Antibiotic-resistant *Neisseria gonorrhoeae* spread faster with more treatment, not more sexual partners

Stephanie M. Fingerhuth1,2,*, Sebastian Bonhoeffer1, Nicola Low2, Christian L. Althaus2

Abstract

The sexually transmitted bacterium *Neisseria gonorrhoeae* has developed resistance to all antibiotic classes that have been used for treatment and strains resistant to multiple antibiotic classes have evolved. In many countries, there is only one antibiotic remaining for empirical *N. gonorrhoeae* treatment and antibiotic management to counteract resistance spread is urgently needed. Understanding dynamics and drivers of resistance spread can provide rationales for antibiotic management. In our study, we first used antibiotic resistance surveillance data to estimate the rates at which antibiotic-resistant *N. gonorrhoeae* spread in two host populations, heterosexual men (HetM) and men who have sex with men (MSM). We found higher rates of spread for MSM (0.86 to 2.38 y\(^{-1}\), mean doubling time: 6 months) compared to HetM (0.24 to 0.86 y\(^{-1}\), mean doubling time: 16 months). We then developed a dynamic transmission model to reproduce the observed dynamics of *N. gonorrhoeae* transmission in populations of heterosexual men and women (HMW) and MSM. We parameterized the model using sexual behavior data and calibrated it to *N. gonorrhoeae* prevalence and incidence data. In the model, antibiotic-resistant *N. gonorrhoeae* spread with a median rate of 0.88 y\(^{-1}\) in HMW and 3.12 y\(^{-1}\) in MSM. These rates correspond to median doubling times of 9 (HMW) and 3 (MSM) months. The model shows the difference in the host population’s treatment rate rather than the difference in the number of sexual partners explains the differential spread of resistance. As higher treatment rates result in faster spread of antibiotic resistance, treatment recommendations for *N. gonorrhoeae* should carefully balance prevention of infection and avoidance of resistance spread.

Keywords

*Neisseria gonorrhoeae* — drug resistance, bacterial — antimicrobial resistance — mathematical model — sexually transmitted infection — epidemiology

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Introduction

Antibiotic-resistant *Neisseria gonorrhoeae* can evolve and spread rapidly [1]. Resistance is commonly observed against the antibiotic classes penicillin, tetracycline and fluoroquinolones [2, 3, 4]. Resistance also emerged against cefixime, an oral third generation cephalosporin, in recent years [2, 3]. Since 2010, cefixime is no longer recommended as first-line treatment [5] following guidelines from the World Health Organization (WHO) that an antibiotic should not be used when more than 5% of *N. gonorrhoeae* isolates are resistant [6]. Injectable ceftriaxone, in combination with oral azithromycin, is now the last antibiotic remaining as recommended first-line treatment [7]. Although other antibiotics are being tested for their safety and efficacy for *N. gonorrhoeae* treatment [8], no new classes of antibiotics are currently available [4] and management of antibiotics is urgently needed to preserve their efficacy. The current management strategy tries to counteract resistance spread by expanded screening and treatment of hosts [9, 10], but the outcome of this strategy is uncertain. Understanding the drivers of resistance spread and anticipating future resistance trends will provide rationales for antibiotic management and help to improve antibiotic treatment strategies.

Men who have sex with men (MSM) host populations have higher levels of antibiotic-resistant *N. gonorrhoeae* than heterosexual host populations [3]. In a study [5] based on the Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) in England and Wales, cefixime-resistant *N. gonorrhoeae* were mainly found in MSM until 2011. The authors suggested that cefixime resistance was circulating in a distinct sexual network of highly active MSM and that bridging between MSM and heterosexuals was necessary for subsequent spread among heterosexual hosts. However, cefixime-resistant *N. gonorrhoeae* might have already been spreading undetectably in the heterosexual host population.

