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Certain attributes of the sexual ecosystem of high-risk MSM have resulted in an altered microbiome with an enhanced propensity to generate and transmit antibiotic resistance

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ABSTRACT

Surveillance data from a number of countries have indicated that antibiotic resistance in *Neisseria gonorrhoea* is strongly associated with men who have sex with men (MSM). This manuscript advances the hypothesis that certain features of the MSM sexual ecosystem may be responsible for this association. It is argued that in comparison with heterosexuals, high-risk MSM (hrMSM) have a higher prevalence of oro-penile, oro-rectal and anal sex which facilitates an enhanced mixing of the pharyngeal, rectal and penile microbiomes. In addition, hrMSM have an increased number of sexual partners per unit time and an increased prevalence of sexual relationships overlapping in time. The increased flux of microbiomes between different body habitats between sexual partners, in combination with the increased connectivity of the sexual network, serve to create a novel high-risk MSM sexual ecosystem with important consequences for the genesis and spread of antibiotic resistance.

Background

The rapid increase in antibiotic resistance in *Neisseria gonorrhoea* poses a real risk that gonorrhoea may become untreatable in the not too distant future [1,2]. A striking and under examined way that this resistance has been patterned over the past decade is how prominently high-risk men who have sex with men (hrMSM) population have featured in the spread of resistance. A number of different definitions of hrMSM have been suggested and used in the literature. These include reporting unprotected anal sex in the previous 6 or 12 months, participating in group sex, using recreational drugs during sex or having had more than 10 sexual partners in the previous 6 or 12 months [3–5]. Because there is no widely agreed upon definition of hrMSM we have used the term to refer to all those reporting any of these higher-risk activities. One estimate of the prevalence of high-risk sexual behaviors is provided by the European MSM Internet Survey (EMIS) of 174209 MSM from across Europe that found that 20% reported over 10 partners in the previous 12 months [6].

A molecular typing investigation of the rapid spread of plasmid mediated quinolone resistance in *N. gonorrhoea* in Scotland found that most cases (23/27) occurred in MSM [7]. In the United States (U.S.), quinolone resistance increased faster and reached higher levels among MSM (42.5% at peak) compared with patterns for heterosexual men (9.1% at peak) [8] (see Fig. 1). A recent survey of *N. gonorrhoea* resistance in the U.S. revealed that MSM have a significantly higher prevalence of resistance to all antibiotics tested (penicillin, cefixime, ceftriaxone, quinolones, tetracycline and azithromycin) [2]. Furthermore, across the surveillance project sites, the appearance of ciprofloxacin resistance in heterosexual men was positively correlated with such resistance having first emerged in MSM living in that area (Spearman rank correlation coefficient was 0.79, $p = 0.002$) [4]. *N. gonorrhoea* resistance to cephalosporins in the United Kingdom and the Netherlands is also more common in MSM than heterosexuals [9,10]. Explanations offered in the literature for this phenomenon include: increased travel of MSM puts them at risk of acquiring resistant mutations abroad [2], circuit parties provide a means to facilitate the spread of resistant sexually transmitted infections (STIs) [11], increased antibiotic usage [2], chemical differences in the rectum compared to other body sites [12,13], and MSM having an increased proportion of asymptomatic pharyngeal and rectal *N. gonorrhoea* infections [1].

In this manuscript, we advance the hypothesis that certain attributes of the hrMSM sexual ecosystem have resulted in a microbiome with an enhanced propensity to transmit antibiotic resistance. This argument is made in two steps. Firstly, we argue

