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Public health measures to control the spread of antimicrobial resistance in *Neisseria gonorrhoeae* in men who have sex with men

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SUMMARY

Gonorrhoea is one of the most common sexually transmitted infections. The control of gonorrhoea is extremely challenging because of the repeated development of resistance to the antibiotics used for its treatment. We explored different strategies to control the spread of antimicrobial resistance and prevent increases in gonorrhoea prevalence. We used a mathematical model that describes gonorrhoea transmission among men who have sex with men and distinguishes gonorrhoea strains sensitive or resistant to three antibiotics. We investigated the impact of combination therapy, switching first-line antibiotics according to resistance thresholds, and other control efforts (reduced sexual risk behaviour, increased treatment rate). Combination therapy can delay the spread of resistance better than using the 5% resistance threshold. Increased treatment rates, expected to enhance gonorrhoea control, may reduce gonorrhoea prevalence only in the short term, but could lead to more resistance and higher prevalence in the long term. Re-treatment of resistant cases with alternative antibiotics can substantially delay the spread of resistance. In conclusion, combination therapy and re-treatment of resistant cases with alternative antibiotics could be the most effective strategies to prevent increases in gonorrhoea prevalence due to antimicrobial resistance.

Key words: Antibiotics, antimicrobial agents, antimicrobial resistance, gonorrhoea, gonorrhoea prevention and control, mathematical model, men who have sex with men.

INTRODUCTION

Gonorrhoea, caused by *Neisseria gonorrhoeae* (NG), is one of the most common sexually transmitted infections (STIs) [1]. The control of gonorrhoea is complicated by the ability of NG to rapidly develop resistance to the antibiotics used for its treatment [2]. Third-generation cephalosporins, such as ceftriaxone and cefixime, are currently the first-line treatment for gonorrhoea in most countries. However, the susceptibility of gonococci to these agents has been decreasing [3–5] and incidental treatment failures have been reported [6, 7]. In the USA, the percentage of urethral NG isolates with high cefixime minimum inhibitory concentration (MIC $\geqslant 0{\cdot}25\ \mu$g/ml) increased from 0·1% in 2006 to 5% in 2010 among men who have sex with men (MSM) in the West

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Census region [5]. Therefore, since 2012, cefixime is no longer recommended for the treatment of gonorrhoea in the USA; ceftriaxone in combination with azithromycin or doxycycline has become the first-line treatment [5]. In The Netherlands, cefotaxime became the first-line therapy for gonorrhoea in 2003 and ceftriaxone in 2006 [3]. The percentage of NG isolates with cefotaxime MIC >0·12 μg/ml rose from 1·2% in 2006 to 8·1% in 2008 [3]. Recently, the first NG strains with resistance to cefixime and ceftriaxone have been identified [6, 8, 9]. Dissemination of these strains in the population could leave gonorrhoea untreatable in some settings, as no alternative first-line treatments are currently available [8]. Therefore, national and international health authorities are investigating strategies to control the spread of cephalosporin resistance and preserve ceftriaxone as an effective first-line treatment [1].

Several modelling studies have addressed the issue of drug resistance [10–21], in specific settings, such as hospitals [18]; for specific pathogens, such as influenza [13], *Staphylococcus aureus* [14], HIV [19], tuberculosis [20]; or by comparing different treatment strategies, such as cycling, switching, or random allocation of two antibiotics [10, 18]. Handel and colleagues investigated the role of compensatory mutations (leading to resistant strains with decreasing fitness loss) in the emergence of drug resistance, using a model for gonorrhoea transmission [16]. They showed that the time to resistance emergence decreases in a nonlinear fashion with treatment levels. A modelling study on gonococcal resistance in the general population of the USA and Canada showed that in the absence of antimicrobial resistance, gonorrhoea control is achievable only when treatment strategies focus on high-risk groups; in the presence of resistance, targeting high-risk groups maximizes dissemination of antimicrobial-resistant strains [11].

The important role of high-risk individuals in the transmission of gonorrhoea, as well as other STIs, is well established [22, 23] and explains the high prevalence of these infections in high-risk groups, such as MSM or commercial sex workers. For this reason, studies on the transmission dynamics of STIs usually focus on specific risk groups and not on the general population. The transmission dynamics of STIs and the impact of public health interventions are determined by sexual contact patterns and these differ considerably between MSM and heterosexuals. Moreover, molecular epidemiology of gonococcal isolates and of NG strains with reduced susceptibility to cefixime indicate distinct transmission networks for MSM and heterosexuals [24, 25]. The prevalence of gonorrhoea is high in MSM, but resistance levels are also high in this group [3–5]. Therefore, the impact of a specific treatment strategy on MSM may be quite different than for heterosexuals [11].

