

# *Epidemiology and Control of Curable Sexually Transmitted Diseases*

## *Opportunities and Problems*

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**Background:** Despite the availability of safe and effective treatment, infection with bacterial sexually transmitted diseases persists at a high prevalence in many populations.

**Goal:** To review the difficulties of parameter estimation when a cure is readily available and to explore the impact of different treatment and screening strategies that might maximize the benefits of using available treatments.

**Study Design:** A standard deterministic model for the spread of a bacterial sexually transmitted disease that causes symptomatic and asymptomatic infections, in which the population is stratified according to sex and sexual activity, is further stratified into two host groups to enable the modeling of different treatment and screening strategies.

**Results:** In the presence of a core group, if an infection has a high transmission probability, then screening for asymptomatic infections has a short-lived benefit. Repeated screening is slightly better if it is not restricted to a fraction of the at-risk population, but targeting of high-risk groups should be effective. Screening to treat asymptomatic infections in men could be beneficial if a substantial fraction of cases remain asymptomatic.

**Conclusions:** After the initial gains achieved through treating symptomatic infections, further reductions in the prevalence of infections can be achieved by finding asymptomatic infections. However, these gains are difficult to achieve, especially in the case of gonorrhea. Because men are likely to have an asymptomatic chlamydial infection, screening of men for chlamydia should be worthwhile.

A SAFE AND EFFECTIVE cure for an infection is the major goal of much medical research. However, once available, designing the optimal strategy for its public health use involves understanding many epidemiologic factors.<sup>1</sup> Here, we use a theoretical framework that has been developed during recent decades and encapsulates our assumptions about the transmission dynamics of bacterial sexually transmitted infections (STIs)<sup>2-4</sup> to evaluate treatment interven-

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tions in developing populations. Starting with a detailed discussion of what we do and do not know about parameter values, this widely used framework is then altered so that the impact of different approaches to finding and treating infections is clear. We do not explore contact tracing because this was the main subject explored by Hethcote and Yorke<sup>2</sup> and is unlikely to be affordable in developing countries.

Syphilis, gonorrhea, and chlamydia, the most common bacterial STIs,<sup>5</sup> can be modeled using the same theoretical framework. The parameter values controlling their epidemiology also seem to be similar, the main differences being in the clinical manifestations of the infections, differences that change the likelihood that those infected will seek care. In any model of the transmission dynamics of an infection, three variables are key: (1) the mean duration of infectiousness, (2) the probability of transmission of infection from someone infectious to a susceptible contact, and (3) the pattern of contacts within the population.<sup>3,6,7</sup> Our knowledge of each of these three factors for treatable bacterial STIs is briefly reviewed. The ethical necessity to treat those identified as infected hampers our ability to study and understand bacterial STIs. This unavoidable situation makes precious the sources of information that we do have—data predating treatment and indirect evidence. However, such sources should be treated with caution and carefully interpreted.

### **Duration of Infectiousness**

The duration of untreated infections is currently the most difficult variable to measure for bacterial sexually transmitted diseases (STDs), given that an infection must be treated as soon as it is identified. Therefore, we have to rely mainly on historical records of infections that were followed in the

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absence of treatment. In interpreting historical reports of the duration of infectiousness, the quality of diagnosis and the ability to identify the time of infection are vital. For syphilis, where the syphilitic chancre could be differentiated from the lesions of chancroid and herpes simplex virus type 2, and where artificial inoculations were used, some data exist that suggest a mean duration of infectiousness for syphilis of approximately 6 months.<sup>8</sup> Similarly, early studies for gonorrhea have to be treated with caution. However, one source suggests that 95% of untreated symptomatic cases had recovered after 6 months, which is consistent with a mean duration of 2 months if we assume a constant recovery rate.<sup>9</sup> In contrast, no historical data exist for a nonspecific infection like chlamydia, for which accurate diagnosis has only recently become available.

In addition to historical studies, opportunities arise for inferences to be drawn from current studies, but these are problematic because of differing diagnostic methods and patient populations. Repeated screening for asymptomatic infection without treatment in the intervening period has shown a rapid spontaneous resolution of chlamydial infection.<sup>10</sup> The available sample was small and the infections asymptomatic, but the data suggest that the infectious period for chlamydia will, on average, be only 2 to 3 months. This seems to contradict recent findings of a contact-tracing study in which men were identified as contacts of infected women where the last sexual contact occurred over 6 months previously.<sup>11</sup> Six of 19 such men were found to be infected, more than would be expected if the rate of spontaneous recovery was between 25% and 50% each month. A number of explanations are possible for this apparent contradiction: (1) the men have high risks of infection and have been reinfected in the subsequent period; (2) the infections identified through contact tracing were in men, whereas the spontaneous resolution observed by Parks and colleagues<sup>10</sup> was mainly in women (infections may be more likely to generate immunity and resolve in women); and (3) that there is heterogeneity in the duration of infection and infectiousness that is host or infection dependent.

