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BRIEF REPORT

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Anterior nasal versus nasal mid-turbinate sampling for a SARS-CoV-2 antigen-detecting rapid test: does localisation or professional collection matter?

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ABSTRACT

Introduction: Most SARS-CoV-2 antigen-detecting rapid diagnostic tests require nasopharyngeal sampling, which is frequently perceived as uncomfortable and requires healthcare professionals, thus limiting scale-up. Nasal sampling could enable self-sampling and increase acceptability. The term nasal sampling is often not used uniformly and sampling protocols differ.

Methods: This manufacturer-independent, prospective diagnostic accuracy study, compared professional anterior nasal and nasal mid-turbinate sampling for a WHO-listed SARS-CoV-2 antigen-detecting rapid diagnostic test. The second group of participants collected a nasal mid-turbinate sample themselves and underwent a professional nasopharyngeal swab for comparison. The reference standard was real-time polymerase chain reaction (RT-PCR) using combined oro-/nasopharyngeal sampling. Individuals with high suspicion of SARS-CoV-2 infection were tested. Sensitivity, specificity, and percent agreement were calculated. Self-sampling was observed without intervention. Feasibility was evaluated by observer and participant questionnaires.

Results: Among 132 symptomatic adults, both professional anterior nasal and nasal mid-turbinate sampling yielded a sensitivity of 86.1% (31/36 RT-PCR positives detected; 95%CI: 71.3–93.9) and a specificity of 100.0% (95%CI: 95.7–100). The positive percent agreement was 100% (95%CI: 89.0–100). Among 96 additional adults, self nasal mid-turbinate and professional nasopharyngeal sampling yielded an identical sensitivity of 91.2% (31/34; 95%CI 77.0–97.0). Specificity was 98.4% (95%CI: 91.4–99.9) with nasal mid-turbinate and 100.0% (95%CI: 94.2–100) with nasopharyngeal sampling. The positive percent agreement was 96.8% (95%CI: 83.8–99.8). Most participants (85.3%) considered self-sampling as easy to perform.

Conclusion: Professional anterior nasal and nasal mid-turbinate sampling are of equivalent accuracy for an antigen-detecting rapid diagnostic test in ambulatory symptomatic adults. Participants were able to reliably perform nasal mid-turbinate sampling themselves, following written and illustrated instructions. Nasal self-sampling will facilitate scaling of SARS-CoV-2 antigen testing.

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Supplemental data for this article can be accessed here.

Introduction

Due to their short turn-around time and ease-of-use, antigen-detecting rapid diagnostic tests (Ag-RDTs) enable new testing strategies for SARS-CoV-2 [1,2]. Currently, most SARS-CoV-2 Ag-RDTs require nasopharyngeal (NP) sampling, which is frequently perceived as uncomfortable and requires healthcare professionals, thus limiting scale-up. Nasal sampling could enable self-sampling and increase acceptability.

The term nasal sampling is often not used uniformly and sampling protocols differ. The US Centres for Disease Control and Prevention (CDC) differentiates anterior nasal (AN) and nasal mid-turbinate (NMT) sampling [3]. Recent studies have demonstrated the equivalence of NMT- compared to NP-sampling for a WHO-listed SARS-CoV-2 Ag-RDT and the feasibility of self-sampling [4–6]. AN-sampling is easier and more convenient than NMT-sampling, but Ag-RDT performance with AN-sampling has not been evaluated.

The objective of this prospective diagnostic accuracy study was a head-to-head comparison of professional AN- and NMT-sampling for a WHO-listed SARS-CoV-2 Ag-RDT. Furthermore, the accuracy and feasibility of self NMT-sampling were evaluated.

Methods

Study design and participants

This was a manufacturer-independent, prospective diagnostic accuracy study comparing two different nasal sampling methods for an Ag-RDT. From the first group of participants, professionally collected AN and NMT samples were taken. In the second group, each participant self-collected a NMT sample and underwent a professional NP swab (Figure 1). The Ag-RDTs were performed directly after sampling at point-of-care by study physicians with a semi-quantitative visual read-out of the test band (categorized as negative, weak positive, positive, or strong positive) as described in a prior study [6]. The reference standard was real-time polymerase chain reaction (RT-PCR) using a combined oro-/nasopharyngeal (OP/NP) sample as described previously [6].

