Models of gonorrhoea transmission from the mouth and saliva

Christopher K Fairley, Vincent J Cornelisse, Jane S Hocking, Eric P F Chow

This Personal View argues for a new framework of gonorrhoea transmission in men who have sex with men in which the oropharynx plays a major role in transmitting gonorrhoea to, or acquiring gonorrhoea from, their partner's oropharynx, penis, or anorectum through either direct contact or via saliva. To avoid preconceived notions of transmission dynamics, we ask readers to imagine that they are investigating a new sexually transmitted infection. On the basis of the existing clinical and epidemiological data for gonorrhoea at the penis, oropharynx, and anorectum site, we develop two models for transmission: the so-called penile model and the so-called oropharyngeal model. We argue that the existing epidemiological data and behavioural data best fit the oropharyngeal model. Our argument rests on the observation that, at the population level, the prevalence of urethral gonorrhoea is too rare to explain the high incidence of oropharynx and anorectum infection. We describe studies of gonorrhoea detection in saliva, saliva use during sex, epidemiological studies of kissing and oropharyngeal gonorrhoea, as well as studies aided by mathematical models. Finally, we argue that the correlation between sexual acts (eg, kissing, oral sex, anal sex, and saliva use) is so high that any epidemiological study that does not measure these factors will be prone to confounding.

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Melbourne Sexual Health Centre, Alfred Health, Carlton, VIC, Australia (Prof C K Fairley PhD, Dr V J Cornelisse PhD, Prof J S Hocking PhD, E P F Chow PhD)**; Central Clinical School, Monash University, Melbourne, VIC, Australia** (Prof C K Fairley, Dr V J Cornelisse, E P F Chow)**; and University of Melbourne, Parkville, VIC, Australia** (Prof J S Hocking)

Correspondence to: Prof Christopher Fairley, Melbourne Sexual Health Centre, Carlton, VIC 3053, Australia **cfairley@mshc.org.au**

Introduction

Imagine this scenario: a new and apparently sexually transmitted infection (STI) is reported for the first time in men who have sex with men (MSM). Public health officials undertake the outbreak investigation recommended by the US Centre of Disease Control and Prevention (CDC), which includes verifying the diagnosis, constructing a working case definition, describing the epidemiology, and developing models that are evaluated and re-evaluated until the transmission dynamics are understood.[1] The new STI is *Neisseria gonorrhoeae*, an organism that is similar to *Neisseria meningitidis*, which is commonly carried in the nasopharynx.[2]

A case is defined as the detection of *N gonorrhoeae* at anogenital or oropharyngeal sites by culture or nucleic acid amplification testing (NAAT). Organisms can also be cultured at the urethra, oropharynx, anorectum, and in saliva.[3–6]

Clinical features, prevalence, and incidence

Urethral gonorrhoea is symptomatic in at least 90% of men following an incubation period of a few days (table 1).[7,8,12,13,21] Symptoms are uncommon at the rectum (<10%) and rare at the oropharynx (<10%).[7,23]

At a population level, the prevalence of urethral gonorrhoea is rare because urethral symptoms develop rapidly and prompt early treatment.[7,8,12] Table 1 provides estimates of the proportion of asymptomatic urethral gonorrhoea from two studies that specifically addressed this question using NAAT.[7,8] Using these studies, together with data for the incubation period and natural history of urethral gonorrhoea and assuming a relatively high incidence of ten cases per 100 person years from studies of HIV pre-exposure prophylaxis (PrEP), it is possible to estimate the point prevalence of urethral gonorrhoea of 0·42% (table 1).[8,12,13,15,22,24]

Oropharyngeal and anorectal gonorrhoea are more common (table 1) because symptoms at these sites are rare and coexisting urethral gonorrhoea is uncommon.[13,15,18,23–25] Estimates from MSM in STI clinic settings suggest a prevalence of up to 10% at the oropharynx or anorectum.[7,18,19,25]

