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THE ROYAL SOCIETY

The transmission dynamics of gonorrhoea: modelling the reported behaviour of infected patients from Newark, New Jersey

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A survey of the sexual behaviour of gonorrhoea patients in Newark was undertaken to evaluate parameters within a model of gonorrhoea transmission. Modelling work aimed to explain observed epidemiological patterns and to explore the potential impact of interventions. Reported behaviours, along with values derived from the literature, were used within a standard deterministic model of gonorrhoea transmission, where the population was stratified according to sex and rates of sex-partner change. The behaviours reported, particularly among women, are insufficient by themselves to explain the continued existence of gonorrhoea within the population. The majority of symptomatic patients seek treatment within a few days, and report that they do not have unprotected sex while symptomatic. The proportion of patients with low numbers of sex partners suggests that sexual mixing between people categorized according to sexual behaviour is near random. To explain the persistence of gonorrhoea, there must be some patients who, when infected, do not seek care in public clinics. In addition, gonorrhoea incidence in the model is sensitive to change, such that very small reductions in risk behaviour could lead to its elimination. This does not accord with the observed failure of many interventions to eliminate infection, suggesting that the modelled infection is too sensitive to change. The model, which has been influential in gonorrhoea epidemiology, is not consistent with the observed epidemiology of gonorrhoea in populations. Alternative models need to explore the observed stability of gonorrhoea before robust modelling conclusions can be drawn on how best to control infection. However, the current results do highlight the potential importance of asymptomatic infections and infections in those who are diseased and do not attend public health services. Screening and contact-tracing to identify asymptomatic infections in both men and women will be more effective in reaching those who maintain the infection within the community rather than simply treating symptomatic cases.

Keywords: *Neisseria gonorrhoeae*; gonorrhoea; mathematical model; sexual behaviour; sexually transmitted infection

1. INTRODUCTION

To develop a better understanding of infectious disease epidemiology, theoretical studies should be carried out iteratively alongside empirical studies of the patterns of infection. Since it was developed by Yorke and colleagues over 20 years ago (Yorke *et al.* 1978; Hethcote & Yorke 1984), a simple deterministic framework for the transmission dynamics of *Neisseria gonorrhoeae* has dominated theoretical studies of this infection. The most complicated model presented in their monograph (Hethcote & Yorke 1984) had a population stratified into two sexes, each with two sexual-activity groups, where people could be susceptible, symptomatically infected or asymptomatically infected. This framework has been a springboard for the inclusion of further behavioural complexity, including additional sexual-activity groups and their patterns of mixing (Garnett & Anderson 1993), more complex transmission probabilities reflecting the distribution of sex acts within sexual partnerships (Garnett & Anderson 1996), and the inclusion of stochastically derived sex-partner networks (Kretzschmar *et al.* 1996; Ghani *et al.* 1997). The approach generally taken has been to estimate some parameters from the literature on gonococcal infection and then, for other parameters, to explore the sensitivity of the system to a range of possible values. This has generated a number of insights, including the observation that there must be a 'core group' maintaining infection within the community (Brunham & Plummer 1990). This is an intuitively straightforward observation that has generated a great deal of discussion (Thomas & Tucker 1996). For the existence of infection there must be a fraction of the population who, when infected, are likely to infect more than one other person, an axiom true for all infectious diseases, but with a particular relevance for sexually transmitted diseases (STDs), where the extreme heterogeneity in the risk of acquiring and transmitting infection means that the fraction of people who propagate

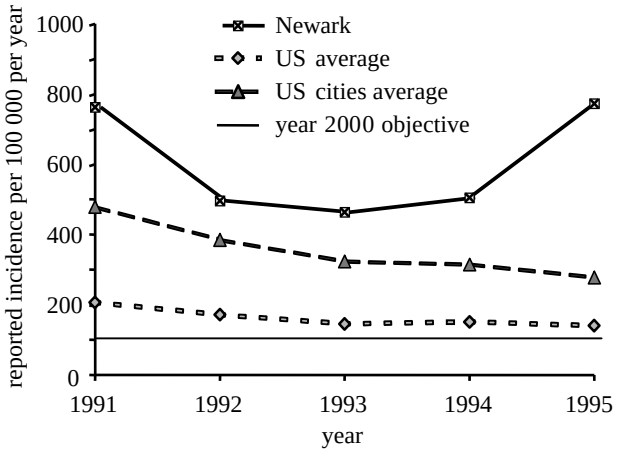

Figure 1. The recent reported incidence of gonorrhoea. The average incidence per 100 000 per year for the USA as a whole, for large cities and for Newark, New Jersey, is compared with the objective incidence for the year 2000 (Division of STD Prevention 1996). The increased incidence in 1995 is probably a product of improved laboratory reporting.

an STD is small (Johnson *et al.* 1993; Laumann *et al.* 1994). This has important implications for control, for if these people can be prevented from becoming infected or infecting others, a disease can be eliminated. However, attempts to put this idea into practice have been rare, with interventions generally following the line of least resistance; for example, treating patients who readily attend public STD clinics. Furthermore, in the literature a number of definitions of the core group have been used, which has hindered meaningful discussions of how best to break the chains of infection that allow STDs to persist (Rothenberg *et al.* 1996). However, despite the difficulty of translating the concept of a core group into an aid for interventions, it has become generally accepted as an explanation for the persistence of STDs within communities (Brunham 1991; Catchpole 1996).

Results from simple models are viewed with suspicion because of their failure to take into account known complexities. To take into account these complexities, other models of STDs have been developed (Garnett & Anderson 1996; Kretzschmar *et al.* 1996; Ghani *et al.* 1997). However, the ability of the simple models to explain observed epidemiological patterns has not been tested, in part because little work has been done in estimating model parameters. This study explores the basic model of gonorrhoea transmission dynamics with data from an empirical study of gonorrhoea patients attending an STD clinic in Newark, New Jersey.

(a) *Gonorrhoea in Newark*

The incidence of gonorrhoea in the United States has declined in the 1990s, but in Newark the decline in the initially higher than average incidence stalled between 1993 and 1994 (figure 1). This prompted a study to identify local risk factors among gonorrhoea patients, possible avenues for control, and the exposure of patients to HIV/AIDS-prevention activities. One focus of the interviews was to estimate the values of parameters required in modelling the spread of infection; the results from this part of the study are presented in this paper.

