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Self-collected gargle fluids and nasopharyngeal swabs as a strategy for molecular diagnostics of respiratory viruses

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ABSTRACT

Diagnosis of respiratory viruses traditionally relies on deep oropharynx or nasopharynx swabs collected by healthcare workers (HCW). However, outpatients must make an appointment, and the procedure can cause discomfort in patients. Self-collecting has the potential as a strategy to improve participants' willingness to participate in diagnostics, surveillance, or studies.

We compared self-collected gargle fluids and nasopharyngeal swabs as a strategy for molecular diagnostics of respiratory viruses and compared the average cycle threshold (Ct)-values with those of samples collected by HCW. The study was conducted among technicians of the Laboratory of Clinical Microbiology and Infectious Diseases, Zwolle, the Netherlands, and their family members, between April 2019 and March 2020. It included a questionnaire regarding the severity and date of first symptoms and an assessment of the sampling experience. The primary outcome was the mean Ct of positive PCRs. Similar mean Ct values were obtained using self- or HCW-collected swabs. In addition, gargle fluids and self-swabbed specimens had comparable detection rates of respiratory viruses. Notably, most participants preferred gargling over self-swabbing. Interestingly, but not surprisingly, the time between the onset of symptoms and sampling was shorter in PCR-positive compared to PCR-negative participants.

Though this study was abrogated by the SARS-CoV-2 pandemic, the results indicate that both self-swabs and gargle fluids are acceptable for diagnosing common respiratory viruses in the outpatient population, including influenza virus, rhinovirus, adenovirus, SARS-CoV-2 and endemic human coronaviruses. Gargling could be considered an alternative sampling strategy and may enhance willingness to participate in screenings or diagnostics for respiratory viruses.

Introduction

Diagnosis of respiratory viruses traditionally relies on deep oropharynx or nasopharynx swabs. However, nasopharyngeal swabs are associated with discomfort [1], and patients may either refuse testing [2] or may prematurely withdraw during the sample collection [1]. Moreover, swabbing may be discouraged in some wards, e.g., haemato-oncology, to avoid bleeding complications in patients with severe thrombocytopenia. Hence, alternative sampling strategies should be considered. Several factors determine the requirements of the sampling method, e.g., the pathogen involved, stage of disease, site of infection, sampling site, and testing strategy.

Gargle fluids have been used in epidemiological and retrospective studies [3–5] to diagnose respiratory infections and colonization, suggesting that gargling is both patient-friendly and effective to sample the upper respiratory tract for viruses. Self-collecting increases responsiveness in the general adult population to participate in screenings [5]. Moreover, gargling does not require assistance from healthcare workers (HCW) [6]. We evaluated two self-collecting strategies for diagnosing respiratory viruses: 1) by self-collecting gargle fluid and 2) by self-swabbing the oropharynx or nasopharynx. In addition, we compared

Abbreviations: AdV, Adenovirus; Ct, Cycle threshold; EnV, Enterovirus; FluA, Influenza virus type A; FluB, Influenza virus type B; HCW, Healthcare workers; HCoV, endemic human coronaviruses; hMPV, human Metapneumovirus; PCR, Polymerase Chain Reaction; PEV, Parechovirus; PIF, Parainfluenza virus; RSV, respiratory syncytial virus.