There are few contemporary data for site-specific incidence of gonorrhoea, other than recent studies of STI screening (done every 3 months) as part of PrEP projects. The incidence of urethral, oropharyngeal, and anorectal gonorrhoea was nine, 15, and 24 infections, respectively, per 100 person years in one trial and in a PrEP demonstration project in Australia the estimates were similar (10·5, 19·7, and 22·6 per 100 person years, respectively).[15,24]

Sexual practices of MSM

Let us initially assume that gonorrhoea can be transmitted through any sexual practices that involve any contact between the three anatomical sites (urethra, oropharynx, or anus), or any exchange of infected fluids between these sites. A large US study[26] of 24787 MSM assessed self-reported sexual practices during a man's most recent sexual act with another man. Kissing was the most common sexual practice (75%), followed by giving (75%) or receiving (73%) oral sex. Anal sex (36% receptive and 34% insertive) and oroanal contact (25%) were less common. However, this study did not assess the frequency of tongue kissing when men had no other sexual contact with partners (ie, kissing-only partners). Tongue kissing was assessed in recent studies[23,27] that found MSM had similar numbers of kissing-only partners as partners who have kissing with sex,[23,27] hence MSM could have more kissing partners than previously appreciated.

Sites of gonorrhoea within sexual partnerships

Only one study[28] has assessed gonorrhoea at different anatomical sites in male couples using NAAT. The study found that 18 of 25 (72%) men with urethral gonorrhoea

	Description of studies and rationale for choice	Estimate and comments
Proportion of urethral gonorrhoea that is symptomatic in men	Barbee et al[7] reported that 216 (8%) urethral or urine samples from 2733 MSM were positive for gonorrhoea. 209 (97%) of the 216 positive samples were symptomatic. Ong et al[8] reported that 242 (3%) urethral and urine samples from 7090 MSM were positive for gonorrhoea. 215 (89%) of the 242 positive samples had urethral symptoms. Of note, men with no symptoms were eight times more likely to report recent contact with a man with gonorrhoea, suggesting they were in the incubation period when they were treated.[8]	The observation by Ong et al that men with asymptomatic urethral gonorrhoea are more likely to be contacts of men with gonorrhoea suggests that their estimate of the proportion who remain asymptomatic might be an overestimate. Given this overestimation, it is likely that at least 90% of MSM develop symptomatic urethral gonorrhoea. Some studies have assessed the presence of symptoms in screening studies or used retrospective recall of symptoms and found asymptomatic infection to be more common. However, these study designs will overestimate asymptomatic infection.[9–11]
Duration of untreated urethral gonorrhoea in men	Data were summarised by Garnett[12] from the preantibiotic era in a review paper. Handsfield et al[10] studied men with asymptomatic urethral gonorrhoea where treatment was withheld until symptoms developed or treatment was requested.[4,12–14]	Estimated to be 3 months.
Incubation period of urethral gonorrhoea in men	Harrison et al[13] reported a mean incubation period of 3·4 days in 44 sailors returning from shore leave who were given placebo prophylaxis.	Estimate taken as 1 week including the time to seek treatment.
Estimate of the prevalence of asymptomatic urethral gonorrhoea	No studies have undertaken community sampling to estimate the point prevalence of urethral gonorrhoea.	We estimated the prevalence of urethral gonorrhoea in MSM using the following estimates: the proportion of men who develop symptoms (90%),[7,8] the incubation period and time to see treatment (1 week),[8] and the duration of untreated asymptomatic gonorrhoea (assumed to be 3 months).[12] We used an incidence of 10 per 100 person years from PrEP studies.[15] Therefore, using incidence data to estimate prevalence (incidence and duration) and assuming 90% of cases were infectious for 1 week and 10% were asymptomatic and lasted 3 months untreated, the point prevalence of urethral gonorrhoea would be 0·42%. This estimate is likely to be lower in populations of MSM not taking PrEP.
Duration of untreated pharyngeal gonorrhoea	Wallin et al used culture to follow 18 individuals with pharyngeal gonorrhoea with repeat cultures every 2 weeks and found that all 18 individuals were negative on two consecutive cultures by week 12 (median time 6 weeks).[16] Using NAAT, a meta-analysis[17] used incidence and prevalence data to estimate an average duration of pharyngeal gonorrhoea to be about 4 months.	Estimate taken of about 3 months.
Duration of untreated anorectal gonorrhoea	There are no empirical studies of untreated anal gonorrhoea. Data from the meta-analysis by Chow et al[17] estimated the duration of untreated anorectal gonorrhoea to be about 12 months.	Estimate taken as 12 months.
Prevalence of anal and oropharyngeal gonorrhoea	Many estimates have been published from sexual health clinics. The rapidly rising proportion of gonorrhoea suggests recent estimates are more accurate.	Taken to be about 10% at the oropharynx and anorectum.[7,18–21]