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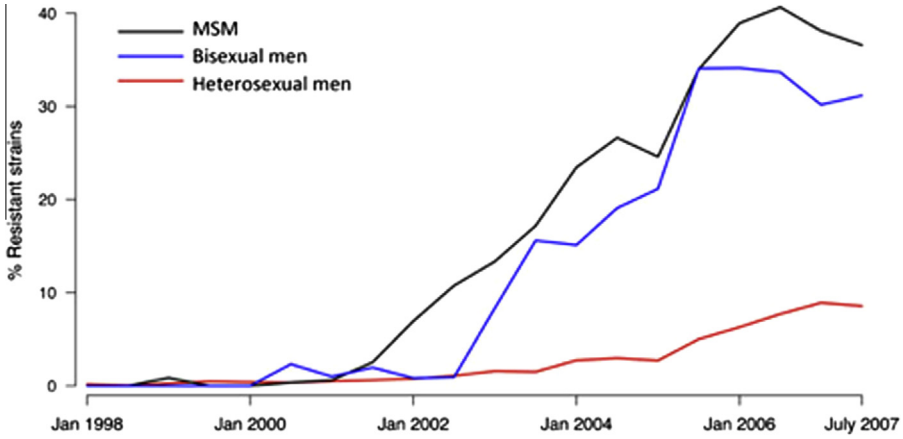

Fig. 1. Semiannual prevalence of resistance to ciprofloxacin in *Neisseria gonorrhoeae* isolates from the Gonococcal Isolate Surveillance Program for men who have sex with men (MSM), heterosexual men, and bisexual men (reproduced from Ref. [8]).

that there are a number of risk-factors found to be more prevalent among hrMSM than heterosexual groups, which could generate important differences in the composition of the microbiomes. Secondly, we claim that the combination of these risk factors results in a novel hrMSM sexual ecosystem with important consequences for the genesis and spread of antibiotic resistance.

The theoretic framework we use is a multi-level ecological-evolutionary framework as it includes a broad range of resistance determinants. In particular, it is becoming increasingly apparent that the selection for antibiotic resistance occurs at multiple interlinked hierarchical levels, from the level of separate genetic sequences (genes, operons, mobile genetic elements), to the cellular and supra-cellular levels (cells, clones, clonal complexes, species, communities, and ecosystems) [14]. At infra-cellular levels, antibiotics influence the abundance and spread of plasmids, transposons and the like [15]. At the level of bacterial clones evidence is accumulating that the spread of particular bacterial clones is responsible for a disproportionate amount of antibiotic resistance around the world [16]. Antibiotic usage is responsible for selecting certain clones and may also lead to the development of genetic exchange communities that share antibiotic resistance genes [15]. Second order selection may then occur, whereby, if both the most fit resistance providing platform and the most resistant clones are selected for, their ability to acquire further resistance traits would be enhanced [14].

Dynamics at each of these levels can influence the genesis and spread of resistance. More generally, the spread of antibiotic resistance depends on the construction of interactive networks able to exchange resistance genes between organisms. An accurate description of the sexual ecosystem, including the makeup of various habitats through which STIs and resistance mechanisms pass and how these components are linked, is thus an important task in understanding the genesis and spread of resistance in STIs.

The hypothesis

Step one: The higher prevalence of three risk factors in hrMSM could generate a distinct sexual ecosystem[1]

1. A more interconnected sexual ecosystem

Penile–anal (henceforth termed anal sex), penile–oral (henceforth termed oral sex) and oro-anal sex have been found to be more frequently practiced in MSM than heterosexual dyads (see Table 1) [17–22]. Although penile–anal sex occurs in heterosexual dyads, it occurs in a limited proportion and where it occurs, it does so infrequently [23,24]. In a representative sample of the U.S. population, for example, 9% of women reported having had anal intercourse in the past year, yet, only 1.2% had anal sex during their most recent sexual event [20]. Oro-anal sex is also regarded as rare in heterosexual dyads [25]. In addition, both members of a MSM (but not a heterosexual) partnership can, and commonly do, practice receptive and insertive anal and oral sex [25]. The net effect of these differences creates a more interconnected ecosystem between the component habitats of the MSM sexual ecology – the penis, rectum and oropharyngeal (PROP) sites. A few key features of the way this ecosystem is connected are outlined in Fig. 2, which compares the MSM and heterosexual sexual ecologies in hypothetical dyads. In the heterosexual dyad, the strongest links are between the two genital habitats and between the two oropharyngeal systems, thereby rendering the rectal ecosystem considerably more isolated than in the MSM dyad. Only the rectum of the woman is part of the sexual ecosystem and it is only linked to the other sites by a relatively lower frequency of anal sex (and this in a minority of couples). In the MSM dyad, not only are all six ecosystems linked, but they are interlinked via multiple pathways. Two caveats should be noted with regard to this diagram. Firstly, not all MSM engage in each of the sexual practices outlined in this diagram. This depiction thus represents a maximal representation of how interconnected the MSM ecosystem could be. Secondly, not all microbiologically relevant sexual practices are represented here – the use of fingers in anal and genital sex is an obvious example – see Table 1 for the prevalence of these behaviors.