Mathematical models can help explain the differential observations of antibiotic-resistant *N. gonorrhoeae*
in different host populations. In 1978, Yorke et al. [11] introduced the concept of core groups to model the transmission of \textit{N. gonorrhoeae}. The concept of core groups describes that an infection can only be maintained in a host population if there is a highly sexually active group of hosts responsible for a disproportionate amount of transmissions. More recent modeling studies have examined the transmission of antibiotic-resistant \textit{N. gonorrhoeae}. Chan et al. [12] found that prevalence rebounds more quickly to a pre-treatment baseline when treatment is focused on the core group. Xiridou et al. [13] developed a \textit{N. gonorrhoeae} transmission model to determine the impact of different treatment strategies on the prevalence of \textit{N. gonorrhoeae} in Dutch MSM. They found that increased treatment rates could increase the spread of resistance, whereas re-treatment could slow it down. Hui et al. [14] used an individual-based \textit{N. gonorrhoeae} transmission model in a heterosexual host population to investigate the effect of a molecular resistance test on transmission. This allowed us to determine the major driver of resistance spread. This allowed us to determine the major driver of resistance spread in HetM and heterosexual host populations.

In this study, we investigated the dynamics and determinants of antibiotic-resistant \textit{N. gonorrhoeae} spread using surveillance data and mathematical modeling. We estimated the rates at which resistance spreads in heterosexual men (HetM) and MSM using surveillance data from the USA and from England and Wales. We then developed a mathematical \textit{N. gonorrhoeae} transmission model to reconstruct the observed dynamics of resistance spread. This allowed us to determine the major driver of resistance spread, and to explore the expected rates at which resistance spreads in MSM and heterosexual host populations.

**Methods**

**Data**

**Data sources** We used data from the GRASP [15, 16] and the Gonococcal Isolate Surveillance Project (GISP) [17]. GRASP is a program of Public Health England (PHE) that monitors antibiotic-resistant \textit{N. gonorrhoeae} in England and Wales. GISP is an equivalent program from the Centers for Disease Control and Prevention (CDC) in the USA. We used Plot Digitizer 2.6.6 [18] to digitize data on the proportion of cefixime- and ciprofloxacin-resistant \textit{N. gonorrhoeae} from figures that were published online (see S1 Table, S2 Table).

**Rate of spread** We determined the rate of resistance spread by assuming that the proportion of antibiotic-resistant \textit{N. gonorrhoeae} follows logistic growth. We used the least squares function \texttt{nls} from the R software environment for statistical computing [19] to fit the following function to the data:

\[
f(t) = \frac{c}{1 + a \exp(-bt)}.
\]

\(f(t)\) represents the proportion of antibiotic-resistant \textit{N. gonorrhoeae} at time \(t\), \(c\) is the maximal proportion of antibiotic-resistant \textit{N. gonorrhoeae} (carrying capacity), \(a\) is the ratio between antibiotic-sensitive and -resistant \textit{N. gonorrhoeae} at time 0, and \(b\) is the rate at which the proportion of antibiotic-resistant \textit{N. gonorrhoeae} increases in the initial exponential growth phase. We only used data from the years before the first decline in the proportion of resistant \textit{N. gonorrhoeae} because we were interested in the rate of resistance spread during the initial exponential growth phase and while the antibiotic was still used.

**Model**

**Transmission model** We developed a mathematical model to describe the spread of antibiotic-resistant \textit{N. gonorrhoeae} in a given host population [12]:

\[
\begin{align*}
S_i &= -S_i \nu \sum_{j=1}^{n} \rho_{ij} \beta_{ij} \frac{I_{Sen_j} + \gamma S_j}{N_j} + \nu \sum_{j=1}^{n} I_{Sen_j}, \\
-\alpha S_i + \alpha N_j - \gamma S_i + \gamma N_j \sum_{j=1}^{n} S_j, \\
I_{Sen_i} &= S_i \nu \sum_{j=1}^{n} \rho_{ij} \beta_{ij} \frac{I_{Sen_j}}{N_j} - \nu I_{Sen_i} - \tau I_{Sen_i}, \\
-\alpha I_{Sen_i} + \gamma I_{Sen_i} + \gamma N_j \sum_{j=1}^{n} I_{Sen_j}, \\
I_{Res_i} &= S_i \nu \sum_{j=1}^{n} \rho_{ij} \beta_{ij} \frac{I_{Res_j}}{N_j} - \nu I_{Res_i} + \tau \mu I_{Sen_i}, \\
-\alpha I_{Res_i} + \gamma I_{Res_i} + \gamma N_j \sum_{j=1}^{n} I_{Res_j},
\end{align*}
\]