2. MATERIAL AND METHODS

(a) *A mathematical model of gonorrhoea*

The mathematical model describes a simplified natural history of gonorrhoea and the contacts within the sexually active population. We can roughly divide sexually active people into three categories with respect to gonorrhoea infection: (i) those that are susceptible (X); (ii) those that are infected and infectious who become or are symptomatic (Y) (this includes the incubation period, which is assumed to be relatively short (Garnett & Anderson 1993)); and (iii) those that are asymptomatically infected and infectious (A). These three categories were used by Hethcote & Yorke (1984). The flow of individuals between these categories is illustrated schematically in figure 2. There is some evidence for strain-specific acquired immunity among populations with very intense exposure to the bacteria (Plummer *et al.* 1989), but further evidence from a population where exposure is less intensive does not support an important role for acquired immunity in gonorrhoea epidemiology (Fox *et al.* 1995). Therefore, on recovery from infection, individuals are assumed to return to the susceptible class.

In the work of Hethcote & Yorke (1984) the population was divided by sex into two sexual-activity groups defined on the basis of rates of sex-partner change. The same categories are used here, except in this case four sexual-activity classes, defined according to rates of partner change, are used. Hethcote & Yorke (1984) defined mixing as varying between random and assortative, using a range of values that could be controlled by a single parameter. The influence of this mixing pattern has since been explored extensively in HIV epidemiology (Jacquez *et al.* 1988; Koopman *et al.* 1988; Anderson *et al.* 1990) and in models of gonorrhoea transmission (Garnett & Anderson 1993).

The mathematical definition of the model is presented in Appendix A. All solutions in § 3 refer to the steady state, which is approached rapidly in this deterministic framework.

The key parameters in a model for the spread of an infectious disease are those determining the duration of infectiousness, the contact pattern within the host population and the likelihood of transmission between contacts. These parameters were explored where possible in the interviews with patients in Newark, but for practical reasons a single study can only generate values for a limited number of parameters. In addition to allowing some of the parameters to be explored directly, the study in Newark prompted us to review the literature for estimates of the values of other parameters and to critically evaluate the mathematical model.

(b) *The study of sexual behaviour among patients infected with gonorrhoea*

Between 12 September 1995 and 31 March 1996 (12 April 1996 for women) all 15–29-year-old patients attending a public STD clinic in Newark, presumptively treated for gonorrhoea, were interviewed subject to the availability of an interviewer within 15 min. The interview was held after the clinical examination, and before an interview with the disease-intervention specialist. Interviews included questions exploring demographic characteristics, sexual behaviour, use of health-care services, substance abuse, exposure to HIV/AIDS-prevention activities, and willingness to adopt specific behaviours. The data presented here are restricted to interviews where cultures were positive for gonococcal infection.

Over the study period, 440 men and 133 women between the ages of 15 and 29 years had positive cultures. Of the 239 men

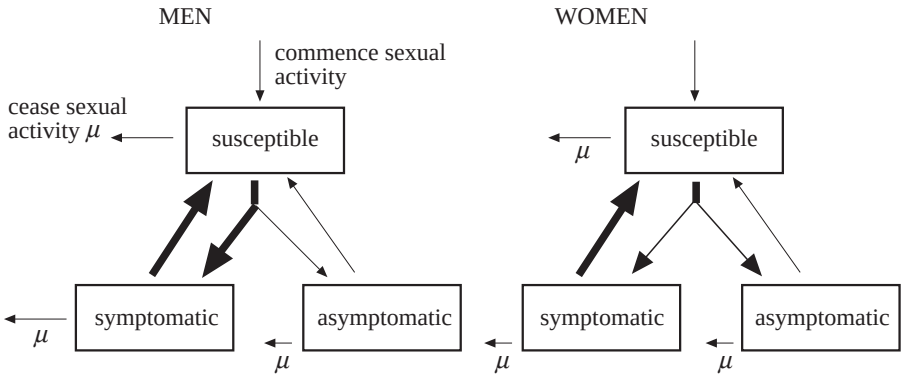

Figure 2. Schematic illustration of the model of gonorrhoea used by Hethcote & Yorke (1984). Men and women have three states with respect to infection, which are shown as boxes with the arrows representing the movement between states. The population is also divided into sexual-activity groups according to rates of sex-partner change.

invited to participate in the study, 25 refused and 214 were enrolled. Of the 53 women invited to participate, four refused and 49 were enrolled. Questions included in the interviews were aimed at exploring the key variables in the model, which are as follows.

(i) The mean duration of infectiousness (D): the time between the emergence of symptoms and treatment is a part of the infectious period and was investigated. Other values for the incubation period and duration of asymptomatic infections were drawn from the literature.

(ii) The number of sex partners (c): in order to compare the behaviour of patients with a random sample of the US population, the number of sex partners over one year was investigated. However, if people only incubate infection and are infectious for a short time, the number of partners over shorter periods than a year is more relevant. The number of sex partners over a month was investigated here. In the model the relevant parameter is the '*rate of sex-partner change*', and it is possible to estimate this rate from the difference in the number of partners over two time periods (Blower *et al*. 1990). However, this would lower the values used and fails to take account of concurrent partnerships (Garnett & Johnson 1997). In our modelling we err on the side of overestimating contacts by using the number of sex partners over a unit of time.

(iii) The transmission probability per sex partnership (β): the relationship between the per sex act probability, measured empirically in earlier studies, and the transmission probability per partnership depends on the number of unprotected sex acts within partnerships. This was investigated among gonorrhoea patients in Newark.

(c) *Parameter values derived from a review of the literature*

Some of the model parameter values could not be derived from reports from symptomatic patients. For example, one area explored in our study was the number of unprotected sex acts within a partnership. This relates to the transmission probability per partnership used in the model, but depends on the transmission probability per act.

(i) *The transmission probability per sex partnership*

If the transmission of infection occurs during sexual intercourse with a certain probability α, the probability that infection does not occur is $(1-\alpha)$, and that infection does not occur after n sex acts is $(1-\alpha)^n$. The transmission probability in the sex partnership β is given by the equation

$$\beta = 1-(1-\alpha)^n. \qquad (1)$$

This relationship is illustrated in figure 3, along with empirical studies of gonorrhoea transmission. Men from a US naval vessel were tested repeatedly for gonococcal infection after four days of liberty, whereupon they reported their number of sex partners and sex acts. The risk of a partner having been infected was estimated by screening the local population of 'registered hostesses', where a prevalence of gonococcal infection of 17.6% was found among 511 women from 35 out of 200 registered bars. The transmission per partner was 0.47 for those with one partner and 0.34 for those with more than one partner. In a model of risk including the number of sex acts and partners, the transmission probability per sex act was 0.25 (Hooper *et al*. 1978). Similarly, for women, in another empirical study, the risk of transmission rose along with the number of sex acts. In this study, 26 women, who, if infected could have only been infected by a male partner identified as a gonorrhoea 'case' in an STD clinic, were interviewed to determine the number of sex acts during which they were exposed to infection. Six out of 12 of these women who had had sex once were infected (giving a per act transmission probability of 0.5), and six out of seven who had had sex twice and seven out of seven who had had sex three times were also infected, suggesting a rapid saturation of the transmission probability to 100% (Platt *et al*. 1983).