Our study addresses the dissemination of resistant NG strains specifically in MSM. This was accomplished by modelling sexual behaviour in MSM, using sexual behaviour data from MSM, and calibrating the model to gonorrhoea prevalence in MSM. In the model, we distinguish NG strains according to whether they are sensitive or resistant to specific antibiotics. We investigate the impact of single therapy (with one antibiotic) and combination therapy (with two antibiotics simultaneously) and how these are affected by other control efforts, such as increased treatment, reduced sexual risk behaviour, and re-treatment of resistant cases. We compare the impact of the two strategies most recommended by national and international guidelines for gonorrhoea treatment: combination therapy and single therapy, switching the first-line antibiotic if resistance exceeds 5% of gonorrhoea cases.

METHODS

The model

We used a deterministic compartmental model to describe the transmission of NG and the spread of antimicrobial resistance among MSM. The model is based on earlier work [10, 11], that we extended to account for re-treatment with second-line antibiotics of gonorrhoea cases with resistance to the first-line antibiotic. A schematic diagram of the model is given in Figure 1. The equations describing the model are given in the online Appendix. Model parameters are summarized in Table 1.

MSM are divided into four sexual risk groups according to the number of sexual partners they have (see also online Appendix and [26]). Individuals with gonorrhoea may be prescribed antibiotic A, antibiotic B, dual therapy with A and B, or a third antibiotic C. In the beginning, every infection is sensitive to these antibiotics. Resistance to an antibiotic agent can develop during treatment with this agent; moreover, infection from an individual with resistant gonorrhoea also results in acquisition of resistance. In the model, we distinguish infected individuals according to the strain they are infected with: a strain