\(X\) denotes the \textit{N. gonorrhoeae} strain (antibiotic-sensitive/-resistant) and \(i\) represents the sexual activity group, \(m = 2\) is the number of \textit{N. gonorrhoeae} strains and \(n = 2\) is the number of sexual activity groups in the host population (Fig. 1). Each sexual activity group consists of susceptible hosts, \(S\), hosts infected with an antibiotic-sensitive strain, \(I_{Sen_i}\), and hosts infected with an antibiotic-resistant strain, \(I_{Res_i}\). Hosts can change their sexual behavior, i.e. change from one activity group to the other, at rate \(\gamma\) [20]. They can also leave or enter the population at rate \(\alpha\). Susceptible hosts become infected depending on the partner change rate, \(\pi\), the transmission probability per partnership, \(\beta\), and the sexual mixing matrix \(\rho\) which describes how many partnerships are formed within and outside the host’s activity group:

\[
\rho = \varepsilon \delta_{ij} + (1-\varepsilon) \frac{\pi_{ij}}{\sum_{k} \rho_{ik} J_{ik}}.
\]
change rates are $\pi_1 = 0.25 \, \text{y}^{-1}$ and $\pi_2 = 4.57 \, \text{y}^{-1}$ with 6.3% of the population being in the high sexual activity group. The obtained partner change rates for MSM are $\pi_1 = 0.41 \, \text{y}^{-1}$ and $\pi_2 = 30.49 \, \text{y}^{-1}$ with 5.3% of the population belonging to the high sexual activity group.

We calibrated the sexual mixing coefficient, $\epsilon$, the fraction of diagnosed and treated infections, $\phi$, the average duration of infection, $D$, and the per partnership transmission probabilities within the low, $\beta_{HL}$, and the high sexual activity group, $\beta_{HH}$, to N. gonorrhoeae prevalence and incidence using the following algorithm:

1. Define prior parameter distributions (Table 1).
2. Define the ranges for the expected prevalence and incidence of diagnosed infections (Table 2) of urethral and cervical N. gonorrhoeae infections for HMW, and urethral, rectal and pharyngeal infections for MSM.
3. Randomly draw $10^7$ parameters sets from prior distributions.
4. Simulate the transmission model until it approaches a resistance-free ($\mu = 0$) endemic equilibrium using the ordinary differential equation solver `runsteady` from the R [19] package `rootSolve` [24].
5. Select the parameters sets (posterior distributions) that result in prevalences and incidences within the defined range.

Information about parameter estimates for N. gonorrhoeae is scarce, so we chose to use non-informative priors for all parameters except the duration of infection which was informed by Garnett et al. [25]. The ranges for the expected prevalence and incidence of diagnosed infections in HMW were based on the National Health and Nutrition Examination Survey [26] and surveillance data [27], both from CDC. For MSM, we used data from the Health in Men Study in Australia [28] (and personal communication with F. Jin). We compared the model predicted prevalence and incidence of diagnosed infections to the prevalence and incidence from data without allowing for resistance in the simulations, because we assumed the data were collected when treatment was mostly effective. We calculated the model incidence of diagnosed and treated infections for sexual activity group $i$ with $\phi \sum_h S_i \pi_h \sum_{n=1}^3 \rho_i \beta_i t_i$ per year.

We set $\alpha = \frac{1}{10} \, \text{y}^{-1}$ because we only considered hosts 16–44 years of age. Since the number of new sexual partners per year refers to the last year only, hosts can switch their sexual activity group at rate $\gamma = 1 \, \text{y}^{-1}$. We set the probability of resistance during treatment to $\mu = 10^{-6}$ [12].

The remaining model parameters ($\tau$, $\nu$, $\beta_{HL}$, $\beta_{HH}$) are composites of other parameters (Table 3). Since $D = \frac{1}{\nu + \tau}$
Next, we studied the transmission of *N. gonorrhoeae* and the spread of resistance in the dynamic transmission model. We calibrated five model parameters to expected

We assumed that the duration of infection is described by a gamma distribution $\Gamma(k, \theta)$ with shape parameter $k = 2$ and scale parameter $\theta = 0.125$ y resulting in an average infectious duration of 0.25 y. Because highly sexually active hosts have less sex acts per partnership, we assumed that the transmission probability within the high activity group cannot be higher than the transmission probability within the low activity group. $M$ and IQR represent the median and interquartile range of the posterior distributions.