MSM=men who have sex with men. NAAT=nucleic acid amplification test. PrEP=pre-exposure prophylaxis.

Table 1: **Studies describing key epidemiological estimates of gonorrhoea**

had a partner with oropharyngeal gonorrhoea and 19 of 25 (76%) men with urethral gonorrhoea had a partner with anorectal gonorrhoea.[28] When the authors of the study assessed oropharyngeal gonorrhoea in 48 couples in which one or more men had oropharyngeal gonorrhoea but no urethral gonorrhoea, there were 11 (23%) couples in which both men were infected at the oropharynx. Similarly, there was a strong concordance of gonorrhoea in the oropharynx of one man and the anorectum of another (11 of 32 men; 34%), again in the absence of urethral gonorrhoea. Gonorrhoea strains were genotyped in this study and were found to be identical between partners.[28]

Risk factors for gonorrhoea

To determine the sexual practices associated with gonorrhoea at each anatomical site (oropharynx, urethra, and anus) studies would need to include all the relevant sexual practices in which these sites, or fluid from these sites, make contact, including kissing and saliva use. Even if this were done, determining which specific sexual practice is responsible for gonorrhoea transmission is difficult because these practices frequently occur together during the same sexual episode. We were unable to identify any published studies that have assessed all potential sexual practices, including kissing and saliva use, in a single study (table 2).

Developing models about transmission

The next step recommended by CDC for investigating a new infection is to develop a model for its transmission.[1] We have developed two potential models for the transmission of gonorrhoea between men. In both models, we have not included direct penis-to-penis or anus-to-anus transmission because these are likely to be rare and data for relevant sexual practices is very limited.

In the penile model (figure), the penis can both transmit gonorrhoea to, and acquire gonorrhoea from, their partner's oropharynx or anus. In this model, other routes of transmission either do not occur or are rare, including direct transmission from the oropharynx to a partner's oropharynx or anus.

This model can easily explain the observed incidence of urethral gonorrhoea. However, with a urethral prevalence of 0·4%, only one in 250 sexual partners