The study took place at the ambulatory SARS-CoV-2 testing facility of Charité University Hospital between 30 November 2020 and 18 January 2021. Participants eligible for inclusion were adults with high clinical suspicion of SARS-CoV-2 infection. For self-sampling, a minimum CEFR (Common European Framework of Reference) language level of B2 (upper intermediate) in German or English was required. Participants were consecutively enrolled, according to laboratory capacity.

The study was continued until at least 30 positive Ag-RDT results were obtained with each sampling method, which is the minimum recommended by the WHO Emergency Use Listing Procedure to demonstrate sample type equivalency [7].

Index test Ag-RDT

The Ag-RDT evaluated was the STANDARD Q COVID-19 Ag Test (SD Biosensor, Inc. Gyeonggi-do, Korea), which is also distributed by Roche in Europe [8]. At the time of the study, the test was commercially available as NP-sampling kit and only for research use as nasal-sampling kit (used for NMT and AN). Differences between the swabs and the procedures of the two test kits have previously been described [4].

Sampling methods

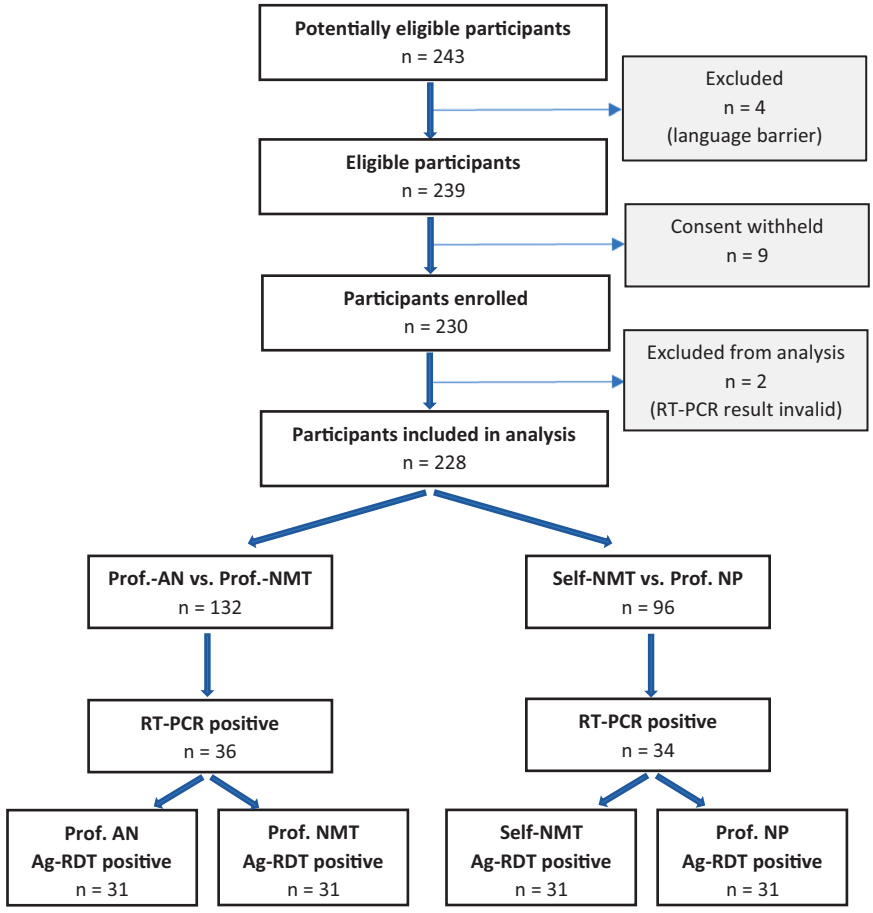
Participants were asked to blow their nose once before sampling. Professional AN- and NMT-sampling followed the CDC guidance for SARS-CoV-2 testing [3]. For AN-sampling, the tip of a swab was inserted into the nose vertically 1–1.5 cm and rotated against the nasal walls for 15 s in both nostrils. For NMT-sampling, while tilting the head back (70°) the swab was inserted horizontally (parallel to the palate) into both nostrils for about 2 cm until resistance occurred, and then rotated 4 times against the nasal walls. Among consecutive participants, the sequence of AN- and NMT-sampling was alternated, followed by OP/NP-sampling for RT-PCR.