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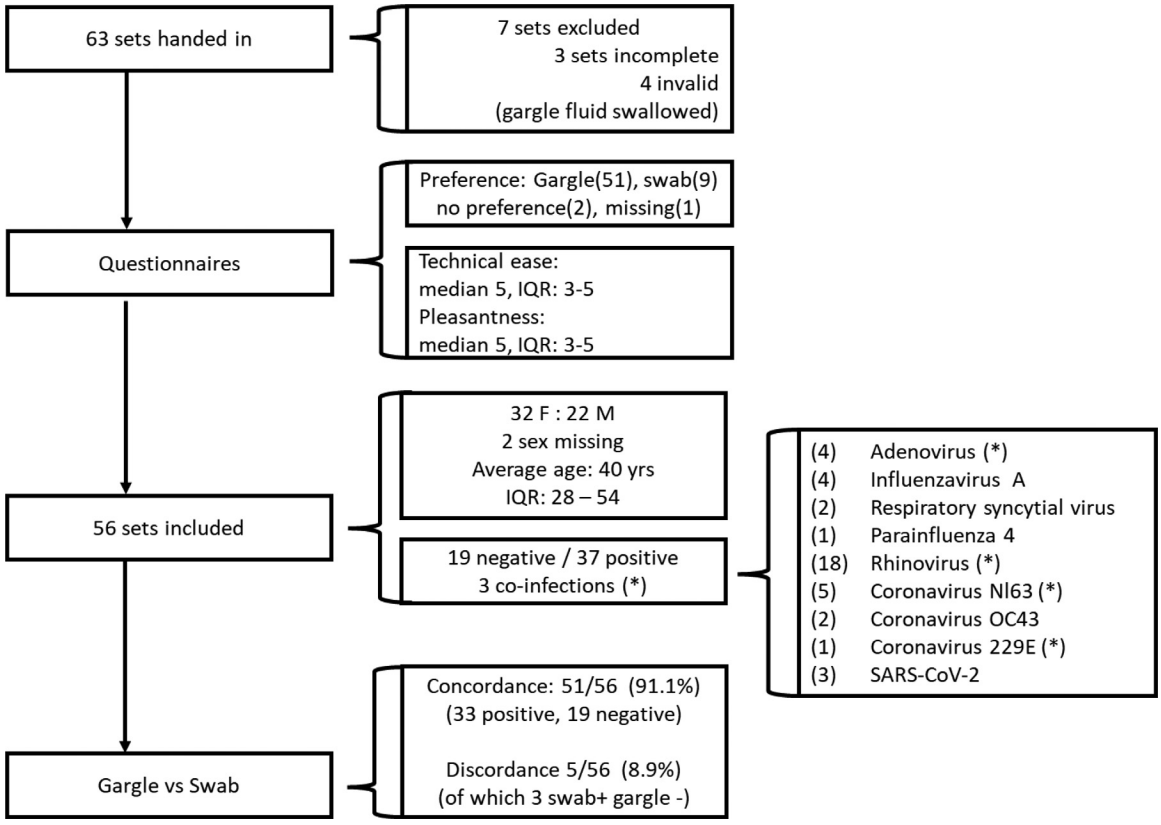

Fig. 1. An overview of the results obtained in the prospective study comparing gargle fluids with oropharynx or nasopharynx swabs. Assessment: participants were asked to score the technical ease of gargling relative to self-swabbing on a scale from 1 (more difficult) to 5 (much simpler). Pleasantness was scored from 1 to 5, indicating a strong preference for self-swabbing and gargling, respectively. * indicates co-infections. IQR: Inter-quartile range.

self-swabbed specimens with a collection of HCW-collected samples for diagnostic accuracy of respiratory viruses. Also, we evaluated participants' preferences for either swabbing or gargling with a questionnaire.

Results

Study population

The study population consisted of 63 participants (Fig. 1). Seven were excluded: three were incomplete, missing either swab or gargle fluid, and four participants swallowed the liquid prior to taking the diagnostic gargle sample. The included participants comprised thirty-two females and twenty-two males (two participants did not register their sex). The average age of the participants was 40 years (ranging from 7 to 70 years).

Participants were requested to sample the site with the most complaints: 37/56 (66%) sampled their throat, 15/56 (27%) sampled their nose, and 4/56 (7%) sampled both nose and throat.

Symptoms and days of illness

Participants were asked for the first day and kind of symptoms, and the sampling day. PCR-positive cases presented earlier (median three days, interquartile range: 2–5 days) than PCR-negative participants (median seven days, interquartile range: 3.5–12 days) ($p<0.05$). Symptoms reported were coughing (29/56, 52%), congestion (32/56, 57%), runny nose (8/56, 14%), pain (29/56, 52%) and fever (8/56, 14%). Three of 56 (5%) participants provided insufficient information. Symptoms did not significantly differ between PCR-positives and PCR-negatives (data not shown).

Table 1
Comparison of qualitative results obtained from gargle fluids with those obtained from swabs.

