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The use and performance of oral–throat rinses to detect pharyngeal *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections

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Abstract

Gonococcal and chlamydial infections in the pharynx can occur as a consequence of oral sex. Currently, diagnosis of these infections typically requires a swab specimen to be collected from the posterior pharynx. However, we assessed the diagnostic adequacy of using commercial mouthwash or water as an oral–throat rinse and subsequent testing with a nucleic acid amplification test (Gen-Probe APTIMA Combo 2 assay; Gen-Probe, San Diego, CA). Mouthwash and water samples, spiked with varying amounts of gonorrhea and chlamydia, remained positive for both organisms for up to 2 weeks after storage at room temperature and 37 °C. A clinical trial compared the test performance of oral–throat rinses to pharyngeal swabs among 561 (250 mouthwash, 311 water) gay and other men who have sex with men. Participants were also surveyed to assess the acceptability, preference, and feasibility of oral–throat rinses in a clinical setting. The prevalence of pharyngeal gonorrhea and chlamydia were 9.5% (53/556) and 1.4% (8/561), respectively. Compared with the pharyngeal swab, mouthwash oral–throat rinses had a sensitivity and specificity for the detection of gonorrhea of 72% and 99.1%, respectively, whereas water had 82% and 99.7%, respectively. Chlamydia prevalence was too low for reliable assessments of test performance. Study participants found oral–throat rinses acceptable, preferable, and feasible when compared with pharyngeal swabs. Further study is needed to investigate discordant results and improve the sensitivity of oral–throat rinses.
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Keywords: *Chlamydia trachomatis*; *Neisseria gonorrhoeae*; Pharynx; Detection

1. Introduction

Among gay and other men who have sex with men (MSM), a substantial number of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections occur at nongenital anatomic sites (Lafferty et al., 1997; Page-Shafer et al., 2002; Sulaiman et al., 1981). Recognition and management of these infections are critical for sexually transmitted disease (STD) control and to improve the sexual health of gay and other MSM. The Centers for Disease Control and Prevention (CDC, 2006) recommends annual pharyngeal testing for gonorrhea in MSM who report performing oral sex in the preceding year. For MSM at higher risk (those who have multiple or anonymous sex partners, who have sex in conjunction with illicit drug use, who use methamphetamine, or whose sex partners participate in these activities), CDC recommends screening every 3 to 6 months.

Pharyngeal infection with gonorrhea or chlamydia is predominately asymptomatic (Bro-Jorgensen and Jensen, 1973; Jebakumar et al., 1995; Lafferty et al., 1997; Page-Shafer et al., 2002). Although pharyngeal pathology is uncommon (Metzger, 1970; Wiesner et al., 1973), there is evidence that these infections, as well as those caused by other sexually transmitted organisms as well as nonsexually transmitted organisms (Bradsha et al., 2006), can be transmitted from the pharynx to the genital tract of sex partners (Bro-Jorgensen and Jensen, 1973; Edwards and Carne, 1998; Lafferty et al., 1997; Soendjojo, 1983; Tice and Rodriguez, 1981), thereby contributing to overall STD

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morbidity within a community. The lack of overt clinical signs for pharyngeal infection and the public health importance of identifying and treating infected individuals require adequate laboratory tools as an aid to the diagnosis.

Traditionally, culture has been used for the detection of pharyngeal infection with gonorrhea or chlamydia. However, nucleic acid amplification tests (NAATs) may be preferable to culture for pharyngeal infection detection owing to their increased test sensitivity (Page-Shafer et al, 2002) and availability in US public and private health laboratories (Dicker et al., 2007). Previous studies have shown increased detection of pharyngeal gonorrhea using ligase chain reaction (Page-Shafer et al., 2002; Stary et al., 1997; Young et al., 2003) and chlamydia using polymerase chain reaction (Jebakumar et al., 1995) on swab specimens. Because pharyngeal specimens have not been cleared by the Food and Drug Administration (FDA) to be tested by NAATs, laboratories must verify the procedure before reporting results to clinicians for patient management (Elder et al., 1997). Only a small number of laboratories, such as the San Francisco Department of Public Health Laboratory (SFDPHL) (Klausner et al., 2002), have verified the performance of NAATs against culture for nongenital infections caused by *N. gonorrhoeae* and *C. trachomatis*. There have been some concerns regarding the potential for some NAATs to cross-react with nongonococcal *Neisseria* spp. and other organisms commonly found in the throat, but the pattern of cross-reaction between tests is not uniform, and there have been no such reports of cross-reactivity when using the Gen-Probe APTIMA Combo 2® assay (Gen-Probe, San Diego, CA) (Whiley et al., 2006).