	Study description	Comment
Proportion of men who have throat gonorrhoea who also have gonorrhoea identified in saliva	Three studies have assessed the proportion of individuals with oropharyngeal gonorrhoea who also have gonorrhoea in saliva. Using culture, the three studies found that 8%, 43%, and 67% of individuals with throat gonorrhoea had gonorrhoea culture positive saliva samples.[3,29,30] Only one study[3] used NAAT and found that saliva was positive in 100% of men who had a positive oropharyngeal swab.	The presence of gonorrhoea detected by culture in saliva when the oropharynx is positive indicates that saliva contains infectious organisms.
Epidemiological papers linking oral sex to oropharyngeal gonorrhoea	In this seminal study,[31] oropharyngeal gonorrhoea was found in 105 (20%) of 526 individuals with gonorrhoea at any site and who practices fellatio compared with 5 (3%) of 161 infected individuals who did not practice fellatio (p<0·001). In a separate study,[32] oropharyngeal gonorrhoea was associated with a higher number of oral sex partners.	Kissing and oral sex are closely correlated and not measuring kissing (which could be involved in transmitting gonorrhoea to the pharynx) could result in unmeasured confounding. No published study has measured all kissing exposures and oral sex.
Few studies have assessed kissing as a risk factor for oropharyngeal gonorrhoea	Templeton[33] found that kissing with sex was associated with oropharyngeal gonorrhoea in a crude (but not adjusted) analysis. However, kissing-only partners were not measured. Cornelisse[34] found both kissing and oral sex were associated with oropharyngeal gonorrhoea but correlation coefficient between kissing and oral sex was 0·87 making adjusted analysis difficult to analyse in this study. Kissing-only partners were not measured. Chow et al[27] found that kissing partners (with or without sex) were associated with oropharyngeal gonorrhoea but not sex partners where kissing did not occur.	Chow study was the only study to assess kissing partners with and without sex.
Site specific concordance of gonorrhoea in male couples	Only one study[35] has analysed site specific concordance in male couples using NAAT. The authors found that 11 (34%) of 32 men with anal gonorrhoea had a partner with throat gonorrhoea. After excluding couples with urethral gonorrhoea, in 48 couples at least one man had throat gonorrhoea and of these, in 11 couples both men had throat gonorrhoea. Genotyping of gonorrhoea samples showed identical strains between partners. The study[35] also showed that a high concordance of anal gonorrhoea in couples where neither man had urethral gonorrhoea but the anal gonorrhoea concordance was much lower when men with throat gonorrhoea were excluded.	The finding that throat to throat and anal to throat concordance was high in the absence of urethral infection suggests transmission between these two sites. Only studies using NAAT were included because of the low sensitivity for culture at the oropharynx and rectum.
Mathematical model	Only two mathematical models have been published using site specific models of gonorrhoea transmission between men.[36,37] The first model did not include transmission by kissing and could not sustain gonorrhoea transmission if the urethral prevalence fell below 1%.[36] The model by Zhang[37] included kissing and was able to sustain infection with a low urethral prevalence of gonorrhoea.	These two models suggest that when the urethral prevalence is low it is difficult to sustain gonorrhoea in an MSM population without invoking transmission between the oropharynx of men. If countries have poor access to health care for individuals with STIs, the urethral prevalence will be high without the need to invoke oropharyngeal transmission between men.
Neisseria meningitidis is transmitted by kissing	*N meningitidis* is from the same genus of bacterial as *N gonorrhoeae*.[2] *N meningitidis* commonly colonise the nasopharynx in about 10% of humans and a risk factor for infection is tongue kissing with multiple partners.	..

MSM=men who have sex with men. NAAT=nucleic acid amplification test.

Table 2: **Evidence to support oropharyngeal transmission**

would have an infected penis, and therefore to generate an observed incidence of 20% per year at the oropharynx or anus site would require about 100 partners per year, even if the probability of transmission is assumed to approach 100% per partner. The key problem with this model is that the prevalence of urethral gonorrhoea is too low to account for the high incidence of oropharyngeal or anorectal gonorrhoea without invoking other transmission routes.

In the oropharyngeal model (figure), the oropharynx can transmit gonorrhoea to, and acquire gonorrhoea from, their partner's oropharynx, penis, or anus through either direct contact or via saliva. This model could explain the observed site-specific incidences at the oropharynx and anus with only about ten partners per year. This prediction is based on the observation that the oropharynx and anus can acquire infection from their partner's oropharynx, which is commonly infected, rather than just the penis, which is rarely infected. This model also allows for direct transmission between the oropharynx of partners by kissing, and kissing is nearly three times as common as fellatio. The data supporting the additional routes of transmission proposed by the oropharyngeal model are further described in table 2.