The duration of infection influences the prevalence of infection by age, which is a product of the age pattern of exposure and the length of time treated and untreated infections last. Short-lived infections are concentrated in the age group where risk behavior is most common. A continued high prevalence in older age groups, as has been observed in cross sectional studies for *Trichomonas vaginalis* among women in whom treatment is not generally provided, suggests a long duration of infectiousness.<sup>12</sup>

### Transmission Probabilities

Because it is often indirect, data about the transmission probability of infection can easily be misinterpreted. Ideally, to estimate the transmission probability, one wants to

observe whether someone becomes infected after sexual intercourse with a known infectious person. However, it is difficult to envision how such studies could be undertaken. The classic study of US Navy personnel on shore leave provided one such opportunity for studying gonorrhea transmission from women to men.<sup>13</sup> This study relied on the assumption that the prevalence of infection found among women in bars on shore accurately represented the prevalence in the sex partners of the men. This prevalence will have been an underestimate because of the sensitivity of the culture methods available at the time. However, culture methods will also have underestimated the fraction of the men infected, albeit to a lesser extent. In addition, any strain-specific acquired immunity in the men may have led to an underestimate of the transmission probability to fully susceptible contacts. Nonetheless, the study indicated that there was a high transmission probability per sex act and suggests that the model of a binomial process determining transmission (i.e., that there is a probability of infection occurring on each sex act) within the partnership is reasonable. In such a case, the transmission probability within the partnership will depend on the number of sex acts. In all but the shortest partnerships, such as those observed in the study, the transmission probability for gonorrhea is likely to saturate to 100% unless some persons are immune.

The necessity to protect subjects from viral infections and the changing patterns of behavior among military personnel make such a study unrepeatable, so that to estimate transmission probabilities for chlamydia and gonorrhea from men to women, we must rely on the prevalence of infection in contact-tracing studies. However, these data rarely allow a good estimate. The first major difficulty is to identify the direction of transmission. Figure 1a illustrates an example where eight infected index men have had their contacts traced and half of these contacts are found to be infected. Assuming that those uninfected neither received appropriate antibiotics nor experienced spontaneous cure, and that they have had sex with the index patient while that patient was infected, then this provides an upper bound of 0.5 for the transmission probability from men to women. However, all the men whose partners were infected could have acquired infection from the traced partner, so the only lower bound on the transmission probability that can be estimated is 0.0—a value that is clearly too low. We learn nothing about the transmission probability from women to men because the design automatically ensures that all the men are infected. If we knew the expected proportion of contacts already infected, then we could adjust accordingly and calculate a transmission probability. However, this expected proportion depends critically on patterns of behavior within the population and the factors determining which sex partners are traced. To estimate the transmission probability, rather than its upper bound, from such contact tracing it is necessary to ensure that the contacts have no other possible

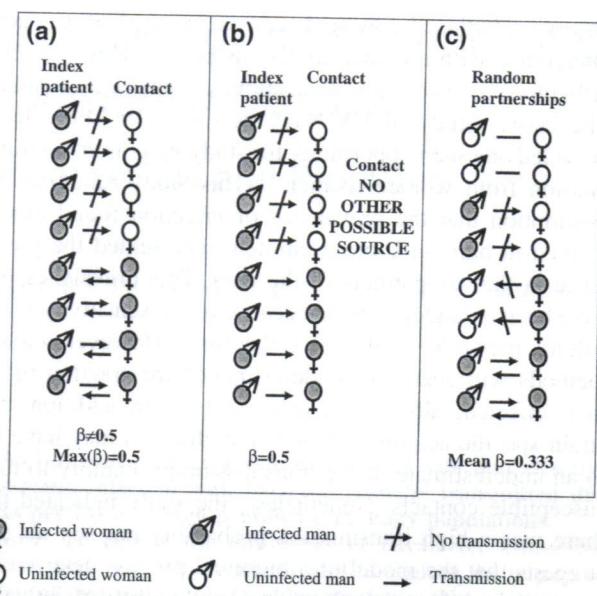


Fig. 1. The interpretation of concordant and discordant sex partnerships depends on the nature of the sample. Type **a** is normal contact-tracing data collected by tracing the partners of infected men and observing the proportion of the women infected. All the males are by definition infected, so we can learn nothing about the transmission probability from women to men in this sample. If all the men were infected by women, the observed transmission probability is 0%, whereas if none of the men were infected by the traced partners, the transmission probability is 50% (the proportion of women infected). This finding allows us to bound the transmission probability from men to women between 0% and 50%. Type **b** is contact-tracing data when all the traced partners can be guaranteed to have no other source of infection. If this is possible, then these data generate an estimate of the transmission probability, which is subject to biases in measuring the proportion infected (Table 1). Type **c** is data where partnerships are sampled at random in the population. Here, we cannot differentiate transmission from men to women and women to men, but can estimate an average transmission probability. Unfortunately, partnerships cannot be sampled on the basis of infection because this would alter the probability of including partnerships where both partners are infected.