		Swab	
		Positive	Negative
Gargle	Positive	32	2
	Negative	3	19

Diagnostic sample quality

Internal controls were used to ensure reliable results. High or absent Ct values for the internal controls reflect poor extraction efficiency or the presence of inhibiting factors. The average Ct value of the internal controls was comparable between swabs and gargle fluid specimens: 30.1±1.1 and 30.1±1.2, respectively. The mean time between sampling and testing was 1.6 days (range 0–9 days).

Verification of self-collected specimens

Nineteen of 56 sets (34%) were negative for any tested respiratory virus, and 37 of 56 (66%) sets received a positive result in at least one material. Three of 37 (8%) positive sets had a double infection: two sets had adenovirus with a lower Ct value of either rhinovirus or HCoV 229E, and one set had rhinovirus with HCoV NL63.

First, we compared the detection rates of self-collected swabs with those in gargle fluids. The concordance between swabs and gargle fluids was 91% (51/56). Although five sets were discordant, the Cohens Kappa coefficient was 0.81, indicating very good agreement (Table 1).

Next, Ct values were compared between paired specimens (swabs *vs.* gargle fluids): Gargle fluids, in general, had higher, but not significant,

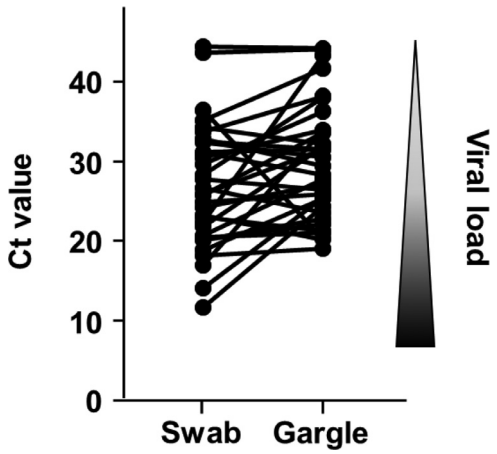

Fig. 2. Connected plot of Ct values found in paired swab fluids and gargled fluids. Target-specific Ct values in paired swabs and gargle fluids showed that Ct values in gargle fluids are on average 3Ct higher than in the paired swab. Ct values are corrected for differences in internal controls.

Ct values than the paired swabs (ΔCt ~3; Fig. 2). Next, we compared paired Ct values from gargle fluids with Ct values from swabs from either the nose or the throat (supplemental Fig. 1). Irrespective of the location of the swabs, Ct values did not differ significantly between swabs and gargle fluids. In addition, no significant difference between Ct values for the most prevalent individual viruses (rhinovirus and human coronaviruses) obtained from swabs and gargle fluids was found.

Given the set-up of this study, we could not compare self-collected swabs with HCW-collected swabs from the same person, we opted to compare the Ct values of the self-collected swabs from this study with the Ct value of HCW-collected swabs from clinical cases and. All Ct values were derived from the same period (April 2019–March 2020), and only the most prevalent viruses were included in this comparison, i.e., rhinovirus, influenza A virus, endemic human coronaviruses (HCoV, NL63, OC43, 229E), and adenovirus (*N*=19, 4, 9, and 6, respectively). The mean and distribution of Ct values were comparable between self-collected swabs and HCW-collected swabs (Fig. 3), and no statistically significant differences were found.

As children younger than 5 years were suggested to have lower Ct values [7], Ct values were plotted against the age of participants. No correlation was found between Ct value and the age of the participants (data not shown).

Evaluation of self-collecting strategies: user acceptability and preferences

Finally, we evaluated the user acceptability and preference for self-collecting using swab or gargle fluid. Participants scored the technical ease and their preference on a 1–5-point scale (with 1 and 5 indicating a strong preference for the swab and gargle fluid, respectively). Technical ease and overall sampling experience favored the gargling-based method (median: 5, IQR: 3–5).

Conclusions

Self-collected swabs are suitable materials for molecular diagnostics of respiratory viruses [8–13] and bacteria in outpatients [2,14]. Though self-collected swabs may be easy to collect, other sampling strategies might be preferred over self-swabbing. The objective of this study was to compare the performance of gargle fluids with self-collected swabs for molecular diagnostics of respiratory viruses in outpatients.