Participants who underwent NMT self-sampling received written and illustrated instructions in German or English. For NMT self-collection, a timing of 15 s was specified in addition to the minimum of 4 rotations. Procedures were observed without answering questions or providing corrections. NMT self-sampling (both nostrils) was followed by professional NP-sampling (through one nostril) for Ag-RDTs and combined OP/NP-sampling (other nostril) for RT-PCR. User acceptability and feasibility of self-sampling were assessed by observer and patient questionnaires.

Results

Participants

The study included 132 participants with professional AN- versus NMT-sampling, and 96 who underwent self



Prof.-AN, professional anterior nasal sampling; prof.-NMT, professional nasal mid-turbinate sampling; self-NMT, self NMT-sampling; prof-NP, professional nasopharyngeal sampling; Ag-RDT, antigen-based rapid diagnostic test; RT-PCR, real-time polymerase chain reaction

Figure 1. Study flow diagram.

NMT-sampling versus professional NP-sampling (Figure 1). Average age was 34.6 years (Standard Deviation [SD] 11.7) with 46.7% females and 20.3% having comorbidities. On the day of testing, 97.4% of participants had one or more symptoms consistent with SARS-CoV-2 infection. Average duration of symptoms at the time of presentation was 3.4 days (SD 3.0). Among participants performing self-sampling, 48 (50.5%) had a prior swab for SARS-CoV-2 been collected, and 50 (52.6%) had a higher education degree (Supplementary Table S1).

Professional an- versus NMT-sampling

Among 132 participants, 36 (27.3%) were RT-PCR-positive for SARS-CoV-2. Professional AN- and NMT-sampling both yielded a sensitivity of 86.1% (31/36 RT-PCR positives detected; 95%CI: 71.3–93.9) and a specificity of 100.0% (95%CI: 95.7–100) compared to RT-PCR. For both sampling methods, the sensitivity was 96.6% (28/29; 95%CI 82.8–99.8) in participants with high viral load, and 42.9% (3/7; 95%CI 15.8–75.0) in participants with low viral load ($\geq/<7.0$ $\log_{10}$ RNA SARS-CoV2/swab) (Table 1, Supplementary Table S2). The positive percent agreement was 100% (95%CI: 89.0–100). There was perfect (100%) inter-reader agreement on results.

Self NMT-sampling versus professional NP-sampling

Among 96 participants, 34 (35.4%) were RT-PCR-positive. Self NMT- and professional NP-sampling yielded identical sensitivities of 91.2% overall (31/34; 95%CI: 77.0–97.0), 100% (25/25; 95%CI 86.7–100) in participants with high viral load, and 66.7% (6/9; 95%CI 35.4–87.9) in participants with low viral load ($\geq/<7.0$ $\log_{10}$ RNA SARS-CoV2/swab). Specificity was 98.4% (95%CI: 91.4–99.9) with self NMT-sampling and 100.0% (95%CI: 94.2–100) with NP-sampling (Table 1, Supplementary Table S3). The positive percent agreement was 96.8% (95%CI: 83.8–99.8). A

Table 1. Sensitivity, specificity, and percent agreements of A) professional AN- versus professional NMT-sampling, and B) self NMT- versus professional NP-sampling. The results are also differentiated by high and low viral load ($\geq$/$<$ 7 $\log_{10}$ SARS-CoV2 RNA copies/ml).

Viral load SARS-CoV2 RNA copies/ml	Sampling method	Sensitivity n/N % (95%CI)	Specificity n/N (%; 95%CI)	Positive Percent Agreement % (95%CI)	Negative Percent Agreement % (95%CI)
(A) Prof.-sampling					
All ($N = 36$)	Prof. AN	31/36 86.1% (71.3–93.9)	96/96 100.0% (95.7–100.0)	31/31 100.0% (88.9–100.0)	96/96 100.0 % (95.9–100.0)
	Prof. NMT	31/36 86.1% (71.3–93.9)	96/96 100.0% (95.7–100.0)		
$\geq$7 $\log_{10}$ ($N = 29$)	Prof. AN	28/29 96.6% (82.8–99.8)			
	Prof. NMT	28/29 96.6% (82.8–99.8)			
$<$7 $\log_{10}$ ($N = 7$)	Prof. AN	3/7 42.9% (15.8–75.0)			
	Prof. NMT	3/7 42.9% (15.8–75.0)			
(B) Self-sampling					
All ($N = 34$)	Self NMT	31/34 91.2% (77.0–97.0)	61/62 98.4% (91.4–99.9)	30/31 96.8% (83.8–99.8)	63/65 96.9% (89.5–99.2)
	Prof. NP	31/34 91.2% (77.0–97.0)	62/62 100% (94.2–100.0)		
$\geq$7 $\log_{10}$ ($N = 25$)	Self NMT	25/25 100.0% (86.7–100.0)			
	Prof. NP	25/25 100.0% (86.7–100.0)			
$<$7 $\log_{10}$ ($N = 9$)	Self NMT	6/9 66.7% (35.4–87.9)			
	Prof. NP	6/9 66.7% (35.4–87.9)			