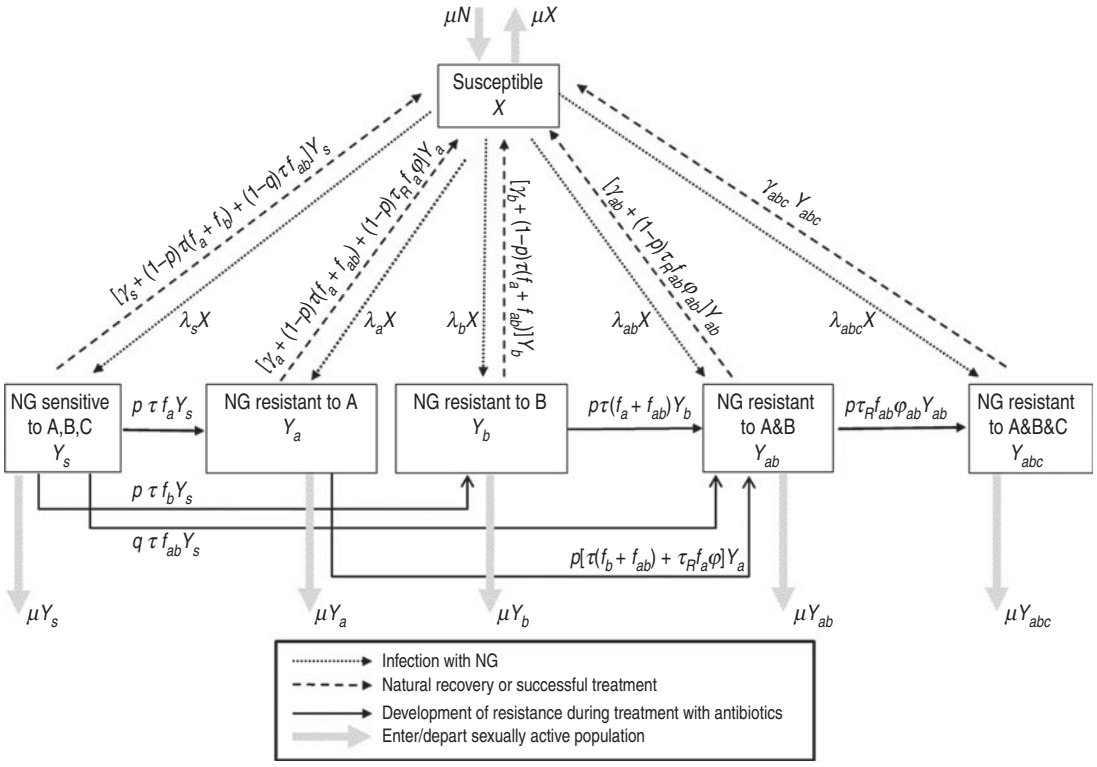

Fig. 1. Flow diagram of the model for the transmission of *Neisseria gonorrhoeae* (NG). Infected individuals are distinguished according to whether they are infected with a strain of NG sensitive to antibiotics A, B, and C (Y_s); resistant to antibiotic A only (Y_a); resistant to antibiotic B only (Y_b); resistant to antibiotics A and B (Y_{ab}); or resistant to antibiotics A, B, and C (Y_{abc}). Model parameters are defined in Table 1.

sensitive to antibiotics A, B, and C; a strain resistant only to A; a strain resistant only to B; a strain resistant to A and B; or a strain resistant to A, B, and C. The third antibiotic C is prescribed only for re-treatment of those with resistance to A and B; therefore, in the model, there are no strains resistant only to C, to A and C, or to B and C. Fitness levels for the resistant strains may be different from those for the sensitive strain: if β_i is the probability of transmission of NG strain $i = s, a, b, ab, abc$, then $\beta_i = c_i\beta_s$, for $i \neq$ s, where c_i denotes the fitness cost of resistance, compared to the sensitive strain s.

Model parameters, uncertainty analysis, and model calibration

To account for uncertainty in model parameters, we assigned a range of possible values to each uncertain parameter and sampled 1000 sets of values from the uniform distribution, using Latin Hypercube Sampling. The model equations were solved numerically with these values. The model was calibrated such that: (i) the prevalence of gonorrhoea when ceftriaxone was introduced as first-line therapy was around 5%, reflecting historical trends in gonorrhoea prevalence in MSM in The Netherlands in 2006–2011 [27] and (ii) in the first 7 years that ceftriaxone was the recommended treatment for gonorrhoea, there were no gonorrhoea cases with ceftriaxone resistance and gonorrhoea prevalence in MSM was more or less stable [27, 28] (Fig. 2).

Single or combination therapy and other control efforts

We examined first the spread of resistance in the case of single therapy with one antibiotic (such as ceftriaxone), designated antibiotic A in the model; individuals developing or acquiring resistance to A cannot be cured successfully with this antibiotic. Subsequently, we investigated the case of combination therapy with two antibiotics, A and B, simultaneously; individuals with dual resistance cannot be cured successfully. We explored the impact on gonorrhoea prevalence of single or combination therapy, along with the following control efforts:

- *Reduction in sexual partners.* Individuals with resistance may return to their health practitioners with

Table 1. *Model parameters*

Symbol	Definition	Values	Source
β_S	Probability of transmission of NG strain sensitive to antibiotics, per act of UAI	0·2–0·26	[32]
γ_i	Natural recovery rate (without treatment) per year, for those infected with strain $i = s, a, b, ab, abc$	2·2–2·6	[22, 33]
τ	Treatment rate per year	0·72–2·64	[23, 34]
c_A, c_B	Fitness cost of resistance against A or B	10%	[35–37]
c_{AB}	Fitness cost of resistance against A and B	20%	[35–37]
N_o	Number of MSM	238 000	[38]
μ	Rate of entering/departing sexually active population	0·018	*
Percentage of individuals that become resistant when treated with			
p	One antibiotic, $\times 10^8$	0·01–0·99	†
q	Two antibiotics simultaneously	p^2	[10]
Parameters relating to treatment scenarios‡			
τ_R	Annual re-treatment rate with secondary regimen, for those with resistance to first-line treatment	$0{\cdot}5\tau$	
ϕ	% of those with resistance to A who would have received A and are re-treated with B	90%	
ϕ_{AB}	% of those with resistance to A and B who would have received combination therapy with A and B and are re-treated with C	90%	
f_j	% treated NG cases prescribed antibiotic j = A, B, AB		

MSM, Men who have sex with men; NG, *Neisseria gonorrhoeae*; UAI, unprotected anal intercourse.
* Model assumption, accounting for 55 years of sexual lifespan (ages 15–69 years).
† Model assumption.
‡ See Methods and online Appendix for explanation of scenarios.

persisting infection and, after counselling, reduce their sexual risk behaviour during the next few months until the infection is cleared. We investigated the impact of a 10% decline in the number of sexual partners of MSM with resistance.