(ii) *Incubation periods*

The incubation period is defined as the period from infection to disease, whereas the latent period is the period from infection to infectiousness. It is not clear when an incubating gonococcal infection becomes infectious (i.e. the latent period is not known). This issue is generally ignored in modelling gonorrhoea transmission dynamics, because the incubation period of disease is assumed to be very short (Brunham & Plummer 1990). For simplicity, we assume that those infected are infectious throughout their incubation period, which allows incubation to be modelled implicitly as part of the infectious period of those who become symptomatic. The incubation period was estimated in 1974 in a prospective study on a naval vessel of men receiving placebo in a double-blinded trial of prophylaxis. For 44 men who developed the disease there was a mean incubation period of three days (median 3.4 days) (Harrison *et al*. 1979). More recently, Sherrard & Barlow (1996) suggested that the average incubation period in men has increased from three to eight days

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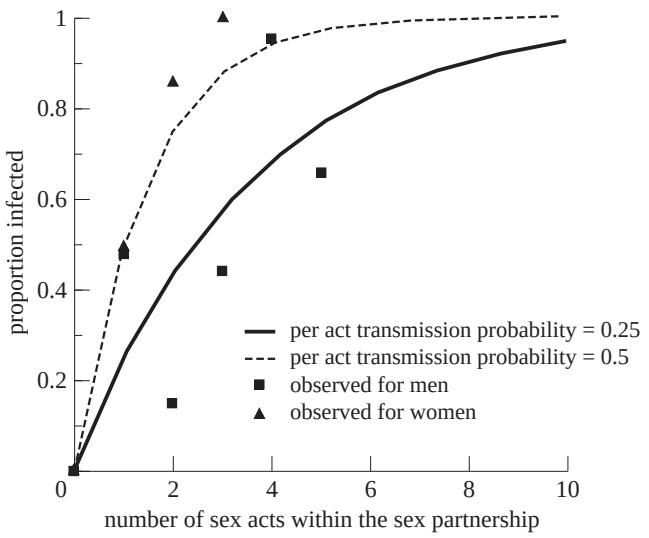

Figure 3. Theoretical and observed (Hooper *et al*. 1978; Platt *et al*. 1983) relationship between transmission probability per sex partnership and the number of sex acts within the partnership for transmission probabilities per sex act. The transmission probability from men to women per act has been estimated as 0.5, and that from women to men at 0.25.

over the past few decades. In a study involving interviewing 1615 male gonorrhoea patients, 228 could identify the day of infection and reported an incubation period with a mean of 8.3 days (median 5.6 days). We use an average eight-day incubation period for men in our model. In the absence of empirical evidence on the incubation period for symptomatic women, we assume that it is the same as that for men.

(iii) *Asymptomatic infections*

The majority of patients in our study were symptomatic and tell us little about the epidemiology of asymptomatic (defined as cases where any symptoms would not lead people to seek care) gonococcal infections. Other studies, which traced the contacts of those infected, have found that a large proportion of the population infected with gonococci are asymptomatic (Handsfield *et al*. 1974). The parameters of the model relating to asymptomatic infection include their incidence, infectiousness and duration: the proportion of newly acquired cases that are asymptomatic is difficult to estimate from prevalent infections, because the proportion that are asymptomatic depends upon the fraction of newly acquired infections that become symptomatic and the relative duration of symptomatic and asymptomatic infections. These durations will in turn depend upon health-care-seeking behaviour and local efforts to find and treat the two types of infection. Hethcote & Yorke (1984) made assumptions about the proportion of newly acquired infections that were asymptomatic (using figures of 5–10% for men and 30–60% for women) based on the assumed duration of infection and the observed proportion of prevalent infections that were asymptomatic. Very few empirical studies are available from which to estimate more reliable figures. Studies from contact-tracing often oversample symptomatic cases who attend a clinic anyway. In a prospective study of 81 infected men on board a naval vessel in the Far East in 1974, only two were asymptomatic (Harrison *et al*. 1979), whereas for women traced by Platt *et al*. (1983) 9 out of 19 had symptoms. Whether those with symptoms in these studies would have sought treatment is not known. The introduction of antimicrobials will have generated a strong selective pressure favouring asymptomatic infections. If remaining asymptomatic is heritable, which appears to be true for the AHU auxotype (Crawford *et al*. 1977), then we would expect the representation of asymptomatic bacteria to increase. However, the success of asymptomatic relative to symptomatic gonococci will depend upon the emphasis of any control strategies, and an increase in screening for asymptomatic infections may help explain the elimination of AHU/IA-1,2 from Seattle (Xia *et al*. 1997).

The relative transmissibility or the duration of untreated asymptomatic infections has not, to our knowledge, been documented. In studies of the transmission probability of gonorrhoea, no distinction was made between symptomatic and asymptomatic sources of infection (Hooper *et al*. 1978; Platt *et al*. 1983). If the transmission probability depends on whether infections are asymptomatic, then the observed transmission probabilities will, in part, have depended upon the fraction of the source population that was asymptomatic. Patients infected with the frequently asymptomatic AHU/IA-1,2 bacterial strain were found to have Gram-negative intracellular diplococci in Gram-stained smears 20% of the time, significantly less than the 48% of times recorded for symptomotic strains, suggesting that the strain may be less infectious (Whittington *et al*. 1994). However, in a study by Potterat *et al*. (1983), contacts of women with pelvic inflammatory disease (PID) were more likely to be asymptomatic. The above studies are inconclusive as to whether asymptomatic infections are less infectious. For the sake of simplicity, we assume that asymptomatic infections are as infectious as symptomatic infections.