source of infection. This was done in the study of Platt and colleagues<sup>14</sup> for a small sample, which suggested a higher transmission probability from men to women than from women to men. A further study design, which would measure the average transmission probability from men to women and women to men, is possible if we observe the concordance of infection in partnerships. However, rather

than identify partnerships through infection, it is necessary that a random sample of partnerships is used that includes those in whom there is no infection to avoid a bias toward partnerships where both are infected. In studies where partnerships are identified through one partner seeking care, it is likely that the transmission probability will be overestimated. This is because the chances of being included will be greater for a partnership where both are infected and could have symptoms and seek care than for a partnership where only one person is infected, has symptoms, and hence would seek care. The direction of transmission would be unclear in such a study, and can tell us nothing about the relative transmissibility from men to women and women to men. The relative prevalence of infection in the two sexes depends on the duration of infections and the distribution of sex behaviors, in addition to the transmission probability; therefore, the data are of little help in detecting whether there is a higher transmission probability from men to women or women to men.

An interesting variation on the contact-tracing studies is the identification of those exposed to test the use of prophylactic treatment. The key factor in interpreting such studies is that subjects were recently exposed, and those who have not already developed symptoms are not excluded. One such study suggests that syphilis has a high transmission probability of approximately 60%, but the means of identifying those that have been "exposed" is not clearly described.<sup>8</sup> For syphilis, there is an additional problem in contact-tracing data because some infected patients are identified with a latent infection that is likely to be no longer infectious. In determining the proportion of contacts that are infected, it is difficult to ensure that the patient was infectious when sexual intercourse occurred. Furthermore, the method of identifying contacts could bias contact-tracing studies to estimate transmission probabilities. If contacts who sought care for symptoms are included, then the study is likely to overestimate transmission probabilities; however, if they are excluded, the transmission probabilities are likely to be underestimated. Table 1 lists possible biases influencing estimates of transmission probabilities in contact-tracing studies.

For transmission to take place, sex has to be unprotected. If the use of condoms within partnerships is measured, then account could be taken of protection in reducing transmis-

TABLE 1. Possible Biases in Estimating the Proportion of Contacts Infected in a Contact-Tracing Study

| Infection               | Bias   | Impact on Estimate of Transmission Probability |
|-------------------------|--|--|
| All                     | Inclusion of source and spread contacts                                      | Overestimate                                   |
| Symptomatic infections  | Inclusion of patients who have attended a clinic because of symptoms         | Overestimate                                   |
| Syphilis                | Inclusion of contacts that occurred while the index was no longer infectious | Underestimate                                  |
| Chlamydia and gonorrhea | Use of insensitive diagnostics in historical data sets                       | Underestimate                                  |
| Chlamydia and gonorrhea | Spontaneous recovery of the contact  | Underestimate                                  |

sion probabilities. However, studies of infected patients who report always using condoms suggest that in addition to unreliable behavioral information, there is a high prevalence of the incorrect, unprotective use of condoms.<sup>15</sup>

### Asymptomatic Infections

Of importance to the transmission of infection and the duration of infectiousness (because symptomatic infections are foreshortened if those infected seek and receive effective treatment) is the proportion of infections that remain asymptomatic. Because symptomatic infections are more likely to be treated, they tend to be shorter lived; therefore, the proportion of asymptomatic infections found at any one time within a population is not a direct measure of incident infections that remain asymptomatic. Additionally, the transmission probability may be different for asymptomatic infections because a smaller, slower-growing bacterial infection may be less transmissible,<sup>3</sup> but symptomatic infections may be less likely to be transmitted because a large proportion of patients attending STD clinics report not having unprotected sex while symptomatic.<sup>16–18</sup> What matters in terms of identifying infections to be treated is not whether detectable signs or symptoms are present, but whether the symptoms are sufficient to induce someone to seek care. Symptoms, and the response to them, are likely to vary greatly between populations, not only because of phenotypic differences in bacteria, but also because of differences in the perception of what constitutes normal reproductive health and how accessible STD treatment services are geographically, financially, and socially. Clearly, because symptoms bring patients to STD clinics, self-referred cases offer no clues as to the proportion of infections that remain asymptomatic. If we know the relative mean durations of asymptomatic and symptomatic infections, the proportion of infections that are asymptomatic in cross-sectional surveys (e.g., like that reported in Handsfield and colleagues<sup>19</sup>) allows an estimate of the proportion of infections that remain asymptomatic. This proportion was estimated to be between 5% and 10% by Hethcote and Yorke<sup>2</sup> on the basis that a symptomatic infection lasts for an average of 6 months. However, as described earlier, 6 months is not a reliable period. In addition, the proportion of infections that are found to be asymptomatic will depend on the context in which they are found, ranging from 25% to 80% asymptomatic in infected women.<sup>9</sup> A better estimate for the proportion of men remaining asymptomatic comes from a prospective study where the development of infection was observed for 14 days and only 2 of 81 infections remained asymptomatic.<sup>20</sup> This may overestimate the proportion of infections that remain asymptomatic because patients were only followed up for 14 days, after which the two asymptomatic infections could still have evolved to symptomatic infections. However, the use of culture lacks some sensitiv-

ity, so some asymptomatic infections might have been missed. Additionally, the careful follow up of patients for signs will include as symptomatic many patients who may not seek care for the observed manifestations. On balance, this study probably provides a lower bound for the proportion of gonococcal infections that are asymptomatic.