- *Increase in treatment rates.* Increases in STI screening could result in higher treatment rates. We examined a 50% increase in the treatment rate.
- *Re-treatment.* With single therapy with antibiotic A, all gonorrhoea cases are first treated with antibiotic A. For those with resistance to A, treatment with antibiotic A results in treatment failure. We investigated the impact of a hypothetical control effort aimed at finding and treating most resistant cases with an alternative (second-line) antibiotic, designated antibiotic B in the model; results are shown with 90% of resistant cases being re-treated. Due to delay in treating first with A and subsequently with B, the treatment rate is lower for re-treatment than that for the first treatment attempt (by 50%: $\tau_R = 0{\cdot}5\tau$). When antibiotic B is used as first-line treatment, re-treatment with A produces similar results; for simplicity, these scenarios are not shown. Using combination therapy with antibiotics A and B, re-treatment was implemented as prescription of a third antibiotic C for MSM infected with NG resistant to A and B.

5% resistance threshold

The World Health Organization recommends a therapeutic success of at least 95% for an antimicrobial agent to be used as first-line therapy [29]. Therefore, when resistance to an antibiotic exceeds 5% of NG cases, this antibiotic is no longer recommended as first-line therapy. Many countries follow this recommendation; therefore, we examined the scenario of switching from antibiotic A to antibiotic B when 5% of NG strains are resistant to A. This scenario was also explored with low adherence to guidelines regarding switching antibiotics upon reaching a resistance threshold, as has occurred in the past [30]. We assumed that when 5% of NG strains are resistant to A, official guidelines recommend switching from antibiotic A to antibiotic B, but only 25% of treated cases received B in the first year and 50% in the second year, while the rest received A; only from the third year were all diagnosed cases treated with B.

RESULTS

Higher treatment rate could result in faster spread of resistance

Results for the scenario of single therapy with antibiotic A are given in Figure 3. When resistance to

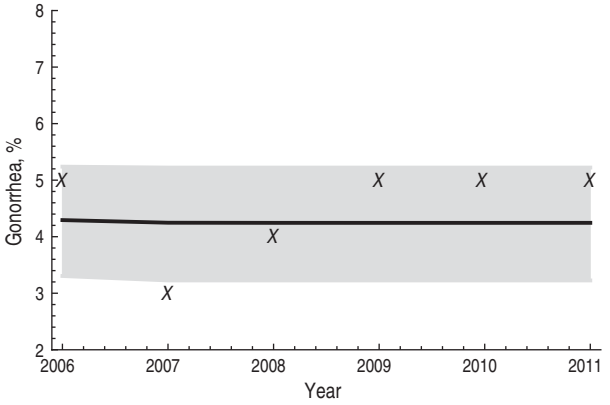

Fig. 2. The prevalence of gonorrhoea infection in the first years after the introduction of ceftriaxone as first-line treatment for gonorrhoea: comparison of model results with data. The black line shows the median and the grey area shows the interquartile range of the 1000 model results from the uncertainty analysis. *X* indicates the percentage of men diagnosed with gonorrhoea in the preceding 12 months in MSM participating in the annual *Schorer Monitor* for years 2006–2011.

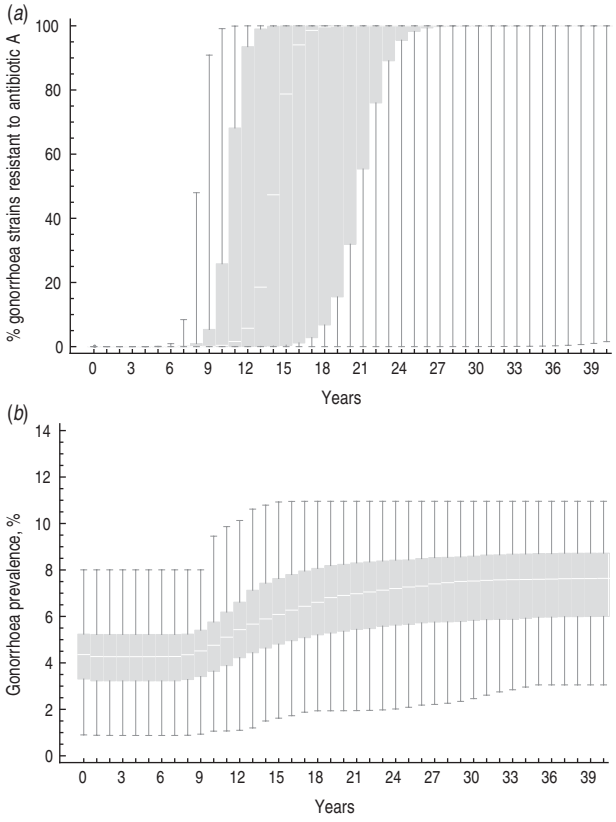

Fig. 3. (*a*) The percentage of gonorrhoea strains with resistance to antibiotic A and (*b*) the prevalence of gonorrhoea, in the first 40 years after the introduction of antibiotic A as first-line therapy. Only antibiotic A was prescribed for the treatment of gonorrhoea. In each year, the white line shows the median, the grey area shows the interquartile range, and the black vertical line segment shows the whole range of the 1000 results from the uncertainty analysis.