We showed that self-collected gargle fluids and oropharynx/nasopharynx swabs had similar accuracy. The average Ct values in gargle fluids were on average 3 Ct higher than in paired swab fluids, which may be explained by the sampling volumes (3 mL for swabs and 10–20 mL for gargle fluids). Importantly, most participants preferred gargling over swabbing, indicating that gargling might reduce the threshold to self-collect for molecular diagnostics and surveillance [5]. However, gargling might be challenging for some patients, as three of the specimens were invalid due to technical errors during collecting. Also, gargling may be contra-indicated in patients with neurologic disorders or in young children due to risk of aspiration.

A potential risk of this study is that non-trained participants may collect insufficient material for sensitive detection of respiratory viruses, thus compromising the sampling quality of the self-collected material. Sampling quality can be assessed by quantifying the amount of human DNA in the sample. We were not able to do this. However, self-collected swabs were found to contain, on average, more human DNA than HCW-collected swabs [8,12], indicating that self-collecting participants applied higher pressure on the swab than HCW. Yet higher amounts of human DNA did not associate with a higher prevalence and/or concentration of respiratory viruses [8,12]. This suggests that, during a respiratory infection, the nasal cavity contains sufficient virus particles to enable molecular detection irrespective of the pressure applied on the swab.

The Ct value of respiratory viruses can serve as a semi-quantitative proxy of the viral load in the collected materials [8,12]. A limitation of this study is that we did not compare paired self-collected and HCW-collected swabs. However, previous studies already showed that: i) a high concordance exists between self-collected swabs and HCW-collected swabs [8,9,11,12], ii) it is acceptable and informative to compare Ct values between two different populations [5,15,16]. Hence, we compared the distribution of Ct values found in this study (self-collected nasopharyngeal swabs) and in our clinical HCW-collected swabs. The distribution of the Ct values was similar (Fig. 3), suggesting that the quality of sampling did not differ between HCW and literate adult participants. Thus this study confirms previous studies with self-collected swabs [9,11,12].

Previous studies also instructed participants in-person how to self-swab [8,11,12], yet providing literate participants with written sampling instructions might suffice (this study, and [9]), thus reducing the need for involvement of HCW. Furthermore, omitting the necessity for HCW to collect swabs can reduce the time from symptom onset to test [10,13], which is important to diagnose the viral etiology as highest sensitivity is found if patients are sampled within the first three to seven days after symptom onset [17–19]. Self-collection allows participants to collect respiratory samples at their convenience. Indeed, the option of self-collecting increased adherence to participation in testing programs [2]. We expect that self-collecting will lower the threshold to test earlier after the onset of symptoms, which is particularly important as we show that PCR-positivity is associated with a shorter period between the first day of illness and the day of sampling.

A typical limitation of any study into diagnosis of common cold is the multitude of respiratory viruses that can cause common cold and their unpredictable prevalence. Hence, many common cold-related studies have limited power at the level of individual viruses [9,11,12], unlike recent studies on SARS-CoV-2. [9] In our study, the respiratory PCR panel tested for 16 different viruses. However, only 9 of them were detected in 36 persons. Of these 9 viruses, only two were frequently present: rhinovirus (*N*=18) and HCoV (*N*=8). The study was abrogated by the introduction of SARS-CoV-2 in our population (March 2020). At that moment, 40 PCR-positive episodes were found in 37 participants (37/57; 66%). This would suffice to detect reasonable effect sizes with 80% power and a significance of 5%, however not at the level of individual viruses. If sufficient (pilot) studies are published, a meta-analysis could be conducted to provide a definite assessment of the validity of self-collecting (swabs and gargle fluids) for diagnosis of all common cold viruses [3,9,18].

