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# Kiss and Tell: Limited Empirical Data on Oropharyngeal *N. gonorrhoeae* among Men Who Have Sex with Men and Implications for Modeling

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"An extraordinary claim requires extraordinary proof." - Marcello Truzzi

In this issue of Sexually Transmitted Diseases, Zhang and colleagues make two bold assertions. First, they conclude that kissing accounts for over 70% of gonorrhea in men who have sex with men (MSM). Second, they suggest that a mouthwash with high efficacy against oropharyngeal *N. gonorrhoeae* could substantially reduce the overall gonorrhea prevalence in MSM. Although anecdotal reports of *N. gonorrhoeae* transmission through kissing exist, conventional wisdom is that gonorrhea transmission through kissing happens rarely, if at all. It is important to clarify that Zhang and colleagues present no empirical evidence of transmission by kissing. Instead, they conclude that kissing must be an important mode of transmission because otherwise their model could not replicate current data on oropharyngeal gonorrhea prevalence among MSM in Australia. Although mathematical models such as that of Zhang and colleagues are vital to the field of STD research, a common limitation of these models is a scarcity of data to inform their construction.

For science to advance, however, we must be open to new ideas and challenges to conventional wisdom. In fact, over the past decades, we have come to understand that oropharyngeal gonorrhea is more common and more likely to be transmitted to other anatomic sites than was previously thought. Thus, it is conceivable that oropharyngeal infections could play a key role in sustaining gonorrhea in MSM via kissing, as suggested by Zhang and colleagues. If so, it is also plausible that a mouthwash with efficacy against oropharyngeal gonorrhea could have a notable population-level impact on gonorrhea. One of the most useful contributions of their modeling exercise is to highlight the numerous unanswered questions related to how a mouthwash-based intervention may affect community-level gonorrhea prevalence. Below, we identify several areas of inquiry that are critical to the development of a more lucid epidemiology of gonorrhea.

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## What is the duration of infection for *N. gonorrhoeae*?

An understanding of oropharyngeal *N. gonorrhoeae* infectivity and the duration of infection is critical to inform valid and robust models. Several studies have identified oropharyngeal *N. gonorrhoeae* using both culture and nucleic acid amplification tests (NAAT)[1]. However much less is known about the duration of infection at different anatomic sites, including the oropharynx, or about relative infectivity. While recent studies have shown that oropharyngeal infections can infect male urethras[2–4], nearly all data related to site-specific infectivity were published before 1982 and based on culture[1,5,6] . Furthermore, as illustrated in a review by Chow[7], data on duration of infection are sparse.

## How likely is *N. gonorrhoeae* transmission from the oropharynx other anatomic sites?

Nearly all of the data on N. gonorrhoeae transmission is limited to heterosexual populations. Early studies estimated the per-contact risk of transmission from infected female genitals to male urethra as approximately 22%[8,9], and approximately 75% from infected male urethras to female genitals[10,11]. Hui et al list transmission probabilities for various sex acts and directionality of risk per unprotected sex acts for MSM, but these probabilities were derived from rectal and oropharyngeal gonorrhea prevalence among MSM in Australia[12] (rather than based in empirical transmission data), and employed extrapolations of penile-vaginal data to anal sex transmission probabilities. Understanding the risk of infection with exposure to N. gonorrhoeae at all anatomic sites is important for properly measuring the ways in which gonorrhea moves through a population.

Very few studies have addressed oropharyngeal *N. gonorrhoeae* transmission to other anatomic sites. Hook and Handsfield note that such transmission has been thought to be rare, but also note that there is evidence of transmission from the oropharynx to the urethra among MSM[13]. In a study conducted in the Seattle STD clinic, receiving fellatio was one of the strongest predictors of urethritis among MSM[14]. Yet, a study in the Philippines found that among more than 2,600 cases of gonococcal urethritis, only 46 cases occurred due to likely oral-genital transfer of *N. gonorrhoeae*[1]. We are not aware of any published reports on the transmission of *N gonorrhoeae* from the oropharynx to female sex partners through cunnilingus. In the HIM study, Jin and colleagues found an association between receptive oral-anal exposure and the risk of rectal *N. gonorrhoeae* infection[15]. However, in a German study of over 2,200 MSM, receptive oral-anal sex was not found to be a risk factor for rectal *N. gonorrhoeae*[16]. Studies conducted in the 1970s reported cases of possible oropharyngeal to oropharyngeal transfer of *N. gonorrhoeae*, although most were small and used culture-based diagnostic methods[5,17]. Importantly, Wiesner et al note, “There were no pairs of heterosexual or homosexual partners who had simultaneous oropharyngeal infection as the only manifestation of gonococcal disease”[5].