antibiotic A emerges and begins spreading in the population (Fig. 3*a*), the prevalence of gonorrhoea starts increasing (Fig. 3*b*). Efforts to enhance gonorrhoea control through increased treatment rates, can result in lower gonorrhoea prevalence in the short term, but higher prevalence in the long term, with single (Fig. 4*a*) or combination (Fig. 4*b*) therapy. Higher treatment rate leads to a decline in gonorrhoea prevalence in the beginning, but the more intensive use of first-line antibiotic(s) speeds up the emergence of resistance, as it renders infectious cases again susceptible to resistant strains, and results in higher numbers of individuals developing resistance. These individuals can further spread the resistant strains because they cannot be cured and remain infectious as untreated cases, resulting in an earlier rise in gonorrhoea prevalence. The initial reduction in gonorrhoea prevalence (due to the higher treatment rate) is maintained longer with combination therapy than with single therapy.

Sexual risk reductions and re-treatment slow down resistance spread

A reduction in the number of sexual partners of MSM with resistant NG strains can delay the spread of resistance and the rise in gonorrhoea prevalence with single (Fig. 4*c*) or combination (Fig. 4*d*) therapy. The increase in gonorrhoea prevalence is delayed considerably and slowed down by re-treatment of resistant NG cases with a second-line antibiotic: antibiotic B for single therapy with A (Fig. 4*e*); or antibiotic C for combination therapy with A and B (Fig. 4*f*). In the case of combination therapy, re-treatment with a third antibiotic delays the emergence of resistance beyond the 40-year horizon that we examine here, such that no increase in gonorrhoea prevalence is observed up to 40 years after the introduction of dual therapy (Fig. 4*f*). Combination therapy with antibiotics A and B (Fig. 4*f*) is only slightly better than single therapy with antibiotic A and re-treatment with antibiotic B (Fig. 4*e*).

Combination therapy is better than using resistance thresholds

In Figure 5*a* we compare combination therapy with the strategy of switching the first-line antibiotic