Discussion

In this Personal View, we chose to describe gonorrhoea as a new infection to avoid existing assumptions about transmission. In this context, we presented two potential models that we generated when we followed the CDC guidelines for investigating new infections and only one model, the oropharyngeal model, was able to easily fit the observed site-specific prevalence and incidence of gonorrhoea. The primary reason the penile model was unable to explain the observed data was that the penis is infected for such a short time that there is insufficient opportunity for transmission to other sites. However, an important caveat of this conclusion is that it only applies in settings with accessible health care, as this is needed to prevent a high prevalence of urethral gonorrhoea.[23,35,38]

If the oropharyngeal model is correct, one might reasonably ask why it has been difficult to previously recognise the important role of the oropharynx in gonorrhoea transmission. The first likely reason is that the high prevalence of oropharyngeal gonorrhoea in MSM has only been recognised following the introduction of frequent oropharyngeal screening in this population using highly-sensitive NAAT since around 2009. Culture misses

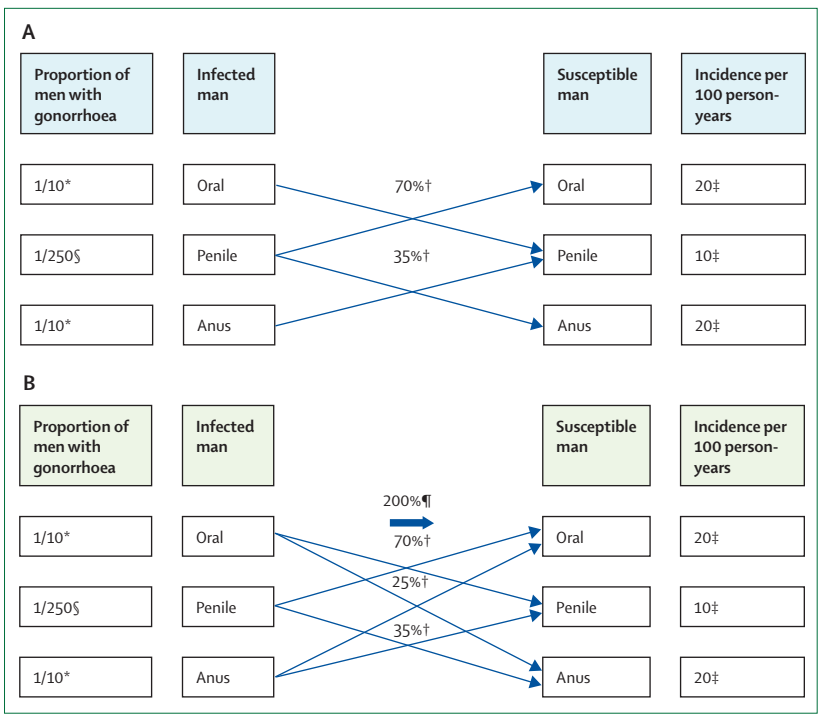

Figure: **Models of gonorrhoea transmission**
(A) Penile model of gonorrhoea transmission. (B) Oropharyngeal model of gonorrhoea transmission. Width of the arrows represents the relative proportion of sexual acts that involve each activity. The percentage is the proportion of sexual acts that involve that activity. *References 7, 8, 18–20, and table 1. †Reference 26. ‡References 15 and 21. §References 7, 8, 12, 15, and table 1. ¶Reference 23.

at least 50–80% of oropharyngeal gonorrhoea, which explains why oropharyngeal gonorrhoea was thought to be much less common in the era before NAAT.[7,18] The second possible reason why the high incidence of oropharyngeal gonorrhoea had not been previously appreciated is because there had been little published work on the incidence or duration of oropharyngeal gonorrhoea. Cohort studies (table 1) of MSM who take PrEP for HIV have now clearly documented a high oropharyngeal incidence of gonorrhoea in this population.[20,24] Importantly though, this high incidence could be an underestimate because it is possible that oropharyngeal gonorrhoea is relatively short lived.[17] Finally, it has also only been appreciated in the past 2 years how commonly MSM tongue kiss, including during non-sexual contact.[23,27] Questions on kissing have not been included in any national sex surveys and only rarely in other studies, except for those measuring the risk of acquiring *N meningitidis*.[2,23,33] However, a large, observational study[27] of 3677 MSM attending a sexual health centre, reported a high frequency of tongue-kissing. Sexually active men attending an STI clinic reported a mean of 4·3 kissing-only partners, 5·0 partners who have kissing with sex, and 1·4 partners who have sex and do not kiss in the preceding 3 months.[27]