Data on isolation of *N. gonorrhoeae* in the saliva are sparse. Hallqvist and Lindgren found only 2 positive saliva samples out of 24 patients with culture-confirmed oropharyngeal *N. gonorrhoeae*[18]. However, in a study of 51 patients with culture-confirmed oropharyngeal *N. gonorrhoeae* infections, 34 (66.7%) also had positive saliva cultures[19]. A more recent study

found that 18% of MSM with oropharyngeal culture positive *N. gonorrhoeae* infections had culture positive saliva specimens, and 97% had NAAT positive saliva specimens[20]. Data are most limited on the potentially infectious role of saliva. In a study by Chow et al, using partner's saliva for lubricant was associated with rectal gonorrhea. However, the analysis appears to have included both MSM who did not use saliva for anal sex and MSM who did not report anal sex at all as the referent groups, and did not control for number of sexual partners[21]. In a study by Dudareva-Vizule et al, MSM were asked about using a partner's saliva as lubricant with three possible responses (yes, no, did not remember); in multivariable analysis, only "did not remember" was associated with rectal gonorrhea[16].

## How much population-level gonorrhea is attributable to oropharyngeal infections?

Again, limited data are available with respect to the prevalence and incidence of oropharyngeal gonorrhea, as well as the population-level impact of transmissions from an infected oropharynx. Incidence of oropharyngeal *N. gonorrhoeae* has been estimated to be 11.2 per 100 per-years among high-risk MSM in a community sample[22] and 0.16 per 100 person-years in a clinic-based sample[23]; prevalence among high-risk MSM seen at STD clinics is between 5 and 15%[16,24–26]. Retrospective record reviews have suggested that transmission from the oropharynx to the male urethra is potentially important[2,4,27], and one case-control analysis estimated the proportion of symptomatic gonococcal urethritis attributable to oral sex to be 34%[3].

## Does mouthwash kill infectious *N. gonorrhoeae* in the oropharynx?

To date, only one study has investigated the effect of mouthwash on oropharyngeal gonorrhea. Led by Chow et al.[28], this study investigated the effect of two alcohol-based mouthwashes compared with saline against *N. gonorrhoeae*, both in vitro and in a small randomized controlled trial among 58 MSM who were culture-positive when returning for treatment for pharyngeal gonorrhea. The authors found an inhibitory effect of both products in vitro at dilutions of 1:2 and 1:4 against a single wild-type isolate of *N. gonorrhoeae*. The study also demonstrated that rinsing and gargling with alcohol-based mouthwash for one minute significantly reduced the proportion of MSM who were culture-positive for gonorrhea on the posterior oropharynx or tonsillar fossae (84% vs. 52%, P=0.013) or tonsillar fossae alone (90% vs. 57%, P=0.016) compared with saline, while culture-positivity at the posterior oropharynx alone (70% vs. 57%, P=0.28) did not reach statistical significance. Although these results suggested that alcohol-based mouthwash may have some inhibitory effect against *N. gonorrhoeae*, it remains unknown whether mouthwashes (alcohol and non-alcohol based) can kill infectious *N. gonorrhoeae* in the oropharynx. In the randomized trial portion of the study, MSM were tested by culture only five minutes after using mouthwash or saline, and it is unknown whether the observed effect would have persisted for a longer duration. Furthermore, the variation in effect observed by pharyngeal site, with a non-significant effect in the posterior oropharynx, suggests that mouthwash may not successfully eliminate infection by *N. gonorrhoeae* in the oropharynx or its transmission to partners. A double-blind randomized clinical trial of mouthwash to prevent *N.*

*gonorrhoeae* is currently ongoing, although both the intervention and control mouthwashes used are alcohol-free.[29] A better understanding of the specific components of mouthwashes that may inhibit *N. gonorrhoeae* is needed.

## Conclusions

The hypotheses proposed by Zhang and colleagues are indeed provocative. Their collective work suggesting that a mouthwash intervention may reduce the duration of oropharyngeal gonorrhea among MSM is novel and innovative. However, estimating the population impact of a mouthwash intervention is more tenuous. Science is open to challenges to the norm, but requires well-documented and clear justifications and assumptions. The modeling exercise by Zhang et al illustrates the dearth of much-needed data on the epidemiology of oropharyngeal gonorrhea. Until a more comprehensive understanding of the key questions we outline above is developed, we advise caution in drawing specific inferences from mathematical models about kissing as a mode of gonorrhea transmission and the population-level effects of a mouthwash intervention.

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