2. In most populations with available comparative information, MSM report having had significantly more sexual partners over the past year and over their lifespan than heterosexual men or women (see Table 1) [17,18,20–22,26–28].
3. A frequent finding is an increased prevalence of sexual relationships overlapping in time (sexual partner concurrency) in MSM compared to heterosexual networks [22,29–35]. This has an effect of increasing the connectedness of the sexual network, whilst removing the protective effect of the gap between partnerships that occur in serial monogamous relationships [36].

[1] It is to important to stress that there are large differences in MSM sexual behavior and the norms which underpin these between different individuals, partnerships and communities both across time and place. As such, the results will not likely be generalizable to MSM more broadly.

Table 1
Comparison of prevalence (reported in percentages) of certain sexual practices by men who have sex with men (MSM) and heterosexual men and women in the USA, Britain and Australia.

Survey description	Type of sex	MSM	Heterosexual men	Heterosexual women
ASHR. A nationally representative sample of 10,173 men and 9134 women aged 16–59 years from Australia in 2001–2 [17,18]	Oral sex insertive (MRS*)	75.9	30.3	
	Oral sex receptive (MRS)	75.1		23.7
	Anal sex insertive (MRS)	37.5	0.9	
	Anal sex receptive (MRS)	29.8		0.7
	Vaginal sex (MRS)		95.9	93.9
	No. sex partners lifetime (mean)	79.1	16.7	6.5
	No. sex partners lifetime (median)	32	8	3
	No. sex partners in last year (mean)	10.7	1.5	1.0
	No. sex partners in last year (median)	2	1	1
NHSLS. A nationally representative probability sample of 1511 men and 1921 women aged 18–59 years from the USA conducted in 1992 [20]	Oral sex insertive	89.5		
	Oral sex receptive	89.5		
	Anal sex insertive	75.7	10	
	Anal sex receptive	81.6		9
NATSAL II. A national probability sample of 11 161 persons aged 16–44 living in the Britain in 2000 [80,81]	Any oral sex in last year	73.6		
	Any anal sex in last year	62.6		
	Any oral sex in last 28 days	57.8		
	Any anal sex in last 28 days	40.2		
	No sex partners last 5 years (Mean)	24.1	3.8	2.4
	No sex partners last 5 years (Median)	4	1	1
ACHA–NCHA 2009. Survey of 25,553 students from 57 universities in the USA in 2009 [28]	Anal sex in last 30 days	53.9	6.1	4.4
	Vaginal sex in last 30 days	2.2	66.9	72.3
	Oral sex in last 30 days	74.5	59.3	59.7
Survey of every second person entering one of two gay bars in Adelaide, Australia, in 1988, $n = 172$ [79]	Analingus insertive	23.6		
	Analingus receptive	47.2		
	Digitoanal insertive	64.5		
	Digitoanal receptive	54.0		
	Oral sex insertive	87.7		
	Oral sex receptive	89.1		
	Anal sex insertive	61.9		
	Anal sex receptive	48.5		

* MRS – at most recent sex, ASHR – Australian Study of Health and Relationships, ACHA–NCHA – ACHA National College Health Assessment, NHSLS – National Health and Social Life Survey, NATSAL – National Surveys of Sexual Attitudes and Lifestyles. Empty cells represent missing data.