The duration of untreated (symptomatic) infections explored in a pre-antibiotic prospective study of gonorrhoea cultures in 73 incarcerated women monitored for four months found that 43% became culture negative (Mahoney *et al*. 1942). However, the results of the study are difficult to interpret. The women all started off with the disease (i.e. there is no indication of how long they had been infected). All of those who became culture negative still had disease symptoms, and 12% of the population became negative and then positive again. Given that they were imprisoned to prevent them being involved in prostitution, it seems more likely that this was a problem with cultures rather than reinfection. Thus, there are no data on the spontaneous resolution of gonorrhoea in women. The same is true of the men studied with asymptomatic infection where 18 men monitored for 7–165 days until treatment remained asymptomatic (Handsfield *et al*. 1974). If asymptomatic infections fail to clear up, their mean duration will be the inverse of the rate at which they are detected and treated, or treated coincidentally. This rate will depend on the rate at which women are screened and how well targeted the screening is. The mean duration of asymptomatic infection typically used in modelling studies is six months (Hethcote & Yorke 1984; Brunham & Plummer 1990; Garnett & Anderson 1993; Kretzschmar *et al*. 1996). This is based on the relationship between the prevalence of symptomatic gonococcal infections in surveys, and the proportion of newly acquired cases that are asymptomatic or symptomatic (Hethcote & Yorke 1984). This relationship is illustrated in figure 4, where the prevalence of symptomatic and asymptomatic infections in men in the model is shown as a function of the proportion of incident infection in men that are asymptomatic. With 5–7% of incident infections remaining asymptomatic, a six month mean duration of asymptomatic infection compared to a 12 day mean duration of symptomatic

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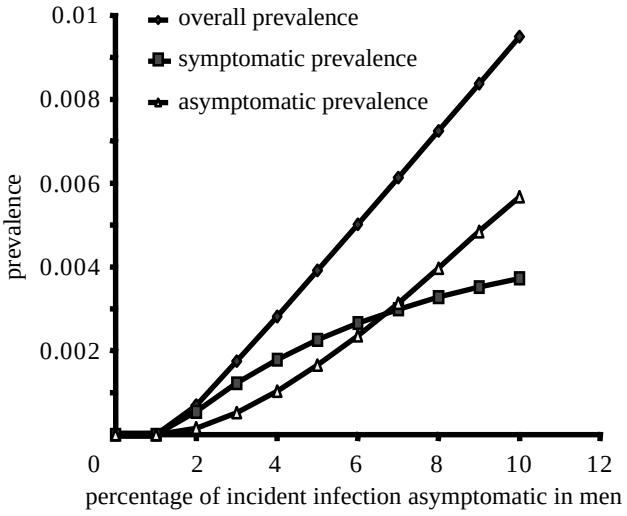

Figure 4. The prevalence of asymptomatic and symptomatic infection in men for different assumptions about the proportion of newly acquired infections in men that are asymptomatic. It was assumed that 40% of newly acquired infections in women remain asymptomatic. Other parameters are those presented in Appendix B. Since more infections are asymptomatic, the prevalence of symptomatic infections also increases because of the increased reproductive rate of the infection. When *ca*. 7% of incident male infections are asymptomatic, the prevalence of asymptomatic infections exceeds the prevalence of symptomatic infections.

infection would give the empirically observed 40–60% proportion of prevalent cases as asymptomatic (Handsfield *et al*. 1974; Potterat *et al*. 1983).

3. RESULTS

(a) *Empirical study results from the Newark STD clinic*

(i) *Duration of symptomatic infections*

Ninety-five per cent of men had urethral discharge, 76% had dysuria and 95% came to the clinic because of their symptoms. The proportion reporting symptoms amongst women was 76%. Sixty per cent of the women reported vaginal discharge and 43% reported abdominal pain. Only 47% of the women came to the clinic because of their symptoms, while 45% came to the clinic because of their partner's symptoms. For those with symptoms, the time between first noticing symptoms and attending the clinic was a mean of 12 and a median of seven days for women, which was longer than the mean of five and median of three days for men (figure 5).

(ii) *Numbers of sex partners*

The number of sex partners patients reported over the last 12 months is compared with reports from a random sample of the US population from the National Health and Social Life Survey (NHSLS) (Laumann *et al*. 1994) (figure 6*a*,*b*). As expected, those infected with gonorrhoea report many more partners. However, many of the women patients report only one partner. Men with gonorrhoea are much more likely to report over five sexual partners over the last year. The difference between male and female patients is more pronounced over one month, a period more likely to be relevant to gonorrhoea (figure 6*c*). Over the last month the men had been in a total of 463 sexual partnerships and the women in 63 sexual partnerships, a discrepancy commonly observed in studies of sexual behaviour, which is anomalous for a random sample because in a closed population the number of heterosexual partnerships formed by men must equal those formed by women. Potential explanations include male overreporting and/or female underreporting, a small fraction of very-high-activity women failing to be captured in the sample (Johnson *et al*. 1993), or rounding errors in the reports of men and women with very many partners (Morris 1993). However, the current study is not from a random sample, but from those infected with an STD. A transmission probability of less than one and different variances between sexes in sex-partner numbers could generate different numbers of partners for men and women with gonorrhoea. For example, a few high-sexual-activity men could be at risk of gonorrhoea and could infect low-activity women. However, if this were the case we would expect more women than men as patients. Most explanations of the sex discrepancy in the mean number of partners in general population surveys hinge on there being greater variance in the numbers of women's sex partners. The reason why high-activity women are not found in our sample could be because they fail to report their true number of partners, because they are treated through other facilities, or because they do not present for treatment as they remain asymptomatic.

For modelling the proportion of men in the lower-activity groups and in the two high-activity groups combined was derived from the NHSLS data, but in Newark many patients had higher numbers of sex partners than reported in the NHSLS (Laumann *et al*. 1994). These behaviours are those of the highest activity group, but there is no available estimate of the fraction of the population they represent. The sexual behaviour of women in the model had to be derived from the behaviour of the men rather than from the very low levels of sexual activity reported (see Appendix A). We assumed that a greater proportion of women had low rates of partner change.

(iii) *Transmission probabilities: sex acts within partnerships*

Condoms are effective barriers to the transmission of bacterial STDs (Cates & Holmes 1996). Patients were asked both about their number of sex acts over the last month and the number of these that were protected by condoms. This provides us with an estimate of the proportion of sex acts that are protected by condoms. Very few people used condoms in all sex acts, although the consistent use of condoms was more common for men with casual partners (figure 7).

