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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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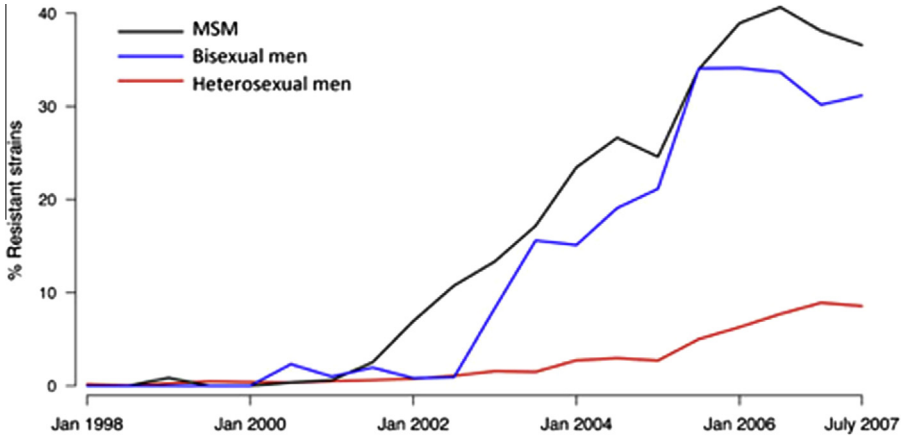

Fig. 1. Semiannual prevalence of resistance to ciprofloxacin in *Neisseria gonorrhoeae* isolates from the Gonococcal Isolate Surveillance Program for men who have sex with men (MSM), heterosexual men, and bisexual men (reproduced from Ref. [8]).

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.