Step two: The combination of these risk factors results in a novel hrMSM sexual ecosystem with important consequences for the genesis and spread of antibiotic resistance

A. Consequences of increased connectivity between the PROP sites

Pharyngeal ecosystem. The prevalence of pharyngeal gonorrhoea in select groups of MSM is between 9% and 15% [37]. The increased frequency of oro-penile and oro-anal sex in MSM noted above likely increases the probability of acquiring pharyngeal gonorrhoea [1]. Three aspects of the pharyngeal milieu may be relevant to the genesis of resistance. Firstly, most pharyngeal gonorrhoea is asymptomatic [38]. Secondly, due to differential antibiotic penetration into genital and pharyngeal sites, the cure rate for pharyngeal gonorrhoea is lower than other sites [39]. Pharyngeal gonococci may therefore have a survival advantage and persist through periods of antibiotic therapy, which may in turn select for antibiotic-resistant forms of gonorrhoea [39,40]. Thirdly, the pharynx provides a location where *N. gonorrhoea* is able to exchange genetic material (including antibiotic resistance genes) with various abundant commensal Neisseriae species. Acquisition of the mosaic form of the penicillin-binding protein 2 (PBP2) from these commensals is thought to have been important in the genesis of cephalosporin resistance [41]. The higher prevalence of *N. gonorrhoea* at this site in MSM, combined with intermittent antibiotic usage, may increase the probability of this process occurring in MSM groups. This is illustrated in Fig. 2, where the pharyngeal *N. gonorrhoea* in individual A acquires a mosaic PBP2 from neisserial commensals, thereby conferring partial resistance to cephalosporins. The mutant *N. gonorrhoea* (red bacterium) can now travel via oral sex to the penis of individual B and then via anal sex to the rectum of A.

Rectal ecosystem. In the rectum, *N. gonorrhoea* is also likely to be an asymptomatic relatively long-lived infection exposed to intermittent antibiotic pressure. Approximately 85% of rectal *N. gonorrhoea* infections are asymptomatic [38]. In addition to antibiotic pressures, it is under selective pressure to adapt to the abundant hydrophobic agents present in the lower gastrointestinal tract (GIT). Survival and fitness can be enhanced by *N. gonorrhoea* acquiring a *mtrR* mutation that effects an increased flux of toxic hydrophobic agents, such as antibiotics, out of the bacteria [12,13]. In a number of studies, rectal isolates of *N. gonorrhoea* from MSM have been found to be more likely to harbor mutations in either the *mtrR* gene or the *mtrR* promoter region [12,42].

The GIT is of special significance as it contains the largest and most diverse microbial community in the human body, including multiple mechanisms for antibiotic resistance. A sexual ecosystem such as the MSM one that includes a significant component in the GIT may provide increased opportunities for STIs to acquire antibiotic resistance mutations. Each gram of fecal matter contains 10^{10}–10^{11} bacterial cells [43]. Given mutation rates of approximately 2×10^{-3} per genome per replication, and genome sizes around 5×10^{6} base pairs, 1 g of fecal matter is likely to include at least one newly occurred instance of every single point mutation possible in bacterial genomes [43]. Therefore, the lower GIT is able to provide a considerable scope of point-mutations and homologous recombination. There are also a large range of resistance conferring plasmids and bacteriophages available for heterologous recombination, as shown in the rectum of MSM A in Fig. 2, who acquires a *mtrR* and a *penB* mutation in addition to a TetM-encoding plasmid conferring resistance to tetracyclines [1].

The GIT mucosa differs from other mucosal sites in important respects. Although all mucosal sites need to tolerate commensal