The number of unprotected sex acts over the last month with their main partner and with all 'casual' partners was reported (figure 8*a*,*b*). Only 16% of male patients reported having sex while symptomatic. For both men and women, the cumulative number of sex acts with 'casual' partners is generally lower than that with a 'main' partner. Many patients had no unprotected sex with 'casual' partners. With their main partner, patients were either exposed to infection or exposed their partner more

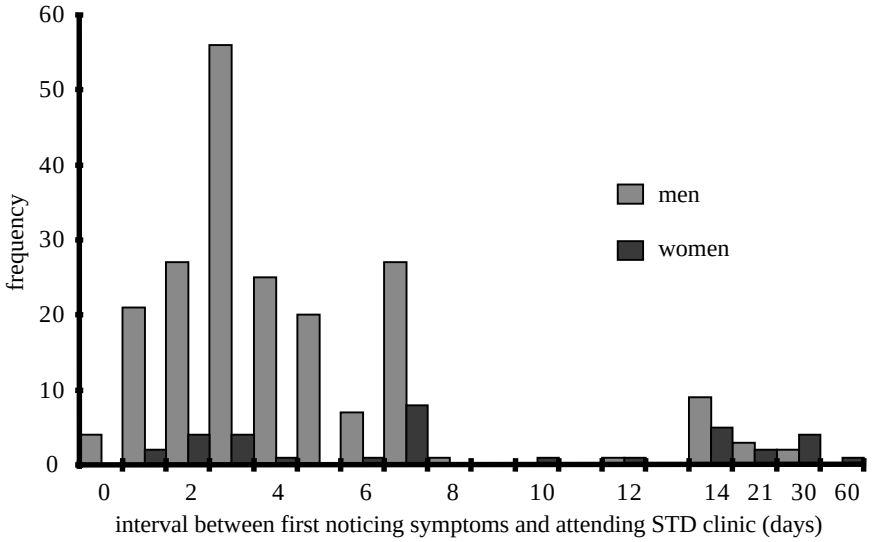

Figure 5. Reported period from the onset of symptoms to being seen at the STD clinic in Newark for patients infected with gonorrhoea.

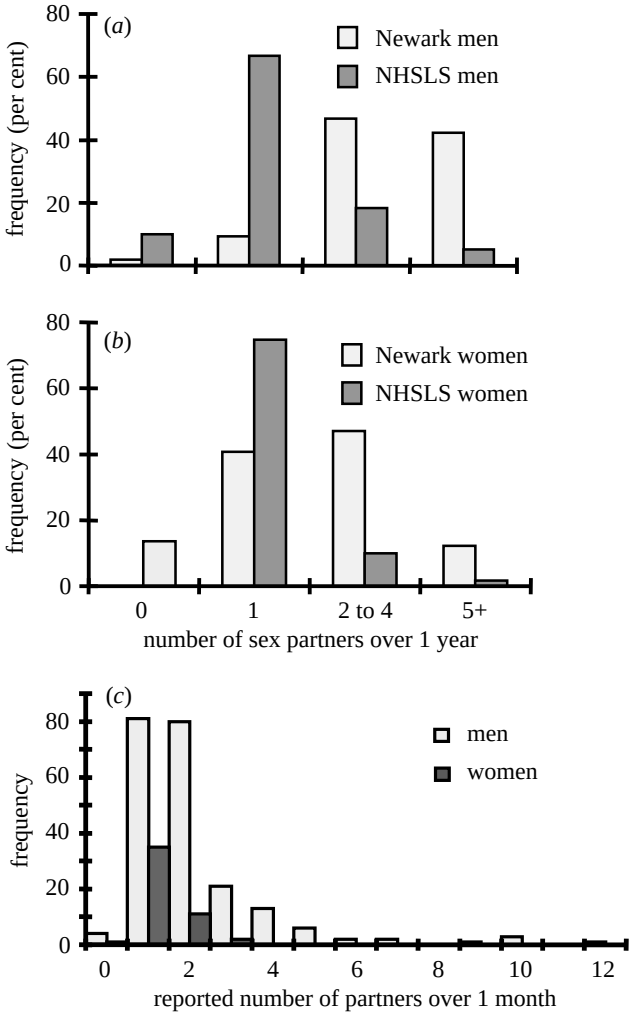

Figure 6. The reported number of sexual partners of men and women infected with gonorrhoea attending the Newark STD clinic. Frequency distribution for the number of sexual partners over one year compared with data from a random sample of the US population for (*a*) men and (*b*) women (Laumann *et al*. 1994); (*c*) shows the number of reported sexual partners over the last month for 214 men and 49 women.

often. We would expect a lower transmission probability with casual partners, but no distinction is made in the model between different types of partnerships. The results in Newark show that transmission probabilities per partnership of 0.8 from men to women, and of 0.6 from women to men, are too high, but they were necessary for the persistence of infection in the model.

(b) *Model results: the prevalence of gonorrhoea*

The set of parameter values used as a basis for simulation results is presented in Appendix B. A number of values, including the duration of asymptomatic infections, the incubation period in women, and the fraction of the population with very high activity could not be based on empirical observations. In the estimates made we have erred on the high side, because the presence of gonorrhoea in the model required such values. When we assume that the transmission probability is near its upper bounds (of one) and that there is a long incubation period, we can still only maintain gonorrhoea in simulations because of asymptomatic infections. Figure 9 shows the endemic level of gonorrhoea as a function of the percentage of newly acquired cases in women and men that are asymptomatic. For comparison with case reports, model results are presented in terms of incidence of disease cases per 100 000 per year. Only when many infections in men or women remain asymptomatic can infection persist. Once infection does persist, small increases in the incidence of asymptomatic cases can generate high incidences of disease.

This sensitivity of disease incidence to small alterations in parameter values is further evidence for the impact of changing the pattern of mixing from assortative to random (figure 10). Assortative mixing restricts infection to the high-activity class, because those infected in the high-activity class only expose others with high activity. Initially, as mixing between different activity classes increases, incidence also increases because chains of infection spread out from the high-activity groups. However, as mixing increases further, the incidence falls as chains of infection break down more often. As mixing moves

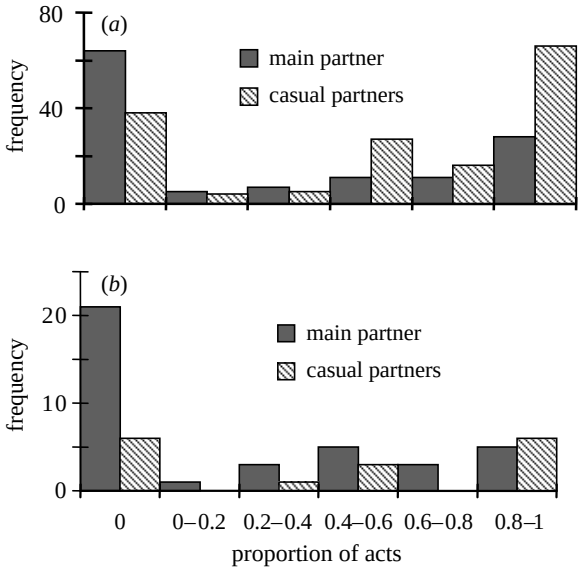

Figure 7. Reported proportion of sex acts, using condoms for protection, with a main partner and with casual partners for (*a*) men and (*b*) women infected with gonorrhoea in Newark, New Jersey.