The principal problem that arises when tongue-kissing is not measured in studies of STIs in MSM is that it results in unmeasured confounding if kissing were a risk factor for gonorrhoea transmission. Indeed, this confounding could have been present in a seminal paper[31] published in 1973 that used culture to assess the risks of acquiring oropharyngeal gonorrhoea. Oropharyngeal gonorrhoea was found in 105 (20%) of 526 individuals with gonorrhoea at any site and who practices fellatio compared with five (3%) of 161 infected individuals who did not practice fellatio (p<0·001).[31] Another paper[32] reported a significantly higher probability of having oropharyngeal gonorrhoea with increasing numbers of oral sex partners. However, neither of these two studies asked about tongue-kissing, which is highly correlated with oral sex within the same sexual act.[31,32] One study[34] has shown that the correlation between the number of partners for oral sex and kissing with sex was 0·87 and therefore separating them statistically is difficult in observational epidemiology without an extremely large sample size.

However, several studies have been published that provide other empirical evidence to support tongue-kissing as a route of transmission for oropharyngeal gonorrhoea (table 2). An Australian cross-sectional study[27] compared kissing practices and the number of sexual partners in those with and without oropharyngeal gonorrhoea, detected by NAAT. This study found that oropharyngeal gonorrhoea was associated with kissing partners, with or without sex, but was not associated with sex-only (no kissing) partners in MSM.[27] The same authors (table 2) presented data from a study[28] of male sexual partnerships in which oropharyngeal gonorrhoea was common in both partners, even in the absence of urethral gonorrhoea in either male partner (table 2). What is also interesting from this study is that the correlation between the oropharynx of one partner and anus of the other partner was also high (11 of 32 men; 34%), again in the absence of urethral gonorrhoea, suggesting transmission between the oropharynx and anus either directly or indirectly via saliva.[28] The specimens were genotyped and found to be identical.

Another study has also suggested that saliva could be the source of anorectal gonorrhoea.[39] In this study of 1312 MSM attending a sexual health clinic, 899 (69%) participants used their partner's saliva as a lubricant for anal sex in the past 3 months. This practice was associated with an increased risk of anal gonorrhoea when adjusted for other confounding factors, including condom use.[39] Similar associations have not been found for chlamydia.[40]

Saliva is also a plausible source of gonorrhoea, having been shown to contain viable *N gonorrhoeae* organisms in MSM who have been diagnosed with oropharyngeal gonorrhoea. In two studies[16,29] from the 1980s, investigators showed that 8–67% of culture positive oropharyngeal gonorrhoea were culture positive in the saliva. Additional studies have confirmed these culture estimates and also showed that *N gonorrhoeae* was invariably present in saliva in men with oropharyngeal gonorrhoea if NAAT was used.[3]

Importantly, the penile model could easily explain gonorrhoea transmission in populations in which the prevalence of urethral gonorrhoea is high. Indigenous populations living in remote areas of Australia are such an example and in these circumstances, poor access to health care results in individuals with symptomatic urethral gonorrhoea continuing to transmit their infections for substantial periods without treatment.[38,41] However, the argument that we present in this Personal View relates to urban populations of MSM, rather than people who live in areas with poor access to health care.