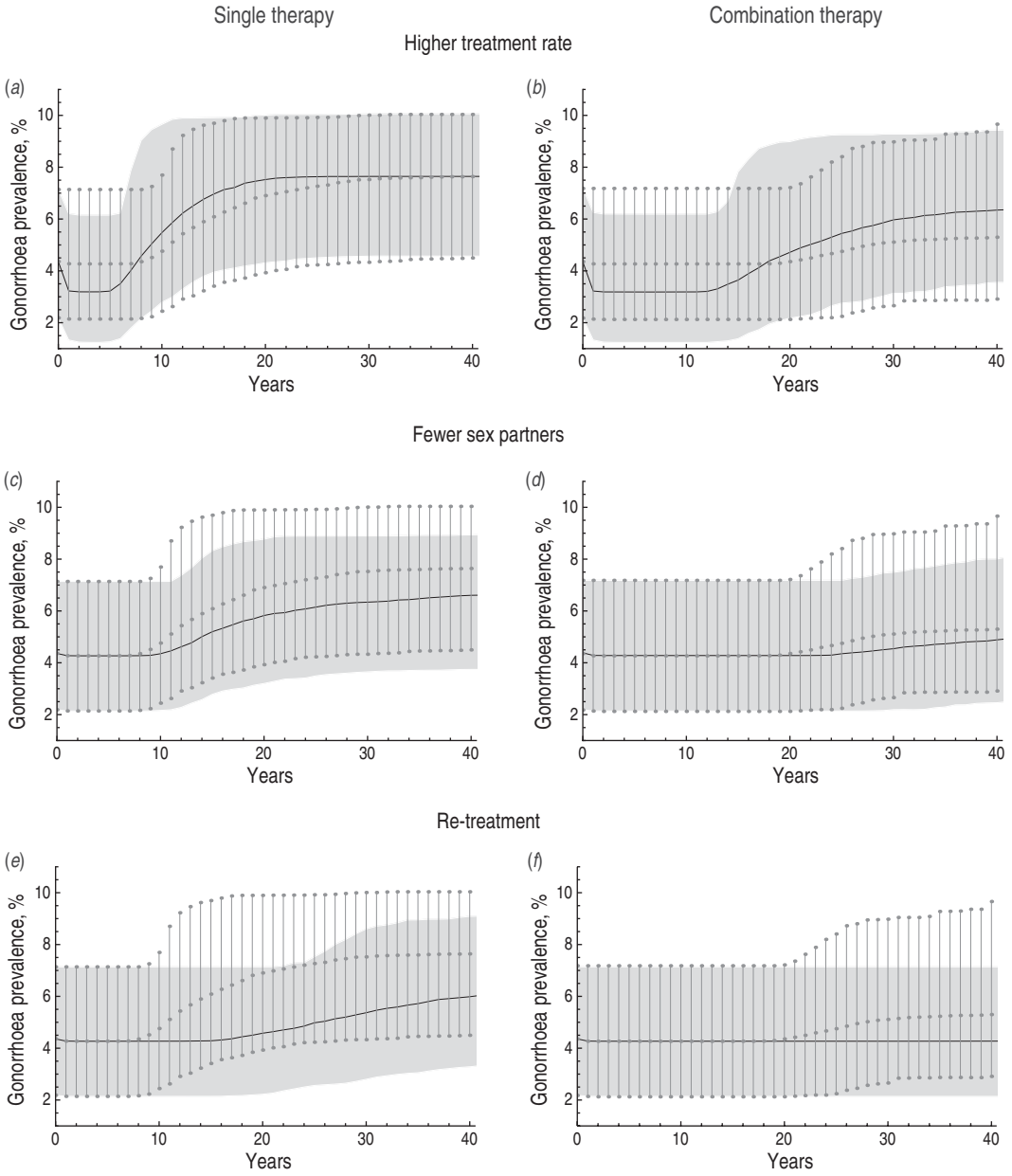

Fig. 4. The prevalence of gonorrhoea with single therapy with antibiotic A (left plots) or combination therapy with antibiotics A and B (right plots). In each plot, the black line shows the median and the grey shaded area shows the 95% uncertainty interval of the 1000 results with the baseline parameters (as in Table 1). The following scenarios are shown with grey dots and grey line segments in each year: (*a, b*) scenarios with 50% higher treatment rate; (*c, d*) scenarios with a 10% decline in the number of sexual partners of MSM with NG strain resistant to the first-line antibiotic(s); (*e, f*) scenarios with re-treatment with an alternative antibiotic for those with resistance to the first-line antibiotic(s).

when the 5% resistance threshold is exceeded. Combination therapy delays the rise in prevalence more than switching antibiotics and ends up at a lower prevalence. If adherence to antibiotic-use recommendations is suboptimal, antibiotic A is used for two more years after exceeding the 5% resistance threshold, resulting in a small increase in gonorrhoea prevalence; subsequently, prevalence declines (due to the new first-line antibiotic) and remains slightly lower than the prevalence with optimal adherence.

The fraction of patients acquiring resistance with single or combination therapy and the fitness cost of resistance

Next we examine the sensitivity of our results on two model assumptions. First, the assumption that the