Because NAATs can detect organisms in urine specimens, they might also be able to detect gonorrhea and chlamydia in oral–throat rinse specimens. Although pharyngeal swab collection requires trained clinicians, oral–throat rinses can be collected by minimally trained staff or may even be amenable to self-collection at nonclinical settings such as in the home or field. Oral–throat rinses have been studied previously as a means to detect the presence of human papillomavirus, *Candida dubliniensis*, and *Pneumocystis carinii* (D'Souza et al., 2005; Helweg-Larsen et al., 1998; Lawton et al., 1992; Tekeli et al., 2005). Mouthwash might be an appropriate rinse agent because its high alcohol content (>15%) could help stabilize gonococcal and chlamydial nucleic acids. However, because commercial mouthwash formulation could change over time and vary by brand and type, changes in formulation or type would require additional verification studies. Thus, water might be a more practical long-term oral–throat rinse agent. The purposes of this study were A) to determine the analytic sensitivity of a nucleic acid amplification assay for *N. gonorrhoeae* and *C. trachomatis*; B) to compare the detection of *N. gonorrhoeae* and *C. trachomatis* from oral–throat rinses versus pharyngeal swabs collected from patients at risk for pharyngeal infection; and C) to assess the acceptability, preference, and feasibility of collecting oral–throat rinses versus pharyngeal swabs.

2. Materials and methods

2.1. Analytic detection

A commercial mouthwash (green FreshBurst® Listerine® [21.6% alcohol] distributed by Pfizer, Morris Plains, NJ) and water were inoculated with *N. gonorrhoeae* or *C. trachomatis* at estimated concentrations of 10 to 10^7 colony forming units (CFUs) or inclusion forming units (IFUs) per milliliter, respectively. Specimens were tested for *N. gonorrhoeae* and *C. trachomatis* by the Gen-Probe APTIMA Combo 2 assay as described in the product insert after incubation at room temperature (25 °C) and 37 °C for 24, 48, 72, and 96 h, and 1 and 2 weeks. Control specimens comprised pristine fluids. The Gen-Probe APTIMA Combo 2 assay uses target capture technology during preamplification specimen processing. The target capture procedure effectively removes any specimen substance that could potentially interfere with nucleic acid amplification. For this reason, inhibition controls are not included with the assay.

2.2. Patient population

Subjects were recruited at the San Francisco municipal STD clinic (City Clinic) from January to June 2006. Eligible individuals for this study were patients 18 years or older undergoing screening or diagnostic testing for STDs where pharyngeal specimen collection was a component of their routine care, who understood English, and who were not previously enrolled in this study or another concurrent pharyngeal infection study. City Clinic guidelines recommend screening gay and other MSM for pharyngeal infection if they had performed fellatio with more than one partner in the previous 2 weeks. In addition, diagnostic testing for pharyngeal infection is performed at the clinician's discretion based on symptoms, signs, or patient request. Informed consent was obtained verbally from all study participants. The study protocol was approved by the University of California San Francisco Committee on Human Research (approval number H9978-27856-01) and the CDC institutional review board (protocol number 4848).