### Patterns of Contact

Starting from a low base, because of societal sensitivity to the study of what are essentially private behaviors, our knowledge of sexual behavior has improved during the period after the emergence of AIDS. Studies of random samples of populations<sup>21–23</sup> and of patients attending STD clinics<sup>18</sup> have informed us about the distribution of many behaviors. Some behaviors, like the number sex partners over a given period in a random sample of the US population and patients with gonorrhea in Newark, New Jersey<sup>18</sup> (Figure 2) are relatively easy to measure. Other relevant behaviors, such as the frequency of sex within partnerships with different characteristics and the pattern of sex partner choice according to risk behaviors, are less straightforward. The number of sex partners reported by the subjects illustrates the existence of great heterogeneity in risk behavior and shows that those infected with gonorrhea have, on average, more sex partners. In addition, Figure 2 illustrates other interesting patterns

1. The number of partners of those infected with gonorrhea during 1 month, if multiplied by the number of months in the year, would generate much higher numbers of partners per year than are reported. This implies that people are most likely to be infected by an STD during transient periods of unusually high levels of partner change.
2. A substantial number of those infected with gonorrhea report low numbers of partners. Although an individual's risk of infection can be increased by their own behavior, it is also greatly influenced by their sex partner's risk. Infection alone is not a good marker of persons likely to transmit infection.
3. The comparison of the reported behavior of men and women is inconsistent, particularly for patients with gonorrhea. This finding may be because women are failing to report their partnerships. However, the male and female patients with gonorrhea were recruited to the study from the same public STD clinic, and fewer women were infected with STDs. Fewer women could be infected than men if there was greater variance in female behavior and those women infected had more partners than men, or if there was a much higher transmission probability from women to men than from men to women. However, the reverse seems to be true in the data. A sex difference in the proportion

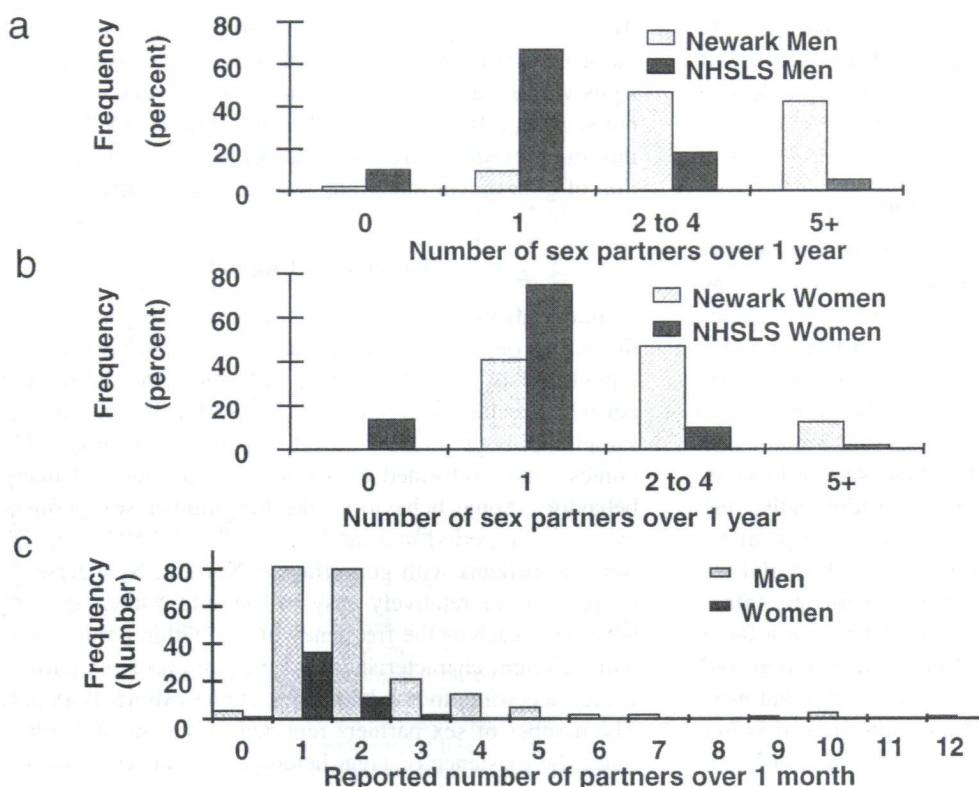


Fig. 2. A comparison of the reported number of sex partners during a 12-month period from **a**, a random sample of men; **b**, a random sample of women<sup>22</sup>; and **c**, a sample of gonorrhea patients<sup>18</sup>. **c**, The number of partners during the previous month was also reported by patients with gonorrhea.

of infections that are symptomatic could explain why there are fewer women than men in the sample, but would not explain why the women report fewer partners. The most likely explanation of this discrepancy is that women with higher risk behavior do not use public STD clinics when infected, but instead access more informal suppliers of antimicrobials.