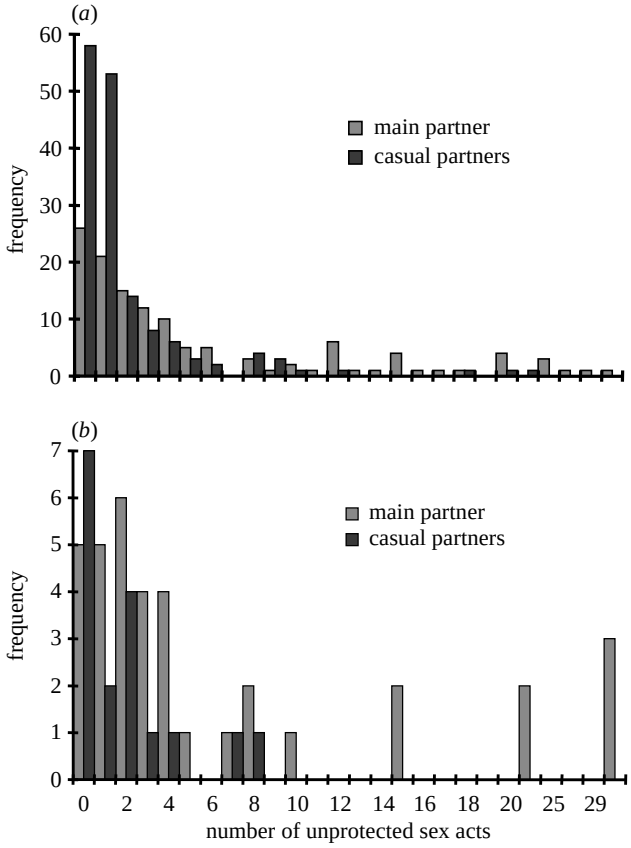

Figure 8. The reported number of unprotected sex acts over the last month with the main sexual partner and all casual sex partners of (*a*) male and (*b*) female patients infected with gonorrhoea.

towards a random pattern, the incidence passes through its observed level until the bacteria are eliminated. The figure also shows the distribution of infection between the sexual activity groups for different patterns of mixing. This can be compared with the observed distribution of

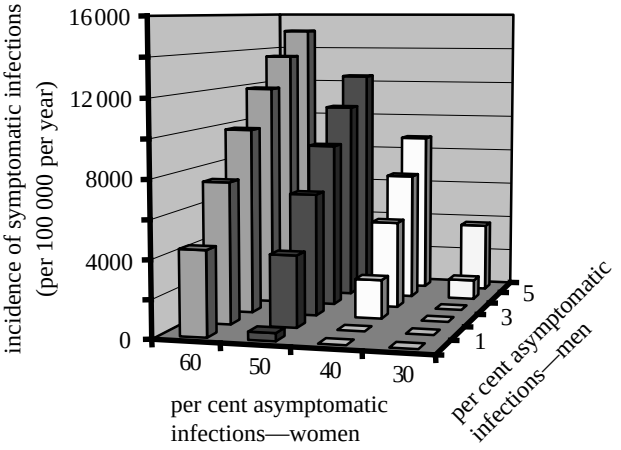

Figure 9. The simulated steady-state incidence of symptomatic gonorrhoea (comparable with reported incidence of gonorrhoea cases in the US). For estimates of parameters see Appendix B. The incidence is shown for different proportions of newly acquired infections that remain asymptomatic in men and in women. Even assuming high-transmission probabilities, only with 50% of infections in women being asymptomatic could infection persist without asymptomatic infections in men. The incidence of symptomatic infections rapidly exceeds that observed, as the proportion of infections that are asymptomatic increases.

activity in gonorrhoea patients. The large numbers of low-activity people who are infected are only possible with near-random mixing; even then, there are fewer low-activity people than observed, suggesting that some of the sampled patients are underreporting their numbers of sexual partners.

(c) *Model results: interventions*

Model parameter values were altered to reflect the changes that would be brought about by interventions (figure 11). As the intensity of an intervention increases, there is a nonlinear decline in the prevalence of gonorrhoea where falls in incidence accelerate when the bacteria near elimination. The elimination of gonorrhoea is more readily achieved by reducing symptomatic durations in men, and asymptomatic durations in women, but is sensitive to reductions in both symptomatic and asymptomatic durations in both men and women (figure 11*a*,*b*). In figure 11*c* we also illustrate the reduction in prevalence achieved through reducing transmission probabilities per partner by a given percentage of their initial value. A reduction in sex-partner change rates across all activity groups gives exactly the same result. Reducing activity in only the small fraction of the population with very high rates of sex-partner change is nearly as effective. The acute sensitivity of gonorrhoea to small changes in parameter values has not been born out by experience, and these results should be interpreted with great caution.

4. DISCUSSION

The aim of our study was to combine data from reports of behaviour of gonorrhoea patients with a review of the literature to derive realistic estimates for all the parameters in the model first developed by Hethcote &

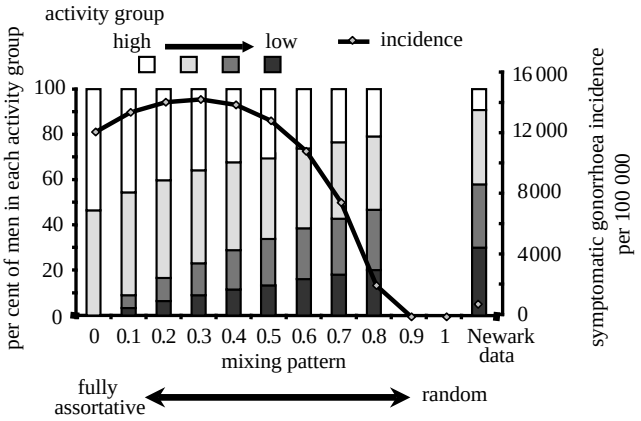

Figure 10. The modelled and observed incidence of symptomatic gonorrhoea infections along with the distribution of activities of those infected. The pattern of mixing, according to rates of sex-partner change, is varied on a scale from fully assortative to random (other parameter values are in Appendix B). Only with near-random mixing are the incidences similar to those observed. However, the proportion of the population in the highest activity group was adjusted to maintain incidence at a reasonable level. Therefore, the distribution of sexual activity in those infected is more informative about the pattern of mixing in the population. Near-random mixing generates a pattern most closely resembling that observed, but there is likely to have been some underreporting of activity.