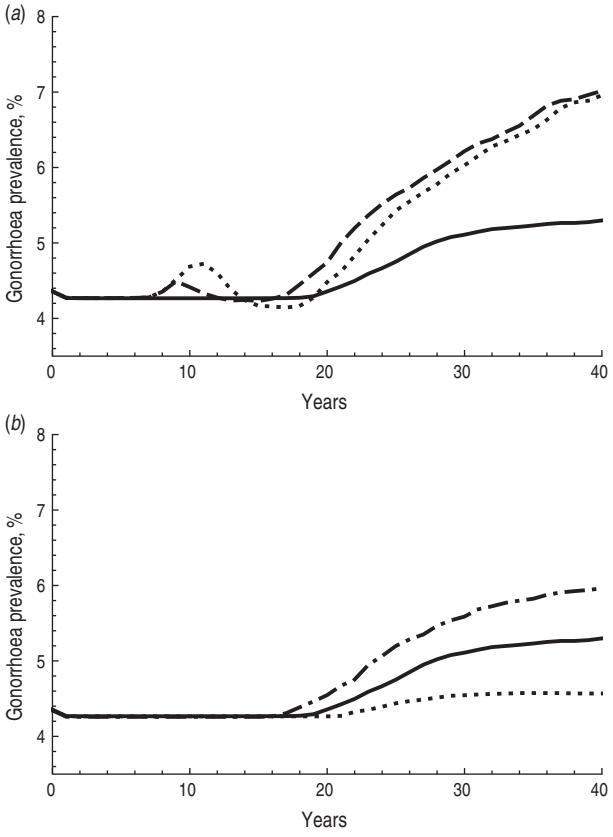

Fig. 5. (*a*) The prevalence of gonorrhoea with different treatment scenarios. Combination therapy with antibiotics A and B (solid line); switching from antibiotic A to antibiotic B when resistance to A exceeds 5% (dashed line); switching from antibiotic A to antibiotic B when resistance to A exceeds 5%, with low adherence: after the change in recommendations, 25% of treated cases receive B in the first year, 50% in the second year, and 100% from the third year onwards (dotted line). (*b*) The prevalence of gonorrhoea after the introduction of combination therapy with different assumptions about the fraction of hosts becoming resistant when treated with two antibiotics simultaneously (q) in relation to the fraction becoming resistant when treated with one antibiotic (p). Solid line: $q = p^2$; dashed-dotted line: $q = 100p^2$; dotted line: $q = 0.01p^2$.

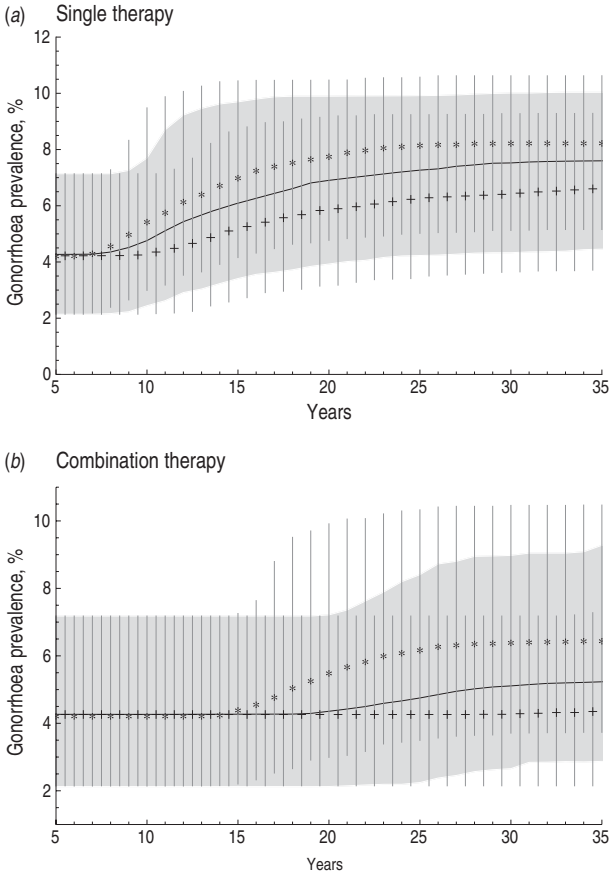

Fig. 6. The prevalence of gonorrhoea with: (*a*) single therapy with one antibiotic, (*b*) combination therapy with two antibiotics. Parameters are as in the main text, with 10% fitness cost (black line shows the median; the shaded area shows the 95% uncertainty interval). The following cases are shown: no fitness cost (*); 20% fitness cost (+); the line segments show the 95% uncertainty intervals.

fraction of hosts becoming resistant when treated with antibiotics A and B simultaneously (q) equals the product of the fraction becoming resistant when treated with A (p) times the fraction becoming resistant when treated with B, (p): $q = p^2$. If that is not true, the impact of combination therapy may be different [10]. Compared to the scenario with $q = p^2$, resistance spreads faster and gonorrhoea prevalence increases earlier with $q > p^2$, while a slower and lower rise in gonorrhoea prevalence is expected if $q < p^2$ (Fig. 5*b*). Second, we assumed that the fitness cost of resistance was 10%. In Figure 6 we present results for the cases of no fitness cost and of 20% fitness cost. If there is no fitness cost, the results of the previous sections are rather optimistic: resistance spreads faster and leads to an earlier rise in gonorrhoea prevalence, for both single (Fig. 6*a*) and combination (Fig. 6*b*) therapy. With higher fitness cost, the increase in gonorrhoea prevalence is smaller and occurs later.