The pattern of risk behavior within partnerships will determine the transmission probability within the partnership. A number of studies have explored how the frequency of sex relates to the number of sex partners.<sup>18,24,25</sup> Unfortunately, it is often difficult to establish the number of sex acts within partnerships, the duration of sex partnerships, and the patterns of barrier contraceptive use in those partnerships, but this is an area that would repay careful study.

Choice of sexual partners can be determined by interviewing the individual where the subject is likely to know the relevant details (e.g., their partners' age, sex, ethnic group, profession). However, the details that are important for STD epidemiology (e.g., number of sexual partners) are less likely to be known. There is an important distinction between regular, stable partners' characteristics and those of infrequent casual partners. Marriage partners are clearly similar in terms of social and demographic variables, but this may not be true for casual partnerships. For example, partners who live together will certainly share a social and

geographic location, though these may have differed initially. If the number of sexual partners correlates with social and demographic variables, the sexual partner choice is likely to lead to people having sex with people with similar behaviors. Studies suggest that mixing may be more random than this<sup>26,27,22</sup> though sampling biases could influence this conclusion.<sup>28</sup>

#### Modeling Interventions: Screening and Treatment Strategies

The detailed estimation of parameters described above is necessary to understand the difference between sexually transmitted organisms and to develop more subtle models of the persistence of infections in developed countries. However, we can use the crude estimates that have been derived in a simple mathematical model to illustrate some general rules about strategies aimed at treating symptomatic and asymptomatic infections in developing countries.

Health policy is a major determinant of whom is treated when infected with an STI and how quickly.<sup>29</sup> A passive healthcare strategy may treat only the symptomatic infections where patients seek care. To treat asymptomatic infections, patients have to be actively sought; contacts can be traced or target populations can be screened. Because the impact of contact tracing was explored by Hethcote and Yorke,<sup>2</sup> we will concentrate on the latter type of active

program: screening and treatment. There are choices regarding how a screening program could operate. It could be integrated into the primary health care system, especially the antenatal or family planning services, and would occur on a continuous basis. We will call such a provision *continuous screening*. In resource-poor settings, it may only be possible to periodically provide treatment from mobile clinics. We term this treatment *periodic screening*. In some areas, the use of mass treatment may be appropriate, as has been trialed in Uganda.<sup>30</sup> Because this different approach to treating asymptomatic infections will have the same epidemiologic outcome as screening and treatment, the two approaches will be considered interchangeably. Some persons may have greater access to care or be more likely to use existing services than others. Repeated screening may, therefore, identify the same low-risk group on subsequent rounds of treatment. Surmounting this problem in practice is difficult, so we will explore the effects of these patterns of inclusion in the model. Programs that reach those amenable to screening will be called *repeat screening*, whereas those that manage to reach throughout the population will be termed *random screening* because a random choice of who is screened occurs at each round. For simplicity, we assume that the likelihood of being in a group repeatedly screened is independent of risk behavior. However, it is likely that the risk of STDs will differ according to access to care, with those at highest risk being the least likely to be screened. This would exacerbate the problems of repeat screening and could be explored in the proposed theoretical framework. However, we explore the impact of the opposite relationship, where a program attempts to identify those with the highest risk of infection and targets screening to high-activity groups. Another factor that could be explored using the framework is the impact of treatment and screening on risk behaviors. It is unlikely that transmission probabilities, time before treatment, and rate of sex-partner change will remain unchanged by the experience of screening, treatment, and associated counseling. However, for simplicity we make the most conservative assumption in our analysis that behavior will not change, but in Methods include mechanisms to allow the experience of treatment to alter behavior.

## Methods

### Mathematical Framework

Despite the many uncertainties in parameter estimates and the simplification of complex behaviors, a useful theoretical framework has been developed to describe the transmission dynamics of bacterial STDs. Since the initial description of this framework by Hethcote and Yorke,<sup>2</sup> many additions have improved the representation of patterns of risk behavior.<sup>31</sup> Nonetheless, conclusions can still be drawn

about the impact of interventions from slightly modified versions of this framework. Here, we use such a modification to explore the impact of different patterns of screening and treatment using best estimates of parameters.