Prof.: professional sampling; self: self-sampling; AN: anterior nasal; NMT: nasal mid-turbinate.

third reader was necessary to agree on the interpretation of one NMT-result, which was ultimately considered negative, but turned out to be false negative based on a positive RT-PCR result.

Feasibility of self NMT-sampling

Deviations of self NMT-sampling included a more vertically-directed angle for sampling ($n = 13$), incorrect depth ($n = 4$ too superficial, $n = 10$ too deep), and reduced swabbing intensity (regarding duration $n = 28$, rotations $n = 12$, and rubbing $n = 36$). Three participants performed only unilateral NMT-sampling (Supplementary Table S3 and S4). On a scale from 1 (easy) to 5 (difficult), 81 (85.3%) participants stated that self NMT-sampling was easy to perform (scale 1 or 2); 13 (13.7%) found it medium easy/difficult (scale 3), and 1 (1.1%) rather difficult (scale 4). Twelve participants suggested that a mark on the swab to guide insertion depth would facilitate self-sampling.

Discussion

Among symptomatic outpatients, the sensitivities in detecting SARS-CoV-2 with an Ag-RDT were identical with professional AN- and NMT-sampling (86.1% overall; 96.6% at high viral load; 42.9% at low viral load). Furthermore, self NMT-sampling yielded the same sensitivity as professional NP-sampling (91.2% overall; 100% at high viral load; 66.7% at low viral load). Thus, our data suggests that AN-sampling is a suitable alternative to NMT- or NP-sampling.

AN- and NMT-sampling protocols may overlap in practice and deviate in details [6]. Participants in this study blew their nose once, on the theoretical assumption that this may increase the virus concentration in

the sampling region. Also, a timing of 15 s was specified for self NMT-sampling in contrast to other protocols [3].

The strengths of the study are the rigorous standardized sampling methods, two independent blinded readers, and an additional semi-quantitative visual readout of the Ag-RDT test band. A limitation of the study is that it was performed in a single centre. Participants were mainly symptomatic with a rather short duration of symptoms and in the majority with high viral load. This study demonstrates the diagnostic equivalence of the sampling methods for patients who are particularly infectious and responsible for transmission, however, it needs confirmation for asymptomatic patients and patients with low viral load. Patients who performed self-sampling were rather young and educated, half of whom already had experienced professional sample collection for SARS-CoV-2. In settings with different prevailing patient characteristics (e.g. less literate) a demonstration or oral instruction might be necessary for self-sampling.

The clinical usefulness of nasal sampling has been demonstrated and acknowledged for SARS-CoV-2 RT-PCR, including self-sampling [9–11], and evidence for Ag-RDTs is growing [4–6,12,13]. The use of dedicated nasal swabs for Ag-RDT is likely to be beneficial, as in an initial study the diagnostic accuracy of nasal sampling using a NP swab (smaller sampling surface, more flexible and more tickling) was slightly worse [5]. With written and illustrated instructions, patients were able to easily perform NMT-sampling. Nasal self-sampling will allow scaling of antigen testing. Considering the diagnostic equivalence, the more convenient self AN-sampling should allow an even broader use.

Ethical approval

This study was approved by the ethics committee of Charité - Universitätsmedizin (EA1/371/20).

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Author contributions

AKL, ON, and CMD designed the study and developed standard operating procedures. ON and CR implemented the study design and performed the laboratory work. AJ enrolled participants and supported the laboratory work. ON, CR, and AKL led the writing of the manuscript. FPM and JS coordinated and supervised the study site. FT and MG led the data analysis. FL provided technical advice. VMC and TCJ were responsible for PCR testing and contributed to the interpretation of the data. JAS supported the study design setup. All authors have reviewed the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

All raw data and analysis code are available upon request to the corresponding author.

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