DISCUSSION

For the treatment of gonorrhoea, combination therapy with two antibiotics may be the most preferable strategy to delay and prevent rises in gonorrhoea prevalence due to the spread of antimicrobial resistance. Switching the first-line antibiotic when the 5% resistance threshold is exceeded can be less efficient. The spread of resistance can be delayed further by

reductions in sexual risk behaviour of MSM infected with resistant strains in the next few months until clearance of the infection. Re-treatment of MSM infected with resistant gonococci could ensure that such infections are cured effectively without further spreading the resistant strains.

Our findings confirm and extend findings from previous modelling studies. The superiority of combination therapy compared to other treatment strategies has been demonstrated previously for bacterial infections and for gonorrhoea in a general population [10, 11]. We found that this also applies to gonorrhoea in the high-risk subpopulation of MSM. We extend these results by showing how combination therapy can be improved or impaired by other control efforts: sexual risk reductions may enhance the impact of combination therapy, but increased treatment rates may weaken it.

Another significant new result from our study is the importance of successful treatment of MSM with resistant gonorrhoea, such that these individuals cannot further transmit the resistant strains: re-treatment after single therapy is almost as effective as combination therapy; and re-treatment after combination therapy delays the emergence and spread of resistance much longer than all the other strategies that we investigated. We acknowledge the difficulty of finding resistant cases, because symptomatic cases usually return to their health practitioners due to persisting symptoms, but asymptomatic cases that have received treatment usually do not seek re-testing. A test of cure that is routinely offered in some countries can help since it is able to detect treatment failures. Moreover, it is possible to perform a sensitivity test along with the administration of antibiotics, in which case individuals infected with resistant strains can be detected, even without a test of cure. Based on these results, our model can be extended to account for differences in symptomatic *vs.* asymptomatic gonorrhoea, such that different testing, screening, and treatment options can be modelled and compared.

As with any modelling study, ours has certain limitations. We assumed that all NG strains have the same characteristics, but differences in fitness or in the duration of the infectious period between different NG strains can be important in the competition between strains [12, 13]. The ranges of some uncertain parameters, such as the natural recovery rate, were rather narrow in order to reduce the wide ranges in the model outcomes. Other simplifications we made were that we did not account for differences between symptomatic and asymptomatic cases or between anatomical locations of gonorrhoea, which could affect the infection duration, infectivity level, or severity of the infection prompting active health-seeking behaviour. This was done mainly due to the lack of data on the characteristics of gonorrhoea infection according to the anatomical site of the infection. Nevertheless, our uncertainty analysis accounted for variation in these parameters. Therefore, it would be interesting to extend the model to account for such differences, but we expect the results would remain qualitatively similar.

Our study highlights the unexpected role of increased treatment rate, leading to short-term gains in reduced prevalence, but adverse long-term effects in faster spread of resistance. This may not be anticipated, since STI screening has been intensely promoted among high-risk populations with the aim of reducing transmission and prevalence. However, more screening results in more cases *receiving* treatment, making it more likely for NG to evolve under the selective pressure of the antibiotic; this could result in earlier emergence of resistance and, in the absence of alternative treatments, in higher numbers of individuals with resistance. Moreover, treatment renders infected individuals susceptible to infection with resistant strains. Therefore, higher treatment rates could eventually lead to higher rates of resistance and higher prevalence unless resistance is actively monitored and re-treated whenever indicated. It should be emphasized, however, that this finding is subject to the specific assumptions and limitations of our study, as outlined in detail in the Methods and Discussion sections. However, earlier modelling studies for gonorrhoea, methicillin-resistant *Staphylococcus aureus* (MRSA), and other bacteria have also shown a positive association between antibiotic use and frequency of resistance [14–16, 21]. Moreover, a recent study in a hospital in Caen, France, found a positive association between fluoroquinolone use and the frequency of MRSA in the hospital [31].

To fight and impede the dissemination of resistant gonorrhoea, combined efforts are necessary. If the use of antibiotics is followed by a later test of cure which identifies resistant cases, this would allow the employment of measures to reduce the dissemination of resistance, such as prescription of alternative treatment and counselling to avoid unprotected sexual contacts at least for the few months following the last positive test. Re-treatment and sexual risk reductions in MSM with resistant gonorrhoea may be more

effective in combating resistance than increasing screening and treatment rates. Surveillance of gonococcal resistance to antibiotics needs strengthening and public health authorities should be alert and prepared to modify their strategies or to introduce supplementary measures when faced with rising ceftriaxon resistance.

SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0950268814002519.

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DECLARATION OF INTEREST

None.

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