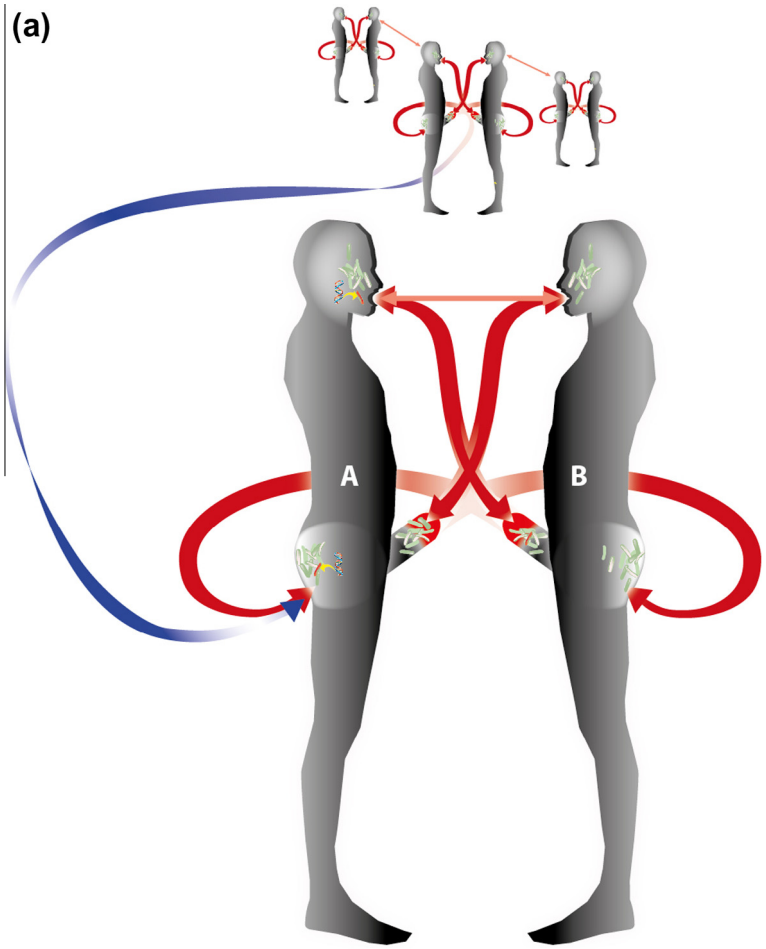

Fig. 2. Two features of the hrMSM sexual ecology (a) which could result in differences in microbiomes, STI spread and the spread of antibiotic resistance using the example of *N. gonorrhoea* (as compared to heterosexual networks – b). (1) Microbes can be transmitted from the rectum to the pharynx and the penis/between the penis, rectum and pharynx within one partnership. The increased prevalence of oro-penile, oro-anal and penile-anal sex leads to an enhanced opportunity for mixing or organisms and genetic material from the GIT, oropharynx and penis. (The oro-anal and digital modes of transmission are not depicted for stylistic reasons.) (2) The increased number of sexual partners and higher prevalence of sexual partner concurrency increase the connectivity of the sexual network thereby making it easier for microbes to spread through the network.

organisms, the size and complexity of the colonic microbiome requires a greater tolerance. As a result, the expression of toll-like receptors and CD14 on the apical surface of the GIT epithelium is strongly down-regulated [44]. In addition, numerous commensals release substances that antagonize inflammatory responses [45]. An ecosystem characterized by enhanced tolerance may facilitate longer-term asymptomatic carriage of *N. gonorrhoea*, which may in turn offer a longer time period for the gonococcus to undergo antibiotic selection pressure and exchange of genetic material.

Highly connected microenvironments, such as the lower GIT, also offer the opportunity for clonal diversification, which enables a higher probability of long-term persistence in complex adaptive landscapes [14]. It has been argued along these lines that there may be an acceleration of the emergence of antibiotic resistance in connected microenvironments such as the GIT [46].

B. Consequences of interconnected sexual networks

An increased number of sexual partners and a higher prevalence of sexual partner concurrency could have at least two relevant effects. Firstly, increasing the connectivity of a sexual network makes it easier for microbes to spread [36,47], thereby potentially affecting the optimum virulence-transmissibility balance of a STI. This, in combination with antimicrobial pressure, may enable microbes with more costly repertoires of resistance genes to spread [48]. Secondly, concurrent partnering removes the gap between new and old partners [36]. This gap may be longer than the time a microbe can survive outside its preferred site of residence, in which case the gap would protect against the spread of that microbe [49]. This protective effect is absent in the setting of concurrent relationships. For example, a number of GIT microbes would not be expected to survive for more than a few days to weeks in the coronal sulcus/urethra. In the setting of serial monogamy with an average gap of a month or longer between relationships, the GIT microbes a man acquires on his penis from anal sex with his previous partner would not survive to be transferred to the GIT of his next partner. In the setting of concurrency or more rapid serial monogamy, this protective effect of partner sequencing is lost.