2.3. Specimen collection and testing

Trained clinicians obtained pharyngeal swab specimens from the posterior pharynx of each patient. Patients were then randomly assigned to receive 10 mL of either mouthwash (FreshBurst® Listerine®) or sterile tap water and instructed to gargle the solution for 10 s and deposit the fluid into a prelabeled sterile specimen container. Oral–throat rinse specimens were left at ambient temperature until the end of each clinic day (maximum of 8 h), when 2 mL of the rinse was transferred to a Gen-Probe APTIMA urine

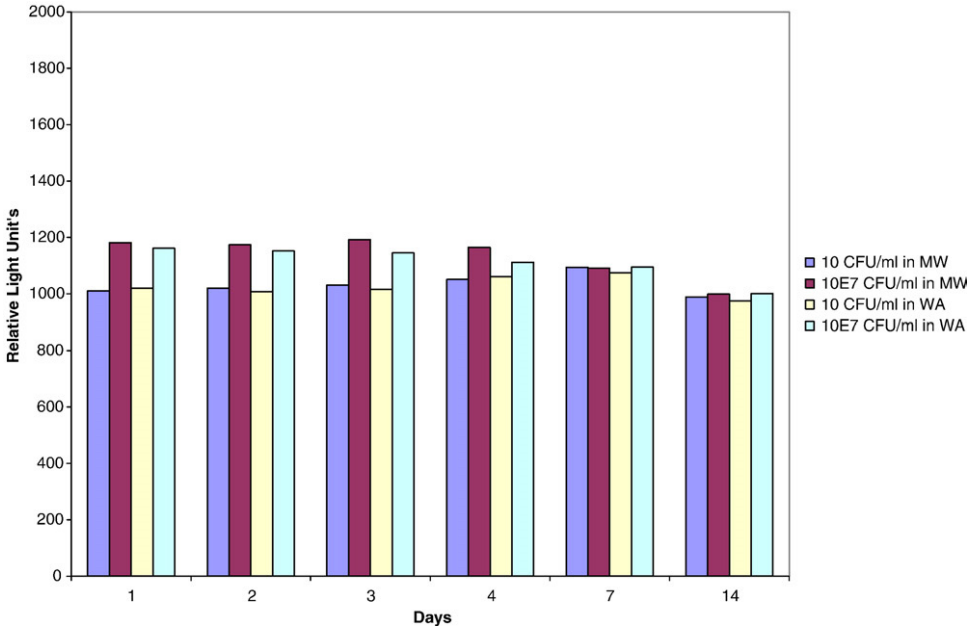

Fig. 1. Detection of *N. gonorrhoeae* in mouthwash (MW) and water (WA) inoculated with either 10 or 10^7 CFUs/mL and tested with the Gen-Probe APTIMA Combo 2® assay at various intervals for up to 14 days of storage at 25 °C.

transport tube containing 2-mL diluent. Once transferred, urine and swab specimens can be stored at 2 to 30 °C for 30 days according to the product insert. We extrapolated this time frame to the oral rinse specimens.

Pharyngeal swabs were tested, as per usual, at the SFDPHL, and the oral–throat rinses were tested at the Laboratory Reference and Research Branch's Chlamydia Laboratory, CDC in Atlanta, GA. Swabs were transported by courier daily to the SFDPHL, whereas the oral–throat rinse specimens were stored in a refrigerator (3 °C) at City Clinic and mailed overnight to Atlanta once weekly. Swabs were tested within 4 days of collection, and oral–throat rinses were tested within 12 days of collection. Specimens were tested for gonorrhea and chlamydia using the Gen-Probe APTIMA Combo 2 assay at both testing facilities.