Our participants were requested to sample the site with the most complaints, resulting in swabbing of the throat (66%), nose (27%), or both (7%). The oropharynx generally contained lower viral loads

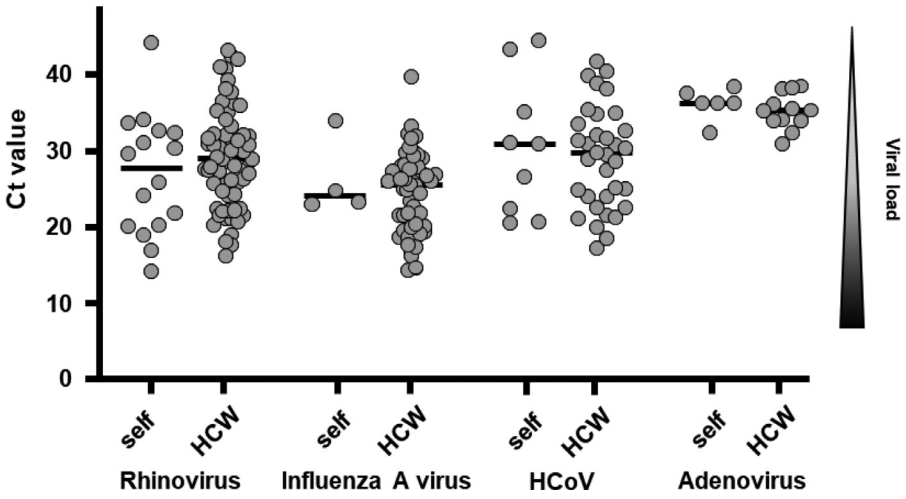

Fig. 3. Comparison of raw Ct values found for adenovirus, influenza A virus, rhinovirus, and the34) endemic human coronaviruses (HCoV) NL63, OC43, 229E between swabs taken by participants in this study (self) and by healthcare practitioners (HCW). From left to right, N = 19, 67, 4, 69, 9, 34, 6, 12. HCoV consist of the following three strains: NL63 (N = 5 and 15 resp.), OC43 (N = 3 & 17 resp.), 229E (N = 1 & 2 resp.). No significant differences were found between self-taken swabs and HCW-taken swabs. The median is represented by a line. For HCW-collected samples, the mean±standard deviations of Ct values are: 29.7±6.6 (N=66, rhinovirus), 24.5±6.3 (N=54, influenza A virus), 29.2±6.9 (N= 34, HCoV), and 35.2±2.3 (N=12, adenovirus). Ct values were corrected for differences in internal controls.

[20,21]. Therefore, it has been recommended to sample both the oropharynx and the nasopharynx [20,21]. However, we had a high positivity rate (70%) while most (66%) of the samples were taken from the oropharynx. In line with our results, previous studies noted that the detection rate of respiratory viruses was similar for the oropharynx and the nasopharynx [2,20]. Participants might have opted for the oropharynx for personal reasons other than symptoms. As far as we know, it is unknown whether clinical symptoms can be used to optimize sampling strategies with minimal impact on patients. Future research could incorporate self-collected samples from both the oropharynx and the nasopharynx and investigate a possible association between clinical symptoms and detection rates of respiratory viruses.

Currently, the SARS-CoV-2 pandemic is ongoing, and it is unknown whether gargling can contribute to the spread of the virus. This will depend on the formation of aerosols and their size [22]. Active gargling is essential as an oral rinse had lower sensitivity than the paired nasopharyngeal swab [23]. Therefore, if opting for gargling, this may best be done privately, and possible safety issues should be carefully considered. However, self-collecting reduces the need for HCW and reduces the consumption of personal protective gear [24].

Summarized, self-collecting by swabbing or gargling can be used in outpatients and allows for rapid and sensitive molecular diagnostics of common respiratory viruses, including influenza A virus, RSV, rhinovirus, adenovirus, and SARS-CoV-2 (this study, [3-5,15,24,25]). It offers possibilities for convenient diagnostics and low-threshold screening strategies.

Materials and methods

Study design: The study was conducted in the Laboratory of Clinical Microbiology and Infectious Diseases (LMMI), Isala Hospital, Zwolle (The Netherlands), between 3 April 2019 and 10 March 2020. Laboratory employees and their close family members showing respiratory infection symptoms were invited to participate in the study, irrespective of the severity and time since the onset of complaints. Participants were requested to fill in a questionnaire regarding their symptoms, the first symptoms and sampling dates, and their sampling experience (ease of sampling and preferred sampling method). The study was terminated when SARS-CoV-2 reached the local population to spare reagents and testing capacity.