Discussion

It is not just in the case of *N. gonorrhoea* that antibiotic resistance has been found to be more prevalent in hrMSM groups [7]. Although study findings have varied, at least one study has found that MSM have an elevated risk for acquiring methicillin-resistant *Staphylococcus aureus* infections [50]. Outbreaks of ciprofloxacin-resistant *Shigella sonnei* [51] and *Campylobacter jejuni* [52], as well as an outbreak of *Shigella* with reduced susceptibility to azithromy-

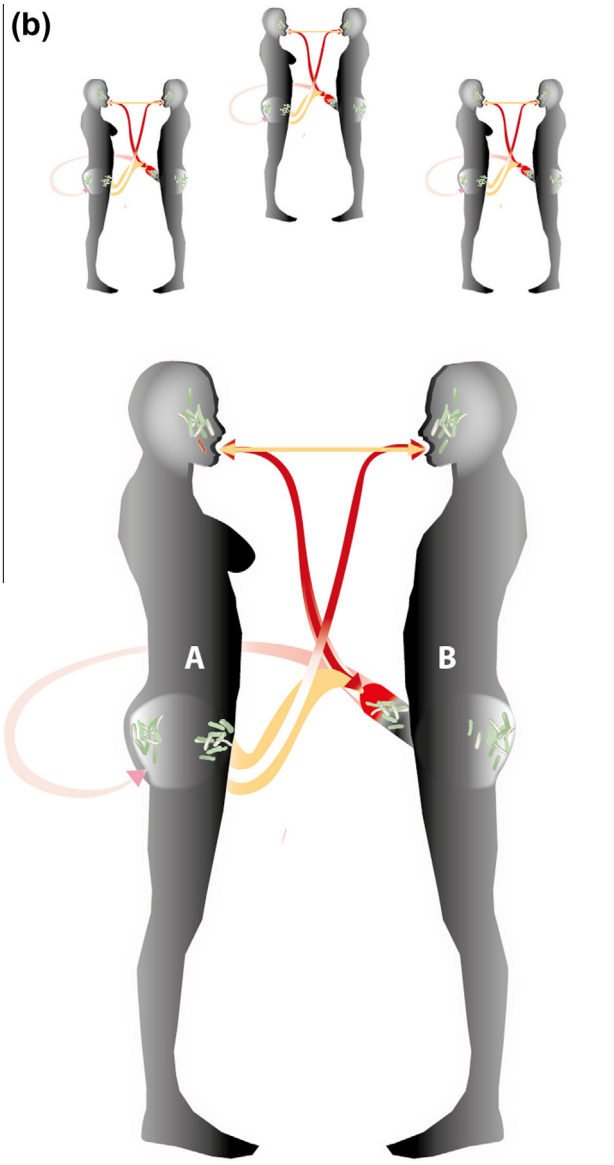

Fig. 2 (*continued*)

cin [53] among MSM have been described. It is possible for the enteric organisms to be sexually transmitted or via the fecal oral route. In a study of 141 *Treponema pallidum* containing genital ulcer specimens from patients from 11 clinics across the United States, samples from MSM (65/82 samples) were found to be more likely than women and other men (8/57 samples) to carry the macrolide-resistance associated A2058M mutation [54].

It should be noted that not all studies have found elevated rates of antibiotic resistance in MSM, and for those studies which have, they may not have adequately controlled for all possible confounders. In addition to the associations between resistance and hrMSM noted above, there are three other lines of evidence which suggest that there may be other singularities in the makeup of the hrMSM microbiome:

Firstly, a number of studies have documented an increase in the incidence and prevalence of a range of viral, bacterial and eukaryotic STIs in MSM groups compared to general male populations. These include organisms whose main mode of transmission is non-sexual: a number of protozoan species [56–58], a range of bacterial species (various *Campylobacter* [52,59] and *Shigella* [57,60] species, *Corynebacterium diphtheria* [61], *Salmonella typhi* [62], *Helicobacters cinaedi* and *fennelliae* [59] and *Neisseria meningitidis* [63]), a number of helminthic species including enterobius and strongyloides [64], and viruses Hepatitis A [57] and C [65].