The population is divided into three categories: susceptible,  $X_{k,l,i}$ , symptomatically infected,  $Y_{k,l,i}$ , and asymptotically infected,  $A_{k,l,i}$ . For simplicity, the incubation period and any strain-specific acquired immunity is ignored. The indices  $k$ ,  $l$ , and  $i$  refer respectively to sex ( $k = 1$  for men,  $k = 2$  for women;  $k'$  denotes the opposite sex from  $k$ ), sexual partner change rate ( $l = 1, \dots, 4$ ) and host group ( $i = 1, 2$ ). The *host group* is a generic stratification of the population that allows some hosts to have different attributes in the model. For example, one host group could have a slower recovery rate from infection, could be more likely to seek treatment, could be more likely to be screened for infection, or could have different risk behaviors represented by differences in transmission probabilities or partner-change rates. The changes in the distribution of infection are described in the following ordinary differential equations:

$$\begin{aligned} \frac{dX_{kli}}{dt} &= \mu N_{kli} - X_{kli} \sum_{l=1}^4 \sum_{i=1}^2 \left( c_{klmij} \rho_{klmij} \beta_{k'j} \left[ \frac{Y_{k'mj} + A_{k'mj}}{N_{k'mj}} \right] \right) \\ &\quad - \mu X_{kli} + \sigma_{kli} Y_{kli} + \sigma'_{kli} A_{kli} \\ \frac{dY_{kli}}{dt} &= \phi_k X_{kli} \sum_{l=1}^4 \sum_{i=1}^2 \left( c_{klmij} \rho_{klmij} \beta_{k'j} \left[ \frac{Y_{k'mj} + A_{k'mj}}{N_{k'mj}} \right] \right) \\ &\quad - (\mu + \sigma_{kli}) Y_{kli} \\ \frac{dA_{kli}}{dt} &= (1 - \phi_k) X_{kli} \sum_{l=1}^4 \sum_{i=1}^2 \left( c_{klmij} \rho_{klmij} \beta_{k'j} \left[ \frac{Y_{k'mj} + A_{k'mj}}{N_{k'mj}} \right] \right) \\ &\quad - (\mu + \sigma'_{kli}) A_{kli} \end{aligned}$$

where,  $N_{kli}$  is the sum of the population across disease states ( $N_{kli} = X_{kli} + Y_{kli} + A_{kli}$ ). The population is assumed to be stable with entry and exit rates equal ( $\mu$ ). The proportion in each sex, activity group, and host group is determined by the initial distribution of the entire population  $N$ . On infection, a fraction,  $\phi_k$ , of infections become symptomatic and have a recovery rate,  $\sigma_{kli}$ , whereas those who remain asymptomatic have a recovery rate,  $\sigma'_{kli}$ . The rate of sexual partner change of someone of sex  $k$ , activity group  $l$ , and host group  $i$  is specific to the activity group  $m$  and host group  $j$  with which they are forming partnerships. Initially, each activity group and host group is assigned a rate of sexual partner change ( $c_{kli}$ ) that applies to partnerships with all other groups. This rate is then used with the number of persons in the group and a mixing parameter ( $\epsilon$ ) to calculate the mixing matrices. The elements of the mixing matrix,  $\rho_{klmij}$ , are the probability that when someone of sex  $k$ , activity group  $l$ , and host group  $i$  form a sex partnership, it

is with someone from activity group  $m$  and host group  $j$  of the opposite sex. The mixing parameter determines where mixing occurs on a scale from fully assortative (like with like,  $\epsilon = 0.0$ ) and random mixing ( $\epsilon = 1.0$ ) according to the rate of sexual-partner change. Mixing between host groups is assumed to be random:

$$\rho_{klmij} = \left[ (1.0 - \epsilon) \delta_{lm} + \epsilon \left( \frac{\sum_{j=1}^2 (N_{k'mj} c_{k'mj})}{\sum_{m=1}^4 \sum_{j=1}^2 (N_{k'mj} c_{k'mj})} \right) \right] \cdot \left( \frac{N_{k'mj} c_{k'mj}}{\sum_{j=1}^2 (N_{k'mj} c_{k'mj})} \right)$$

where  $\delta_{lm}$  is the identity matrix.

Because the mixing matrix is calculated separately for each sex, the possibility exists that there is an imbalance between the partnerships formed by the activity and host group of one sex with an activity and host group of the other sex. Such a discrepancy  $\Delta_{lmij}$  is measured and used to adjust partner change rates between groups:

$$\Delta_{lmij} = \frac{\rho_{k'mlji} c_{k'mj} N_{k'mj}}{\rho_{klmij} c_{kli} N_{kli}}$$

$$c_{klmij} = c_{kli} \Delta_{lmij}^\theta$$

$$c_{k'mlji} = c_{k'mj} \Delta_{lmij}^{-(1-\theta)}$$

where  $\theta$  determines the extent to which the two sexes compromise to balance the supply and demand in sexual partnerships. Because there is little evidence on which to base an estimate of this parameter, we assume that there is an equal compromise (i.e.,  $\theta = 0.5$ ). This same mechanism for balancing the formation of partnerships can be used throughout simulations to adjust patterns of mixing in response to changes in behavior after treatment or screening. Such changes in behavior could be modeled by moving people from one host group to another with a lower rate of sexual-partner change. A reduction in the number of partnerships formed by one person would necessarily alter the partnerships formed by others. Such changes are likely to be dramatic if it is those who are infected (and, therefore, likely to have more partners) who change their behavior.