Sampling: Participants were provided with a bag containing instructions, 20 mL sterile NaCl 0.9% (Braun Melsungen AG, Germany), a 20 mL receptacle (Sterilin, U.K.), and a thin nasopharyngeal swab and 1 mL of modified liquid amies solution (COPAN, Italy). Participants were requested to obtain an oropharynx or nasopharynx specimen, depending on the site with most complaints. After that, participants were requested to take a sip of water, rinse their teeth and spit the water out. This step removes inhibitory factors, e.g. polysaccharides due to leftovers of meals [26]. After a brief, self-induced cough, a saline solution was sipped, and gargling commenced. Gargle fluids were collected in the sterile 20 mL tube provided. Materials were kept in the fridge till testing. Our sampling instructions can be found in the supplemental data.

Targets: Each sample was tested for influenza A and B virus, respiratory syncytial virus (RSV), human parainfluenza viruses 1–4, rhinovirus, human metapneumovirus (hMPV), enterovirus, parechovirus, adenovirus, endemic human coronaviruses (HCoV) NL63, OC43, and 229E and the pandemic coronavirus SARS-CoV-2. PCRs were performed as described previously (Supplemental table 1) [27–31].

Tests: A fixed amount of phocine herpes virus and equine arteritis virus stocks were added to 200 μL of the samples as internal controls. Total nucleic acids were extracted from the samples using NucliSens easyMag (BioMerieux, France) and eluted in 110 μL elution buffer (NucliSens Buffer 3, BioMerieux, France). Ten microliters of the eluate were mixed with 15 μL of Taqman® Fast Virus 1-step master mix (Thermo Fisher, CA, USA) and 5 μL oligos.

Samples were analyzed on an ABI7500 (Thermo Fisher, CA, USA) using the following temperature program: 10 min at 50 ˚C,15 min at 95 ˚C, 45 cycles of 30 s at 95 ˚C, and 1 min at 60 ˚C. All tests were conducted according to standard protocols in an ISO 15189:2012-certified laboratory. Participants were informed if a virus was detected in their samples.

Correction of Ct values: Observed Ct values were plotted as raw Ct values and as Ct values corrected for differences in internal controls (IC-corrected). The used formula was e.g. $Ct_{target\ /\ gargle} - (Ct_{IC\ /\ gargle} - Average\ (Ct_{IC})) = IC\text{-corrected}\ Ct_{target\ /\ gargle}$.

Comparator group: The comparator group consisted of all clinical respiratory swabs submitted by health care workers from 3 April 2019 to 10 March 2020 (i.e., the same period as the study period). Data (Ct values of adenovirus, hCoV (NL63, 229E, OC43), influenza A virus and rhinovirus) were retrospectively collected from the laboratory information system.

Ethical statement: The local Medical Ethical committee of Isala Hospital, Zwolle, the Netherlands, approved the study (METC Isala, #15684). This study was conducted per relevant guidelines and regulations. Participants or their parents provided written informed consent to anonymously register and analyze the data. PCR results were communicated to participants. Participants were advised to consult their general practitioner irrespective of the PCR outcome.

Statistics: Data was analyzed using Prism version 9.0.0. (GraphPad Software, CA, USA). A 2-sided unpaired t-test was performed to compare the Ct values in swabs taken by healthcare professionals versus self-swabs and the Ct values obtained by self-swabbing and gargling. A two-

tailed Mann-Whitney-U test, excluding outliers, was used to compare the duration between the first day of illness and the sampling day for PCR-positive and PCR-negative participants. A p-value of ≤ 0.05 is considered significant.

Retrospective power calculations were completed in Statulator [32]. At least 32 PCR-positive result pairs were needed to detect a reasonable effect size (0.5) with 80% power and a significance level of 5% (one sided) within subjects. Assuming 50% of the participants will be positive for a respiratory virus, at least 64 participants needed to be included in the study.

Author contributions

JF conceived the study. All authors (JF, JR, GW) contributed to analyzing the data and writing the manuscript.

Declaration of Competing Interests

JWAR consults for IDbyDNA. The other authors declare that the research was conducted in absence of any commercial or financial relationships.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcvp.2022.100116.

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