Secondly, there are considerable differences in the strains of *Chlamydia trachoma* and *N. gonorrhoea* that circulate in MSM and heterosexual networks. As far as *C. trachoma* is concerned, genovars E, D, I, J and F are highly prevalent in heterosexual populations around the world, while genovars G, D, J, L2b predominate in MSM populations [66,67]. Detailed genetic analysis of why there is such a segregation of strain circulation according to sexual orientation and site of infection concluded that both tissue tropisms, as well as epidemiological network structures were responsible [66]. There are also clear differences in the strains of *N. gonorrhoea* circulating in MSM and heterosexual networks. This remains the case when the strains are typed by auxotypes [68], serotypes [69] or phylogenetically [70].

Thirdly, no etiology is found in a higher proportion of non-gonococcal urethritis (NGU) and pharyngitis cases in MSMs (as compared with heterosexual men) [71]. The fact that the pathogen-negative cases of NGU in MSM were significantly more likely to report unprotected oral sex as the only exposure increases the possibility that other (untested for) oropharyngeal pathogens may play an etiological role in NGU [71]. Likewise, in MSM the practice of oro-penile sex has been found to be associated with pharyngitis independent of the presence of pharyngeal *N. gonorrhoea* [72]. In a similar vein, no known pathogen is found in a considerable proportion of MSM with proctitis [64,73,74].

These three types of evidence suggest that there may be more extensive differences in the makeup of the hrMSM microflora, as compared with men who have sex with women (MSW). What determines these differences? There are a number of alternative explanations for variations in antibiotic resistance prevalence by sexual orientation that merit further investigation. Whilst increased travel by MSMs has been hypothesized to be relevant, detailed multivariate studies have not found travel to be a predictor of resistance [2,9]. Much of the travel data in the United States analyses was missing meaning that an association cannot be ruled out. Recent usage of antibiotics is another possibility. One study found that MSM with a diagnosis of gonorrhoea were more likely to report previous antibiotic usage than MSW. After controlling for this, however, MSM remained a significant risk factor for *N. gonorrhoea* resistance to all classes of antibiotics tested [2].

Although the relationship is debated, HIV-infection has been associated with various forms of antibiotic resistant infections [75–77]. Elevated resistance rates in hrMSM groups could be caused by a higher prevalence of HIV. For example, a recent study revealed a univariate relationship between cephalosporin resistance in *N. gonorrhoea* and HIV infection. However, this relationship disappeared on multivariate testing [9].

A further possibility and one that could explain why the link between hrMSM and gonorrhoea antibiotic resistance may be a recent phenomenon is that the resistance is driven by increased rates of oral sex in hrMSM. A number of sexual behavior surveys in MSM have noted a substitution of anal sex for oral sex as a way of decreasing the risk of HIV acquisition [78,79]. This could lead to the genesis and spread of resistance through the pathways outlined above.

Testing the hypothesis

One way to test this hypothesis would be to follow up high-risk cohorts of MSM and MSW (and their partners) by regular sampling and characterizing their rectal, urethral, coronal-sulcal and oropharyngeal microbiomes, mobilomes and resistomes. Special emphasis could be placed on assessing the presence and properties

of *N. gonorrhoea*, including the genesis and movement of antibiotic resistance determinants. The assessment of the microbiomes would best be conducted within a multi-level ecological framework that pays careful attention to factors at each level which could influence the creation and spread of antibiotic resistance. This would require close sexual behavioral monitoring in order to accurately track how changes in the microbiomes correlate with particular sexual practices and practices of their partner(s).

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Conflict of interest statement

The authors declare that they have no conflict of interest.

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Nil.

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