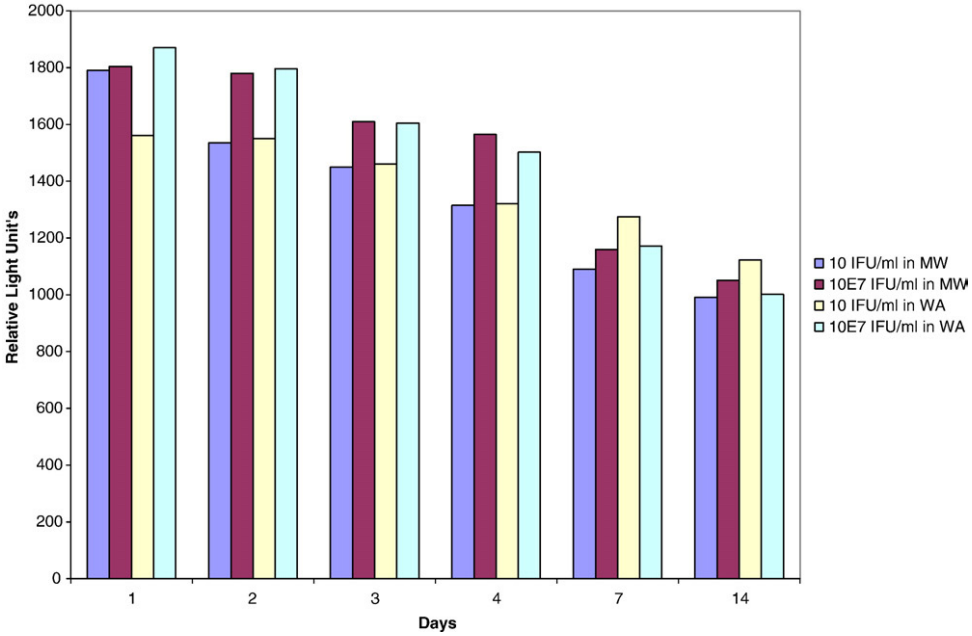

Fig. 2. Detection of *C. trachomatis* in mouthwash (MW) and water (WA) inoculated with either 10 or 10^7 IFUs per milliliter and tested with the Gen-Probe APTIMA Combo 2® assay at various intervals for up to 14 days storage at 25 °C.

Table 1
Sensitivity, specificity, PPV, and NPV of oral–throat rinses compared with pharyngeal swabs for the detection of gonorrhea and chlamydia infection, San Francisco City Clinic, 2006

Specimen	Infection	Total tested	Sensitivity (rinse positive/swab positive), exact 95% CI	Specificity (rinse negative/swab negative), exact 95% CI	PPV, exact 95% CI	NPV, exact 95% CI
Mouthwash	GC (*N. gonorrhoeae*)	246	72% (18/25) 51–88%	99.1% (219/221) 97–100%	90% (18/20) 68–99%	97% (219/226) 94–99%
	CT (*C. trachomatis*)	250	100% (1/1) 3–100%	100% (249/249) 99–100%	100% (1/1) 3–100%	100% (249/249) 99–100%
Water	GC (*N. gonorrhoeae*)	310	82% (23/28) 63–94%	99.7% (281/282) 98–100%	96% (23/24) 79–100%	98% (281/286) 96–99%
	CT (*C. trachomatis*)	311	100% (7/7) 59–100%	99.7% (303/304) 98–100%	88% (7/8) 47–100%	100% (303/303) 99–100%

2.4. Participant acceptability survey

Subjects were given a brief self-administered questionnaire after gargling the oral–throat rinse. The following questions were asked to address acceptability, preference, and feasibility respectively: 1) How easy was gargling the liquid? 2) Did you prefer gargling the liquid to the throat swab the clinician collected? 3) Would you be willing to do it again?

2.5. Statistical analysis

SAS software, version 9.1 (SAS Institute, Cary, NC), was used to merge data tables, calculate exact confidence intervals (CIs), and perform cross-tabulations and χ^2 analysis. Sensitivity, specificity, and positive predictive value (PPV) and negative predictive value (NPV) estimates were calculated using the pharyngeal swab specimen as the reference standard.

3. Results

3.1. Analytic detection

All spiked specimens maintained at 25 °C were positive for *N. gonorrhoeae*- and *C. trachomatis*-specific RNA sequences, whereas uninoculated fluid remained negative (Figs. 1 and 2). Relative light units (RLUs) declined but remained far above the negative cutoff for up to 14 days postinoculation. Similar results were observed with specimens incubated at 37 °C.

