indicating that the performance of MTS may be inferior to OPS or NPS and potential equivalence of NPS and OPS, an additional 46 participants were enrolled to have an NPS and OPS collected in UTM. Three were not tested due to specimen collection/transport errors. Of the 43 tested, 46.5% were female, mean age was 54.9 years old (range 28–86) and 58.1% were hospitalized. All but 1 participant had a symptomatic infection with symptom onset on or after the day of diagnostic test swab. The mean days from symptom onset to study swabs was 11.1 (range 1–44, symptom onset unknown for 1), for discrepant results the mean was 13.6 (Supplementary Table 2). The mean days from diagnostic test to study sampling was 6.5 (range 0–30). 90.7% were positive at either site (Table 2) and the positive agreement for OPS was 82.1% (95% CI 67.3–91.0) compared to 87.2% for NPS (73.3–94.4) ($P = 0.755$, Fisher's exact test). The mean E gene Ct value for NPS was 27.25 and OPS was 29.31 ($P = 0.0004$) (Supplementary Table 2). The initial diagnostic test samples in this group were OPS ($n = 30$, 69.8%), NPS ($n = 10$, 23.2%), endotracheal tube aspirate ($n = 2$, 4.7%), and MTS ($n = 1$, 2.3%). The times of receipt and sample processing were not recorded for this study, but would have been similar to the first study.

Combining the results from the 2 groups (OPS APTIMA vs NPS UTM and OPS UTM vs NPS UTM) a total 79 individuals were tested and 67 samples were positive by NPS or OPS. The positive agreement for OPS was 86.5% (95% CI 76.4–92.7) and for NPS 91.1% (95% CI 81.8–95.8). Removing individuals with an initial OPS diagnostic test gave positive agreements of 87.5% (95% CI 73.9–94.5) for OPS and 95.0% (95% CI 83.5–99.1) for NPS. Of the total 77 tested, 44.1% were female, mean age was 50.2 (range 18–86), 58.1% were hospitalized, the mean days from symptom onset to study sampling was 10.8 (range 1–44, symptom onset unknown for 3), and the mean days from diagnostic test to study sampling was 5.2 (range 0–30).

4. Discussion

Our study demonstrates that NPS are still the ideal upper respiratory specimen type for SARS-CoV-2 detection but OPS are comparable, whereas a MTS is likely inferior to NPS or OPS. Consequently, when NPS are not available or collection via this method is challenging, OPS are a suitable alternative specimen type for SARS-CoV-2 detection.

These findings are in line with the findings of a systematic meta-analysis by Lee et al., 2021 that found 6 studies assessing OPS vs NPS and 6 assessing MTS vs NPS (including the preprint data on our NPS/OPS/MTS comparison). The pooled percent positive was similar for OPS and NPS, 84% (95% CI: 57%–100%) vs 88% (95% CI: 73%–98%), respectively, but much lower for MTS (84% (95% CI:65%–97%) for MTS vs 97% (95% CI:92%–100%) for NPS). Saliva was also assessed in this meta-analysis, which found saliva detected 88% (95% CI 81%–93%) of positives compared to 94% (95% CI 90%–98%) by NPS. It was noted by the authors of this meta-analysis that there was significant heterogeneity in the study designs and whether details on the type of swab and time of swabbing from symptom onset were included, which we describe. In this manuscript we improved upon the comment by Lee et al., 2021 that many studies did not consistently follow Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines by including as much information as possible in this manuscript to adhere to the guidelines. Additionally, we provide a larger data set than most other studies included in the meta-analysis.

Regarding swab types, the findings of our study pertaining to MTS differ from a high-quality study by Tu et al., 2020 that prospectively compared patient collected MTS to the reference standard of health care worker collected NPS in people with unknown COVID-19 status. Tu et al., 2020 found good sensitivity for MTS collected by the patient (96.2% [97.5% CI 87–100]). Other than collecting prospectively in patients with unknown COVID-19 status, the Tu et al., 2020 study differs from ours in that they used foam swabs, which may be better than conventional polyester or flocked swabs. Foam swabs may be superior due to their size, which may result in more consistent collection through more robust abrasion of the cells in the nasal passage and once fully inserted into the nose, allow for a true midturbinate collection. It is noteworthy that the Panbio antigen test also uses a foam swab and seems to have similar sensitivity for NP and nasal swabs (Abbott, 2020). Results with a nonfoam swab may be improved by squeezing the naris against the swab while rotating, which we have found results in similar sensitivity to OPS run on the Abbott ID NOW [unpublished data].