This basic model is adjusted to represent different interventions. The rate of treatment of those with symptomatic infections is raised by increasing the value of  $\sigma_{kli}$ , whereas continual screening would generate an increase in the recovery rate of both those with symptoms  $\sigma_{kli}$  and without symptoms  $\sigma'_{kli}$ . The increase in recovery rate is calculated from the fraction of those treated each year or month ( $F$ ). The additional rate of recovery,  $\tau$ , is given by the relationship  $\tau = -\ln(1-F)$ , which is described by Blower et al.<sup>32</sup>

Different likelihoods of being screened can be represented by restricting increases in the recovery rate to one

host group. If being found to have an infection and being treated had no impact on risk behavior, then people would recover into the same host group. Although a change in treatment-seeking behavior, condom use or partner change can be represented by recovery into the second host group with a different set of parameters, which changes the meaning of the differentiation between host groups. In resource-poor settings, a continuous improvement in the rate of treating symptomatic or asymptomatic infections may not be possible, whereas periodic access to mobile facilities may. This can be modeled by moving a fraction of those infected into the susceptible class at given intervals. Again, this could be restricted to symptomatic persons, representing improved management of disease, or to both symptomatic and asymptomatic persons, representing screening and treatment or mass presumptive therapy. The recovery could be restricted to one host group of persons who can access such services, and targeting can be reflected by having different proportions treated according to sex or sexual activity group.

The model was solved numerically using a Runge-Kutta method. A baseline set of parameters estimated for gonorrhea (as a representative STD) from a review of the literature is used (Table 2), which generates a mean prevalence of infection of 6.63%. This would represent the prevalence in the absence of any intervention and is sufficiently large for the model to provide reasonable qualitative insights into the relative merits of different interventions. When infection becomes more scarce and is near its threshold for persistence, other factors not captured by this model structure must become important. Therefore, the results presented here are most pertinent to the development of policy in resource-poor settings where there is currently a high prevalence of STDs.

## Results

The continuous treatment of symptomatic infections has a significant impact on the prevalence of infection (Figure 3). This assumes that the transmission probability per partnership in those with symptoms is the same as for those without symptoms. In some contexts, patients report that they do not have unprotected sex while symptomatic.<sup>16-18</sup> However, this may not be universally true, and protective measures such as condoms may not be used correctly.<sup>15</sup> Furthermore, it could be that asymptomatic infections are less infectious.<sup>3</sup> The impact of treating symptomatic infection depends on our assumptions about the rate of treatment. Treating a given fraction of symptomatic persons each year will have little effect; however, if services are available, those with disease are likely to seek treatment rapidly, and a yearly fraction treated is unreasonably slow. Because of the effort of finding or reaching those infected, the treatment of asymptomatic patients will always be on a slower time

TABLE 2. Baseline Parameters Relevant to Gonorrhea Used in Simulations\*

| Parameter                                      | Symbol(s)                                     | Value(s) |
|--|---|----------|
| Transmission probabilities                     |   |          |
| Men to women                                   | $\beta_{1j}$                                  | 0.8      |
| Women to men                                   | $\beta_{2j}$                                  | 0.6      |
| Mean duration of infection                     |   |          |
| Men  | $1/\sigma_{1ii}$ and $1/\sigma_{2ii}$         | 2 months |
| Women  | $1/\sigma_{2ii}$ and $1/\sigma_{2ii}$         | 6 months |
| Proportion of infections remaining symptomatic |   |          |
| Men  | $\phi_1$                                      | 0.95     |
| Women  | $\phi_2$                                      | 0.4      |
| Proportion in activity groups                  |   |          |
| Group 1  | $(N_{k11} + N_{k12})/\sum_i \sum_j (N_{kij})$ | 0.02     |
| Group 2  | $(N_{k21} + N_{k22})/\sum_i \sum_j (N_{kij})$ | 0.08     |
| Group 3  | $(N_{k31} + N_{k32})/\sum_i \sum_j (N_{kij})$ | 0.3      |
| Group 4  | $(N_{k41} + N_{k42})/\sum_i \sum_j (N_{kij})$ | 0.6      |
| Mean rate of sex-partner change                |   |          |
| Group 1  | $c_{k1i}$                                     | 28.75/y  |
| Group 2  | $c_{k2i}$                                     | 7.1875/y |
| Group 3  | $c_{k3i}$                                     | 2.3/y    |
| Group 4  | $c_{k4i}$                                     | 0.575/y  |
| Mean duration sexual activity                  | $1/\mu$                                       | 15 y     |
| Mixing parameter                               | $\varepsilon$                                 | 0.35     |

\*The same generic values were used for parameters that could in theory differ in the model as specified. In these cases, the subscripts in the symbols column refer to all possibilities unless the relevant subscript is specified. The subdivision of the population is based on observed behaviors.<sup>23</sup>

scale. Delays will occur either in the wait for patients to access the services that provide an opportunity for screening (e.g., antenatal care), in reaching people when screening, or when mass treatment involves outreach. Therefore, treating asymptomatic women can have an impact on prevalence, but any decline will be less easily achieved than the initial declines achieved by providing symptomatic patients with ready access to care.