3.2. Clinical study

Forty-eight percent of eligible patients (566/1172) were enrolled into the study. A total of 556 subjects were tested for gonorrhea, and 561 were tested for chlamydia (Table 1). The overall prevalence of pharyngeal gonococcal and chlamydial infection was 9.5% (53/556) and 1.4% (8/561), respectively. The sensitivity estimate of NAATs for gonorrhea detection using mouthwash rinses was lower than that for water rinses (72% [95% CI, 51–88%] versus 82% [95% CI, 63–94%]), but the difference was not significant (χ^2= 0.7758, P = 0.3784). The specificity estimates of the mouthwash and water rinses were both high for gonorrhea (>99.1%). The PPVs for gonorrhea were 90% and 96%, whereas the NPVs were 97% and 98% for mouthwash and water, respectively (Table 1). The sensitivity estimate for chlamydial detection was high for both mouthwash and water (100%), as was the specificity estimate (>99.7%). The PPV for detection of *C. trachomatis* chlamydia was moderate for water (88%) and high for mouthwash (100%), whereas the NPV was high for both rinses (100%).

3.3. Acceptability of oral–throat rinse

A total of 561 subjects completed the questionnaire; 250 from the mouthwash rinse group and 311 from the water

Table 2
Acceptability, preference, and feasibility of oral–throat rinses compared with pharyngeal swabs for the detection of gonorrhea and chlamydia infection, San Francisco City Clinic, 2006

Specimen	Acceptability	Preference	Feasibility
Mouthwash	Very easy, 75% (187/250) Easy, 18% (44/250) Neither hard nor easy, 7% (17/250) Hard, 1% (2/250) Very hard, 0% (0/250)	Yes, 50% (126/250) No, 10% (24/250) I do not know/no preference, 40% (100/250)	Yes, 97% (242/250) No, 0.4% (1/250) I do not know/no preference, 3% (7/250)
Water	Very easy, 76% (237/311) Easy, 19% (59/311) Neither hard nor easy, 4% (13/311) Hard, 1% (2/311) Very hard, 0% (0/310)	Yes, 49% (151/310) No, 9% (28/310) I do not know/no preference, 42% (131/310)	Yes, 96% (298/310) No, 2% (5/310) I do not know/no preference, 2% (7/310)

rinse group (Table 2). The acceptability of mouthwash versus water oral–throat rinses was similar, with most subjects reporting that gargling the rinse was either very easy or easy (mouthwash, 92.4%; water, 95.2%; χ^2= 1.877, P = 0.1707). Preference was similar between the 2 groups as well, with approximately half of the respondents preferring the oral–throat rinse (mouthwash, 50.4%; water, 48.7%; χ^2= 0.1891, P = 0.6636), whereas most of the remaining respondents in both groups had no preference. Feasibility was also similar, with almost all reporting they would be willing to gargle a rinse again (mouthwash, 96.8%; water, 96.1%; χ^2= 0.3695, P = 0.5433).

4. Discussion

The increasing recognition of pharyngeal *N. gonorrhoeae* and *C. trachomatis* infections (Kent et al., 2005; Page-Shafer et al., 2002; Sulaiman et al., 1981) and their role in the continued spread of STDs have caused clinicians to request increasing diagnostic support from the clinical microbiology laboratory. Although NAATs for *N. gonorrhoeae* and *C. trachomatis* are not cleared by the FDA for pharyngeal specimens, their diagnostic utility has been proven (Jebakumar et al., 1995; Page-Shafer et al., 2002; Stary et al., 1997; Young et al., 2003). We extended studies that examined the performance of NAATs for pharyngeal swabs to oral–throat rinses because those tests do not rely on culture isolation, and an oral–throat rinse might be better at detecting infections than swab sampling. Our in vitro analysis clearly demonstrated the ability of the Gen-Probe APTIMA Combo 2® assay to detect both *N. gonorrhoeae* and *C. trachomatis* in mouthwash and sterile water. There was a little, if any, difference in the change of signal among various concentrations, incubation time, or temperature.