Another variability in the literature is the method of OPS collection. We swabbed under the uvula/posterior pharynx and between both peritonsillar pillars as per guidelines (Centers for Disease Control and Prevention, 2021; World Health Organization, 2021). However, other publications did not swab all of these areas. For instance, Wang X et al., 2020 only swabbed both sides of the oropharynx and reported 73% of patients with a positive NPS tested negative by OPS. Palmas et al., 2020 only swabbed the posterior pharynx and showed inferior performance of the OPS and higher Ct values when compared to a MTS. Therefore, the method used for OPS collection should be considered in future studies and meta-analysis.

Variability in specimen collection has also been seen with saliva, another alternative to NPS (Lee et al., 2021). Saliva poses a swab free alternative but must be collected in consistently and in a manner that makes it feasible for the laboratory to process in high volumes such as in saline or UTM (Berenger et al., 2021).

There are some biases associated with this study. First, the COVID-19 status was known *a priori* of participants. This is a frequent bias in most studies (Lee et al., 2021) and will only be remedied by studies such as one in Denmark that will compare OPS to NPS and saliva prospectively (Todsens et al., 2021). Second, sampling was not done in the acute period of illness. Third, a majority of the diagnostic samples collected was not the NPS in both studies (majority MTS in the first and OPS in the second). This may have biased the results in favor of the OPS or MTS or to including patients with lower viral loads. When the samples originally diagnosed with OPS were removed from the pooled analysis, the positive agreement for OPS was similar than when included and slightly higher for NPS, thus creating a potential bias towards NPS. We would actually expect that OPS may be

disadvantaged in our study due to the delay from symptom onset to study collection (mean 11 days) as many studies have shown that OPS have poor performance when sampled later in disease (Barocas et al., 2020; Patel et al., 2021; Wang H et al., 2020). Fourth, sequential sampling (NPS first, then MT and OPS) may have affected participant cooperation with subsequent swabs, which could have impacted the quality of sample collection for MTS or OPS. The collectors did not report this as an issue but some participants did refuse subsequent swabs and were excluded from the analysis.

Two other caveats are pertinent to our study. First, we did not record if the participants were symptomatic at the time of swabbing, which could impact viral shedding dynamics at different anatomical sites. Second, although our study had a larger sample size than many other studies, we did not have enough participants to say with 95% certainty that MTS was 10% less sensitive than NPS and OPS or that OPS was ~5% less sensitive than NPS.

In our jurisdiction, MTS were initially implemented due to a publication early on in the pandemic demonstrating lower Ct values than OPS (Zou et al., 2020). Despite education and routine observation of collectors at COVID-19 community assessment centres, multiple accounts of sampling the anterior nares were reported. Based on our results and familiarity of collectors with OPS (as opposed to MTS), we recommend in our jurisdiction the collection of OPS if NPS are not available or preferred by patients or collectors in the community. Due to the overabundance of evidence that NPS are still the reference standard, these are still used for patients presenting to urgent care, emergency or hospital.

Authors' contributions

B Berenger: Conceptualization, Methodology, Formal Analysis, Data Curation, Writing-Original Draft Supervision, Project Administration

K Fonseca: Conceptualization, Methodology, Writing-Review and Editing

A Schneider: Investigation, Writing-Review and Editing

Jia Hu: Investigation, Supervision, Project administration, Writing-Review and Editing

Nathan Zelyas: Conceptualization, Methodology, Writing-Review and Editing

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Declaration of competing interest

The authors report no conflicts of interest relevant to this article.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.diagmicrobio.2021.115618](https://doi.org/10.1016/j.diagmicrobio.2021.115618).

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