Some published papers suggest that the proportion of incident urethral gonorrhoea infections that are asymptomatic is greater than the 10% that we have estimated in table 1.[9–11] These were largely screening studies and had relied on retrospective recall of symptoms and are therefore likely to be biased towards overestimating asymptomatic infections. It is also true that clinic-based studies might underestimate asymptomatic infections, although the results of these studies will depend on how many asymptomatic individuals present for screening in the respective clinics. PrEP studies with STI screening three times a month provides an opportunity for more accurate estimates of asymptomatic incident urethral infection, although none of these studies have yet published such specific data.[15,24]

Mathematical modelling can provide some insight into the plausibility of specific transmission routes between different anatomical sites.[36,37] There have been three published models using transmission between anatomical sites.[36,37,42] The first model did not include kissing but importantly showed that gonorrhoea could not be sustained in a population when the prevalence of urethral gonorrhoea was low.[36] The second model, which included kissing as a possible transmission route, was able to sustain gonorrhoea transmission in the population even with a low prevalence of urethral gonorrhoea.[37] The final model tested several different scenarios using a urethral prevalence of about 5%.[42] This model found that endemic transmission could be sustained without transmission through kissing but the urethral prevalence that these authors used (5·1%) was much higher than we consider to be present in MSM populations with accessible health care.[42] However, this final study did highlight the paucity of available data for constructing such models and called for additional research to clarify the transmission dynamics.[42]

We have not discussed the transmission of gonorrhoea in heterosexual individuals but if our proposed modes of transmission in MSM are valid, it seems likely that they would also apply for heterosexuals. At this point in time however, almost no data are available for this group because screening of the oropharynx in heterosexual populations is not recommended. However, one study[31] from the 1970s provided estimates of oropharyngeal infection in heterosexual people at high risk and found that oropharyngeal infection was higher in women (32 of 538 women; 6·0%) than in men (three of 217 men; 1·4%). If the risk of transmission between men and women from kissing was the same as homosexual men then this proposal would argue against kissing as the key transmission risk. However the so-called missionary position is the most common sexual position in heterosexual couples, which involves the man lying on top of the woman. Therefore, if gonorrhoea was to be transmitted through kissing, kissing could be expected to result in men passing gonorrhoea more commonly to women than the reverse.[43] Gonorrhoea transmission by kissing between opposite-sex partners has received little attention. However, one study[44] described a sexual network (consisting of two males and five females), in which six of these seven individuals were diagnosed with oropharyngeal gonorrhoea in the absence of urogenital gonorrhoea, supporting the idea that, in this network, gonorrhoea was probably transmitted by kissing. Further discussion of transmission in heterosexuals is beyond the scope of this Personal View but, given the global importance of the organism on health, more research is urgently required.

It is important to accurately understand the transmission of gonorrhoea between men, because this will provide the opportunity for prevention strategies. If the oropharyngeal model is correct then condoms will be of little value for control, even if they will prevent some urethral infections. MSM rarely use condoms for orogenital intercourse, and since the widespread uptake of PrEP, MSM are increasingly not using condoms for anal intercourse, thus further undermining the effectiveness of condoms to prevent gonorrhoea transmission.[45] A potential, alternative prevention strategy for gonorrhoea is the use of antibacterial mouthwash to prevent oropharyngeal gonorrhoea, which is currently under evaluation in a large randomised controlled trial,[46] after it proved useful in a small trial[47] that found a reduction in culture positive gonorrhoea 5 min after mouthwash use. If antibacterial mouthwash were effective, a mathematical model has predicted substantial reductions in the population prevalence of gonorrhoea if 50% of MSM used mouthwash every day.[37] Observational studies have found oroanal sex (ie, so-called rimming) and the use of saliva as a lubricant for anal sex to be risk factors for anorectal gonorrhoea, so reducing these practices can also offer some potential reductions in prevalence.[39,48]

Finally, we must acknowledge the insights of earlier investigators in the 1980s who raised kissing as a potential route of transmission. Indeed, Hutt and Judson[29] said in their discussion that "we believe that prior epidemiological studies have not been adequate to disprove this hypothesis". More than 30 years later, data for kissing practices are still very scarce and almost no studies have linked these data to biological diagnoses of gonorrhoea.

Contributors

CKF conceived the idea of this debate and prepared the first draft. All authors made a substantial contribution to the design of this paper, provided important intellectual content, approved the final version, and agreed to be accountable for all aspects of the work.

Declaration of interests

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