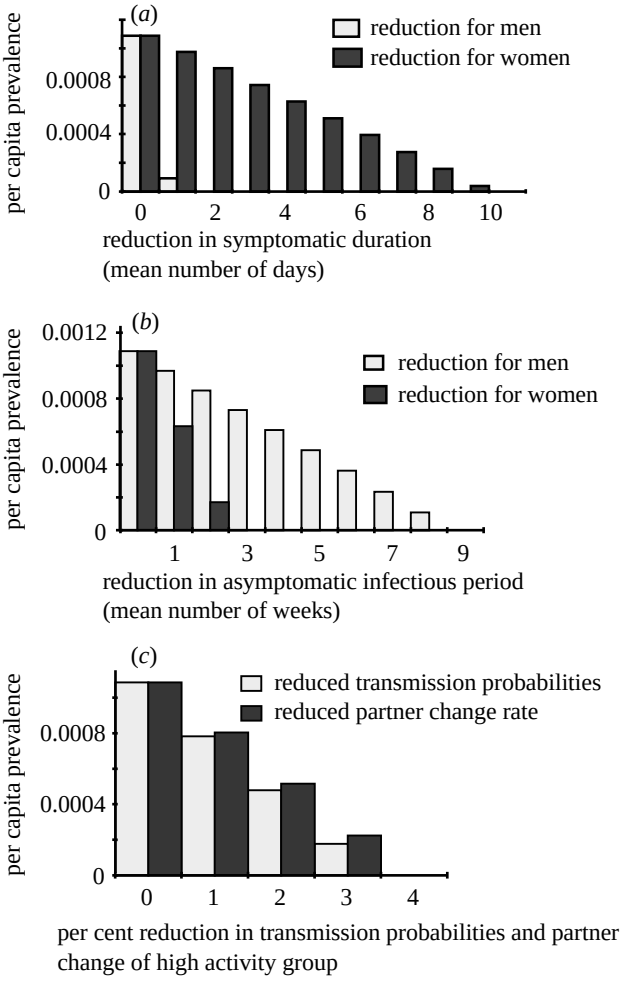

Figure 11. The impact of interventions on the endemic prevalence of gonorrhoea: (*a*) the impact of reducing the average duration of symptomatic infection for men or women by a given number of days; (*b*) the impact of reducing the mean duration of infectiousness in asymptomatic cases in men or women; (*c*) the impact of reducing the transmission probabilities from men to women and vice versa by a given percentage, and reducing the rate of sex-partner change of the highest activity group by a given percentage.

Yorke (1984). This exercise has raised two fundamental questions. First, why are the reported behaviours only adequate for the persistence of gonorrhoea if we make extreme assumptions about transmission probabilities and asymptomatic infections? Second, for observed incidences of gonorrhoea, why is the model incidence unrealistically sensitive to small changes in parameter values? The answer to the first question probably lies in problems with the reported behaviours or biases in attendance at public STD clinics (in particular there must be women with higher rates of sex-partner change within the population), or our understanding of the importance of asymptomatic infections, whereas the answer to the second question probably lies in inadequacies of the model.

The existence of a 'core group' of people who have very high-risk behaviours has been a ready answer to the question of how gonorrhoea persists. Attempts to demonstrate the existence of core groups have focused on certain sections within populations having a higher risk of infection (Rothenberg 1983; Potterat *et al.* 1985). The core group must include those who have a high risk of transmitting as well as acquiring infection (Potterat *et al.* 1985), and our results indicate that, according to self-reported behaviours, very few patients infected with gonorrhoea would fall within the core group. This could be because the patients attending the STD clinic are greatly underreporting their sexual activity, or because those people with the highest levels of risk do not attend public STD clinics. The small number of women attending the clinic, and their reports of low numbers of partners, suggest that those women with the greatest risk of transmitting gonorrhoea do not attend the clinic. A complementary explanation is that the mean duration of asymptomatic infections (which has remained unmeasured) has been greatly underestimated in previous studies of gonorrhoea.

In the model a number of biological and behavioural variables cannot be reliably estimated. The pattern of sexual mixing has received considerable attention. Models have illustrated the importance of this pattern (Garnett & Anderson 1993, 1996; Jacquez *et al.* 1988; Koopman *et al.* 1988; Anderson *et al.* 1990; Anderson & May 1991). Empirical studies are hampered by the sensitivity of identifying sexual partners, but a number of studies of patients with bacterial STDs (Granath *et al.* 1991; Renton *et al.* 1995; Garnett *et al.* 1996) and of the general population (Laumann *et al.* 1994) suggest that mixing is near random. However, the modelling of sex-partner networks and simulated sampling indicate that in such studies there is likely to be a bias away from assortative mixing (Ghani *et al.* 1998). Nonetheless, the distribution of behaviours of patients in the Newark STD clinic suggests that the pattern of mixing must be fairly near random.

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The acquisition of strain-specific acquired immunity to gonorrhoea has been suggested by studies of serotypes in a high-risk community (Plummer *et al.* 1989). This could be included in our model, but would only compound the problems identified as any reduction in susceptibility will decrease the chance of infection persisting in a population. The existence of gonococcal strains would help explain the ability of the bacteria to overcome herd immunity and why there is not a higher prevalence of infection in those with the highest activity, but could not explain the lack of an identifiable core group in our patient population. It could be that strain-specific immunity led to an underestimate of the transmission probability of gonorrhoea in the studies of Hooper *et al.* (1978) and Platt *et al.* (1983). However, this is unlikely to have had a major effect on transmission in the context of the former study, which was of two normally separate populations meeting, and the latter study, which was a lower-prevalence community than that in Nairobi (Plummer *et al.* 1989).

In model results, because a larger proportion of newly acquired infections in men is symptomatic, the modelled incidence of gonorrhoea is more sensitive to reductions in the male than the female symptomatic period. However, there is more scope for shortening the longer female symptomatic infectious period. In both cases, our model results assumed that all men and women with symptoms continue to have unprotected sex, whereas our empirical results suggest that very few patients expose their partners to risk when symptomatic. Our figures are in line with those of (i) Potterat *et al.* (1987), who found that 75% of symptomatic men denied continuing sexual activity after the onset of symptoms; and (ii) Upchurch *et al.* (1990), who found that 30% of patients reported having sex while symptomatic. Similarly, the reported delays before attending clinics are in agreement with a study by Hook *et al.* (1997), who found that 144 out of 154 men (93.5%) and 12 out of 16 women (75%) infected with gonorrhoea attended STD clinics within a week of developing symptoms. Hence, the incubation period before symptoms appear is likely to be a more critical part of the infectious period than the symptomatic infection in those with symptoms.