The analytical sensitivity of testing as determined by the inoculation of mouthwash and water fluids with known concentrations of *N. gonorrhoeae* and *C. trachomatis* was shown to be as few as 10 organisms/mL of fluid. However, this is likely an overestimate of the true analytic sensitivity because the inoculum measured was based on viable organism counts rather than nucleic acid targets. A more accurate estimate of analytic sensitivity was not necessary because the RLUs generated from the in vitro study were similar to those from the clinical study (data not shown).

Detection of low numbers of *N. gonorrhoeae* and *C. trachomatis* organisms in water and mouthwash was demonstrated under laboratory conditions, but in vivo oral–throat rinses were found to be less sensitive than pharyngeal swabs for detecting gonorrhea, the current standard of care in San Francisco. However, the sensitivity and specificity of oral rinse specimens might be sufficient for screening high-risk individuals who do not access regular clinical STD testing services. The chlamydial prevalence was too low in our study population for us to make reliable assessments of the performance of oral–throat rinses compared with pharyngeal swabs. Men found oral–throat rinses acceptable, preferable, and feasible.

The reasons for the lower test sensitivity of the oral–throat rinses compared with the pharyngeal swab for detection of *N. gonorrhoeae* may include differences in organism burden due to dilution or handling and transportation of specimens to testing facilities. Although pharyngeal swabs concentrate infectious material onto the cotton tip surface, oral–throat rinses dilute the material into 10 mL of fluid, perhaps leading to lower concentrations of nucleic acid in the final tested specimen. Centrifugation of the oral rinse fluid before adding it to the transport diluent may concentrate any organisms and increase the sensitivity estimate. In addition, although subjects were instructed to gargle for 10 s, anecdotal reports from clinicians indicated that, sometimes, patients gargled for just a few seconds or simply “swished” the rinse, which may have been inadequate to sample the posterior oropharynx. Although these observations were not stratified to fluid, there may be less hesitation to gargle with water compared with mouthwash, and such a difference may have contributed to the difference in sensitivity. Strict adherence to gargling and perhaps a longer gargle interval may increase the sensitivity. Lastly, the pharyngeal swabs were tested within a few days of collection at the nearby SFDPHL, whereas the oral–throat rinses were mailed to Atlanta and tested 5 to 12 days after specimen collection. During this extra time, nucleic acid in the oral–throat rinse samples might have degraded because of enzymes found in the oral cavity. However, clinical oral–throat rinse specimens that initially tested positive remained positive when left at ambient temperature for at least 40 days at room temperature (data not shown).

The few false-positive oral–throat rinse tests may not have been truly false-positive results. Our analysis used pharyngeal swab results as the reference standard, and the data may be adversely impacted by suboptimal swab collection such as limited or no contact with a focal mucosal infection in the posterior pharynx. In addition, oral–throat rinses represent a general oral mucosal specimen and may detect infection missed by a swab of the posterior pharynx. Gonorrhea has previously been detected within the anterior oral cavity (Schmidt et al., 1961; Tikjob et al., 1985).

The specificity of NAATs must be evaluated before using them with nongenital anatomic site specimens. The Gen-Probe APTIMA Combo 2® test does not appear to cross-react with nongonococcal *Neisseria* spp. (Whiley et al., 2006). Therefore, if the number of gonococcal infections were the total of specimens positive by either swab or oral–throat rinse, then the overall sensitivity of the oral–throat procedures would have been greater but nevertheless remain below that for the swab collection procedure.

In conclusion, oral–throat rinse fluid, particularly water, may be a feasible clinical specimen for the detection of pharyngeal gonorrhea. A larger study with a greater number of both gonococcal and chlamydial infections would enhance performance estimates for oral–throat rinses and perhaps

identify correlates of negative specimens. The results of this pilot study were promising and justify further research before recommending oral rinses fluids as a specimen type for pharyngeal gonorrhea and chlamydia infections.

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