### Table 1. Prior distributions and posterior estimates of model parameters.

<table>
<thead>
<tr>
<th>parameter</th>
<th>description</th>
<th>priors</th>
<th>$M_{\text{MSM}}$</th>
<th>IQR$_{\text{MSM}}$</th>
<th>$M_{\text{HMW}}$</th>
<th>IQR$_{\text{HMW}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\epsilon$</td>
<td>sexual mixing coefficient</td>
<td>$\gamma(0.1)$</td>
<td>0.57</td>
<td>0.30-0.80</td>
<td>0.73</td>
<td>0.53-0.89</td>
</tr>
<tr>
<td>$\phi$</td>
<td>fraction of diagnosed and treated infections</td>
<td>$\gamma(0.1)$</td>
<td>0.64</td>
<td>0.48-0.81</td>
<td>0.50</td>
<td>0.36-0.66</td>
</tr>
<tr>
<td>$D$</td>
<td>average duration of infection (years)</td>
<td>$\Gamma(2, 0.125)$</td>
<td>0.19</td>
<td>0.14-0.25</td>
<td>0.55</td>
<td>0.46-0.66</td>
</tr>
<tr>
<td>$\beta_{LL}$</td>
<td>transmission probability within low activity group</td>
<td>$\gamma(0.1)$</td>
<td>0.59</td>
<td>0.42-0.77</td>
<td>0.87</td>
<td>0.79-0.94</td>
</tr>
<tr>
<td>$\beta_{HH}$</td>
<td>transmission probability within high activity group</td>
<td>$\gamma(0, \beta_{LL})$</td>
<td>0.30</td>
<td>0.25-0.40</td>
<td>0.72</td>
<td>0.63-0.81</td>
</tr>
</tbody>
</table>

Prevalence and incidence ranges for HMW were based on the National Health and Nutrition Examination Survey [26] and surveillance data [27], both from CDC. For MSM, prevalence and incidence ranges were based on the Health in Men Study in Australia [28] (and personal communication with F. Jin). The upper and lower bound of the ranges for the high and low sexual activity groups are given by the lower and upper bound of the overall population.

and $\phi = \frac{1}{\tau + \tau}$, the treatment rate is $\tau = \frac{\phi}{1 - \phi}$, and the spontaneous recovery rate is $\nu = \frac{1}{U D}$. $\beta_{LL}$ and $\beta_{HH}$ are the transmission probabilities per partnership between hosts of the high and low activity groups. We assumed that the between-group transmission probabilities are given by the geometric mean of the within-group transmission probabilities.

### Results

We fitted a logistic growth model to the proportion of antibiotic-resistant *N. gonorrhoeae* as observed in the two gonococcal surveillance programs (Fig. 2). The proportion of cefixime-resistant *N. gonorrhoeae* in GRASP appears to increase for both HetM and MSM after 2006. Ciprofloxacin-resistant *N. gonorrhoeae* in HetM and MSM were spreading in all observed host populations after the year 2000. For a given antibiotic and surveillance program, the rates of resistance spread were consistently higher for MSM than for HetM (Table 4). The average rate of resistance spread was 0.53 y$^{-1}$ for HetM and 1.46 y$^{-1}$ for MSM, corresponding to doubling times of 1.3 y (HetM) and 0.5 y (MSM) during the initial exponential growth phase.