Shortening the asymptomatic period is more effective in women than in men, because of the greater likelihood of women becoming asymptomatically infected. This result depends upon the same asymptomatic infectious duration for men and women, an improbable but standard assumption. If the asymptomatic infection lasted longer in men, because of less-intensive screening they would play a more significant role as a reservoir for infection, and reducing the duration of asymptomatic infections in men could play an important role in the control of gonorrhoea.

The infection is sensitive to slight reductions in the transmission probability or the rate of sex-partner change. A small reduction in activity of those with very many partners is almost as effective as reducing activity across the population, which is the justification for targeted interventions. However, our results suggest that asymptomatic infections are most important in maintaining infection, so that targeting patients in STD clinics may not be the most effective strategy.

As highlighted above, the modelled interventions have to be interpreted with caution. The sensitivity of gonorrhoea in the model to reductions in risk is unrealistic. To explain this we must look more critically at the model's structure. First, the model fails to take chance into account. Second, the model assumes that we have a single at-risk population rather than a number of linked populations. Third, the model fails to take into account the detailed sex-partner network structures. The model we present has been fundamental in STD epidemiology for a number of years, but our results suggest that new models need to be developed. To some extent this has been happening. Conceptual models of gonorrhoea transmission have explored the complex social and geographical patterns involved (Wasserheit & Aral 1996), and empirical studies of these patterns have taken place (Rothenberg & Narramore 1996). However, the studies of models developed to include movement between the core and non-core (Stigum *et al.* 1997), and to include network structures (Kretzschmar *et al.* 1996; Ghani *et al.* 1997), have so far not explored their ability to generate observed epidemiological pattern. Such validation will be an important step in developing a theoretical understanding of gonorrhoea transmission dynamics.

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APPENDIX A. MODEL DEFINITION

For each sex, k, ($k = 1$) for men and $k = 2$ for women, (k' refers to the opposite sex from k) the susceptible (X_{ki}), symptomatic infected (Y_{ki}), and asymptomatic infected (A_{ki}), classes are stratified into the four groups, i, according to their mean rate of sex-partner change, c_{ki}. The rate of movement between classes depends on the following ordinary differential equations:

$$\frac{\mathrm{d}X_{k,i}}{\mathrm{d}t} = \mu N_k \phi_{k,i} - \mu X_{k,i} - X_{k,i}\beta_k c_{k,i}\rho_{k,ij}\frac{(Y_{k'j} + A_{k'j})}{N_{k'j}} + \sigma_k Y_{ki} + \gamma_k A_{ki},$$

$$\frac{\mathrm{d}Y_{k,i}}{\mathrm{d}t} = \theta_k X_{k,i}\beta_k c_{k,i}\rho_{k,ij}\frac{(Y_{k'j} + A_{k'j})}{N_{k'j}} - (\mu + \sigma_k)Y_{k,i},$$

$$\frac{\mathrm{d}A_{k,i}}{\mathrm{d}t} = (1 - \theta_k)X_{k,i}\beta_k c_{k,i}\rho_{k,ij}\frac{(Y_{k'j} + A_{k'j})}{N_{k'j}} - (\mu + \gamma_k)A_{k,i}.$$

In these equations β_k is the transmission probability per sex-partnership from sex k' to sex k (an estimate for these transmission probabilities was based on earlier studies (Hooper *et al.* 1978; Platt *et al.* 1983). The value ρ_{kij} refers to the probability that when someone of sex k from group i forms a sex-partnership, it is with someone from group j. The value of ρ_{kij} is assumed to vary on a scale from fully assortative to random, defined by the parameter ϵ.

$$\rho_{kij} = \epsilon\delta_{ij} + (1 - \epsilon)\frac{c_{k'j}N_{k'j}}{\sum_s c_{k's}N_{k's}},$$

where $\delta_{ij} = 1$ when $i = j$ and $\delta_{ij} = 0$ when $i \neq j$. When $\epsilon = 1$ then mixing is fully assortative, whereas when $\epsilon = 0$ it is random. It is necessary that the partnerships

formed by the activity groups of one sex balance with those formed by the opposite sex, such that

$$\rho_{kij} c_{ki} N_{ki} = \rho_{k'ji} c_{k'j} N_{k'j}.$$

This balance was maintained by assuming that ϵ was the same for the mixing matrix of men with women and vice versa, and that the number of sex-partnerships supplied by an activity group, $N_{ki}c_{ki}$, was the same for the men and women for each group. This last condition was used to calculate the rate of sex-partner change for women:

$$c_{2i} = (c_{1i}N_{1i})/N_{2i}.$$

The proportion of women in each activity group was estimated from the broad groups of Laumann *et al.* (1994) and assumes that there is a larger fraction of low-activity women than is the case for men. The mechanism of generating a balance between sexual-activity classes, altering the rate of sex-partner change of women in activity groups, was chosen because this behaviour was the least well-defined in our data.

A proportion θ_k of infections for sex k become symptomatic and receive treatment at a sex-dependent rate σ_k. Other infections remain asymptomatic and are treated or resolve at a sex-dependent rate γ_k. The rate μ is both the rate at which individuals leave the sexually active population represented by the model and the per capita rate of entry. The equality of these two rates keeps the population constant. The proportion ϕ_{ki} is the proportion of the sex k who enter the sexual activity group i. Steady-state solutions of the model were calculated numerically using a Runge–Kutta method.

APPENDIX B. THE BASIC SET OF MODEL PARAMETER VALUES USED IN THE SIMULATIONS

parameter	symbol	value (men)	value (women)
entry and exit from population	μ	0.2	0.2
proportion in each activity group	$\phi_{k,i}$	$i = 1$:0.0055 $i = 2$:0.0445 $i = 3$:0.2 $i = 4$:0.75	$i = 1$:0.0055 $i = 2$:0.0145 $i = 3$:0.1 $i = 4$:0.88
mean rate of sex-partner change per year	$c_{k,i}$	$i = 1$:40.0 $i = 2$:10.0 $i = 3$:2.4 $i = 4$:0.5	$i = 1$:40.0 $i = 2$:30.7 $i = 3$:4.8 $i = 4$:0.43
recovery rate ($=1$/mean duration) in symptomatic infections (day^{-1})	σ_k	1/13	1/20
recovery rate ($=1$/mean duration) in asymptomatic infections (day^{-1})	γ_k	1/185	1/185
transmission probability per partnership	β_k	men to women 0.8	women to men 0.6
proportion asymptomatic	θ_k	0.05	0.4
pattern of mixing	ϵ	0.8	0.8

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