Next, we studied the transmission of *N. gonorrhoeae* and the spread of resistance in the dynamic transmission model. We calibrated five model parameters to expected

![Figure 2. Increase in antibiotic-resistant N. gonorrhoeae. Points show data from antibiotic resistance surveillance programs (GRASP and GISP). Dashed lines indicate the fit of the logistic growth model to the data. For a given antibiotic and surveillance program, the rates of spread in MSM (green) are consistently higher than those in HetM (blue).](image-url)
Table 3. Composite model parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tau$</td>
<td>treatment rate per year</td>
<td>$\phi / D$</td>
</tr>
<tr>
<td>$\nu$</td>
<td>spontaneous recovery rate per year</td>
<td>$1 / \phi$</td>
</tr>
<tr>
<td>$\beta_{HH}$</td>
<td>transmission probability per partnership between high sexual activity hosts</td>
<td>$\sqrt{\beta_{LL} \beta_{HH}}$</td>
</tr>
<tr>
<td>$\beta_{LL}$</td>
<td>transmission probability per partnership between low sexual activity hosts</td>
<td>$\sqrt{\beta_{HH}}$</td>
</tr>
</tbody>
</table>

The composite model parameters $\tau$ and $\nu$ relate to other model parameters with $D = \frac{1}{\tau \nu}$ and $\phi = \frac{1}{\nu \tau}$. We assumed that the transmission probabilities between hosts of different sexual activity groups are given by the geometric mean of the transmission probabilities for hosts within each group.

Table 4. Rates of resistance spread in N. gonorrhoeae surveillance programs.

<table>
<thead>
<tr>
<th>Program</th>
<th>Antibiotic</th>
<th>Years</th>
<th>Host Population</th>
<th>Rate</th>
<th>CI of Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRASP</td>
<td>Cefixime</td>
<td>2004–2010</td>
<td>HetM</td>
<td>0.86 y$^{-1}$</td>
<td>0.73–1.00 y$^{-1}$</td>
</tr>
<tr>
<td>GRASP</td>
<td>Cefixime</td>
<td>2004–2010</td>
<td>MSM</td>
<td>2.38 y$^{-1}$</td>
<td>1.72–3.03 y$^{-1}$</td>
</tr>
<tr>
<td>GRASP</td>
<td>Ciprofloxacin</td>
<td>2000–2009</td>
<td>HetM</td>
<td>0.24 y$^{-1}$</td>
<td>0.03–0.45 y$^{-1}$</td>
</tr>
<tr>
<td>GRASP</td>
<td>Ciprofloxacin</td>
<td>2000–2009</td>
<td>MSM</td>
<td>1.15 y$^{-1}$</td>
<td>0.76–1.54 y$^{-1}$</td>
</tr>
<tr>
<td>GISP</td>
<td>Ciprofloxacin</td>
<td>1995–2006</td>
<td>HetM</td>
<td>0.50 y$^{-1}$</td>
<td>0.45–0.55 y$^{-1}$</td>
</tr>
<tr>
<td>GISP</td>
<td>Ciprofloxacin</td>
<td>1995–2006</td>
<td>MSM</td>
<td>0.86 y$^{-1}$</td>
<td>0.66–1.06 y$^{-1}$</td>
</tr>
</tbody>
</table>

Estimated rates of resistance spread from the Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP, England and Wales) and from the Gonococcal Isolate Surveillance Project (GISP, USA). CI: 95% confidence interval.

prevalence and incidence in MSM and HMW host populations. The posterior distributions of the parameters were based on 2,501 parameter sets for HMW and 63,696 parameter sets for MSM (Fig. 3, Table 1). Distributions of the modeled prevalence and incidence of diagnosed infections after calibration are provided as Supporting Information (S1 Figure, S2 Figure, S3 Table). The sexual mixing coefficient showed a tendency towards assortative mixing in both MSM and HMW (Fig. 3a). The fraction of diagnosed and treated infections tended to be higher in MSM compared to HMW (Fig. 3b), whereas the infectious duration was considerably shorter in MSM (median: 6.6 months, IQR: 5.5–7.9 months) (Fig. 3c). The transmission probabilities per partnership were generally higher in HMW than in MSM (Fig. 3d, 3e).

After calibration, we used the dynamic transmission model to study the spread of antibiotic-resistant N. gonorrhoeae. The proportion of antibiotic-resistant N. gonorrhoeae increased faster in MSM than in HMW (Fig. 4). In HMW, the median of all simulations reached 5% resistance in fewer than 4.5 y and 50% resistance in fewer than 7.8 y after appearance of the first antibiotic-resistant N. gonorrhoeae infection. In the MSM population, the median of all simulations reached a resistance level of 5% in fewer than 1.7 y and 50% in fewer than 2.6 y after resistance first appears in the population. The range spanned by all simulations was much wider in HMW than in MSM: 95% of all simulations reached the 5% threshold in fewer than 2.7–7.7 y (HMW), compared with 1.1–2.2 y (MSM).

Antibiotic-sensitive and -resistant N. gonorrhoeae share the same resource for growth, i.e. the susceptible hosts. The rate at which one strain replaces the other strain in the host population is given by the difference in their net growth rates. We assume that the transmission probabilities and the infectious duration of the two strains are the same, so the difference in their net growth rates is given by $\tau - \tau \mu$. Since $\mu \ll 1$, we can ignore the second term and the rate at which the antibiotic-resistant...
The faster spread of antibiotic-resistant \( N. \) gonorrhoeae compared with heterosexual hosts, as the major driver for the faster spread of antibiotic-resistant \( N. \) gonorrhoeae.

To our knowledge, this is the first study to have analyzed and interpreted \( N. \) gonorrhoeae antibiotic resistance surveillance data in a dynamic and quantitative manner. The transmission model was parameterized using sexual behavior data for HMW and MSM from Natsal-2, a large probability sample survey of sexual behavior. Calibrating the model to observed prevalence and incidence rates allowed us to use largely uninformative priors for the model parameters. Given the substantial uncertainty regarding \( N. \) gonorrhoeae transmission and infection parameters, the model calibration makes our model outcomes robust to changes in parameters and also allowed us to rely on few assumptions about the natural history of \( N. \) gonorrhoeae infection.

The limitations to our study need to be taken into consideration when interpreting the findings. First, we used data from different sources, although all were collected in high income countries. The antibiotic resistance surveillance data are from programs in England and Wales and the USA. The mathematical transmission model was parameterized using British sexual behavior data and calibrated to prevalence and incidence rates from the USA (HMW) and Australia (MSM). For simplicity, we modeled the heterosexual and MSM host populations separately although there is some mixing between them. We assumed the sexual behavior of heterosexual men and women to be the same and pooled their behavioral data. Second, we assumed complete resistance against the antibiotic, i.e. 100% treatment failure. We further assumed that treatment of the sensitive strain is 100% efficacious. Both assumptions might explain why antibiotic-resistant \( N. \) gonorrhoeae spread at somewhat higher rates in the dynamic transmission model than estimated from data. Lower rates of spread could also be caused by fitness costs associated with resistance mutations. However, since fitness costs are rarely reported for \( N. \) gonorrhoeae and compensatory mutations seem to be acquired rapidly [29, 30], we did not consider them here. Third, we restricted our model to resistance to one antibiotic with no alternative treatment or interventions. This is why we observe complete replacement of the antibiotic-sensitive strain in the model, a phenomenon that has not been observed in surveillance data. Finally, we assumed that the per partnership transmission probabilities and infectious durations in the model represent average values for \( N. \) gonorrhoeae infections at different infection sites (urethral, pharyngeal, anal, cervical).

The estimated posterior distributions of the parameters fit within the range of previously used values, and provide some insights into sexual mixing and the natural history of \( N. \) gonorrhoeae. The sexual mixing coefficient tends to be assortative for both HMW and MSM host populations in our model. Quantifying the degree of sex-


Figure 4. Spread of antibiotic resistance in the transmission model. Ranges indicating 50% of all simulations are shown in dark color, and ranges indicating 95% of all simulations are shown in light color. The continuous lines describe the median proportion of antibiotic-resistant \( N. \) gonorrhoeae for all simulations. The black dotted line indicates the 5% threshold.

Figure 5. Distribution of treatment rates in HMW and MSM. Treatment rates closely approximate the rates of resistance spread. The median treatment rate was 0.88 y\(^{-1}\) in HMW and 3.12 y\(^{-1}\) in MSM.

Discussion

In this study, we quantified the rate at which antibiotic-resistant \( N. \) gonorrhoeae spread in heterosexual and MSM populations. We used data from two different surveillance programs and estimated that the proportion of ciprofloxacin- and cefixime-resistant \( N. \) gonorrhoeae doubles on average every 1.3 y in HetM and 0.5 y in MSM. The faster spread of antibiotic-resistant \( N. \) gonorrhoeae in MSM than in heterosexual hosts was corroborated using a dynamic transmission model, which was calibrated to observed prevalence and incidence rates. The model allowed us to identify the higher treatment rates in MSM,
ual mixing is difficult and largely depends on the study population, but our finding is consistent with other studies indicating assortative sexual mixing in the general population [31, 20]. The posterior estimates of the fraction of diagnosed and treated infections are consistent with the notion that a large proportion of *N. gonorrhoeae* infections are symptomatic, and that this proportion is expected to be higher in men than in women [32, 33, 34]. The average infectious duration was the only parameter with an informative prior, but we found marked differences between the infectious duration in HMW (6.6 months) and MSM (2.3 months). Per sex act transmission probabilities are generally considered to be lower from women to men than vice versa [35, 36, 37]. In our model, the median of the per partnership transmission probability was lower in MSM hosts than in HMW for both sexual activity groups. This could be explained by different numbers of sex acts per partnership in the two populations. The low transmission probability within the highly active MSM group (median: 30%) could reflect a single or a small number of sex acts per partnership. In contrast, the high transmission probability for HMW within the low sexual activity group (median: 87%) could be a result of a larger number of sex acts per partnership in those individuals. Furthermore, condom use is more frequent in MSM than in HMW [22], which could explain part of the observed differences in transmission probabilities.

Our study found that the treatment rate is the driving force of resistance spread. Xiridou et al. [13] found that resistance could spread faster when the treatment rate was higher, but they did not identify the connection between treatment rate and resistance spread. Chan et al. [12] found that focusing treatment on the core group leads to a faster rebound to pre-treatment prevalence than equal treatment of the entire host population. Unfortunately, our findings cannot be compared with Chan et al. because they do not report the proportion of antibiotic-resistant *N. gonorrhoeae*.

It was shown previously that treatment is the main selective force acting on resistance evolution due to the selective advantage to the resistant pathogen [38, 39]. We now expand this concept by showing that treatment rates determine the rates of resistance spread even when the host populations has a heterogeneous contact structure. The intuitive argument that a faster spread of an infection, due to a higher number of sexual partners, will result in a faster spread of resistance does not hold. Instead, the proportion of resistant infections spreads equally in host populations with different number of partners as long as they receive treatment at the same rate. For *N. gonorrhoeae*, this insight clashes with the currently prevailing notion that more screening and treatment can limit the spread of antibiotic-resistant *N. gonorrhoeae* [10, 9]. As soon as antibiotic-resistant pathogens are frequent enough to evade stochastic extinction, expanded treatment will foster their spread. Our findings also show that bridging between the HetM and the MSM host populations might not have been necessary for cefixime-resistance to spread in the HetM population after 2010 [5]. It is likely that cefixime-resistant *N. gonorrhoeae* had already been present in the HetM population but were spreading at a lower rate than in the MSM population.

The results of our study will be useful for future *N. gonorrhoeae* research and for guiding treatment recommendations. The *N. gonorrhoeae* transmission model describes observed prevalence and incidence rates well and can reconstruct the spread of antibiotic-resistant *N. gonorrhoeae*. Estimating rates of resistance spread is useful for projecting future resistance levels and the expected time it will take until a certain threshold in the proportion of antibiotic-resistant *N. gonorrhoeae* is reached. Until now, treatment recommendations for *N. gonorrhoeae* are subject to change when 5% of *N. gonorrhoeae* isolates show resistance against a given antibiotic [6]. Our study shows the importance of the rate of spread: a level of 5% resistance results in a marginal increase to 8% in the following year if resistance spreads logistically at rate 0.53 y$^{-1}$ (HetM mean estimate from Table 4), but reaches 18% in the next year if resistance spreads at rate 1.46 y$^{-1}$ (MSM mean estimate from Table 4). Public health authorities could use surveillance data and adapt thresholds for treatment recommendation change to specific host populations using the method we describe. Our study challenges the currently prevailing notion that more screening and treatment will limit the spread of *N. gonorrhoeae*, as higher treatment rates will ultimately result in faster spread of antibiotic resistance. Future treatment recommendations for *N. gonorrhoeae* should carefully balance prevention of *N. gonorrhoeae* infection and avoidance of resistance spread.

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