Rather than provide an infrastructure for care in all areas, it may be more practical in resource-poor settings to have mobile service visiting areas. Such outreach could treat those with symptomatic disease, screen for and treat asymptomatic infections, or provide mass treatment. Figure 4 illustrates the impact that such a program targeted at asymptomatic infections could have over and above a baseline rapid treatment of disease. For an infection such as gonorrhea, such programs would only have an impact if people were contacted at short intervals because of the rapid rate with which the prevalence of infection returns to its original level. The bounce back is rapid because of the high transmission probabilities, the existence of a core group, and the lack of any acquired immunity. These assumptions appear reasonable for gonorrhea and chlamydia, but are worst-case assumptions. The more reliant an organism is on a long duration of infectiousness, the slower the return of infection between treatments. If the people reached each time are a random selection of the population, at first each round progressively further reduces the prevalence. This cumulative impact is lessened by repeatedly reaching the same people.

Because women have a greater burden of morbidity and come into contact with health services more frequently through family planning and antenatal services, the impact of the programs in Figures 3 and 4 are based on only screening for asymptomatic infections in women. Figure 5 illustrates the additional benefits of a continuous effort to treat a fraction of asymptomatic infected men each year. The benefits clearly depend on what is assumed about the natural history of infection. The more likely infections are to remain asymptomatic and the longer asymptomatic infections last, the greater the treatment impact. The estimated parameters for gonorrhea in men, with only 5% remaining asymptomatic, suggest that asymptomatic infections in men are of little consequence. However, for parameters that may be more relevant for chlamydia, the treatment of asymptomatic infections in men can contribute significantly to reducing overall prevalence.

A possibility suggested for chlamydia by the observed high rate of spontaneous recovery<sup>10</sup> and the observed yield of infected men in contact-tracing sex partners<sup>11</sup> is that there is a bimodal distribution of duration of infectiousness. The impact of such a possibility is explored in Figure 6 for repeated mass treatment or screening of men, women, or both. Because we assume that 95% of men and only 40% of women are symptomatic, screening women has a greater impact regardless of the distribution. In both cases, screening men has a marked impact, even in the unlikely scenario that women are not screened. Screening both men and women achieves slightly more if some men do have long-lived infections.

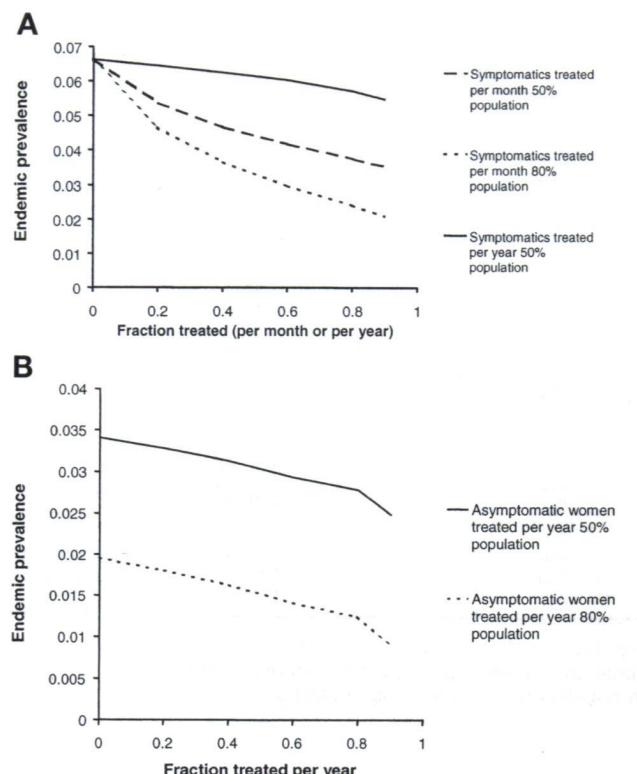


Fig. 3. The impact of continuous treatment of **A** symptomatic infections and **B** asymptomatic infections. Baseline parameters are used (Table 2) starting from a position where there is no treatment of symptomatic or asymptomatic cases, which consequently have the same mean duration. Two assumptions are made about the proportion of the population that can be reached by treatment (50% or 80%). The endemic prevalence is determined for different rates of treating symptomatic cases, or starting from 80% of symptomatic cases (from either 50% or 80% of the population) treated each month, then a fraction of asymptomatic women are also treated each year. Treatment of symptomatic patients has little impact if the fraction treated is based on a yearly value. A good service should be able to treat those with symptoms more rapidly and at a monthly rate. The impact that this strategy has on prevalence is limited because of the pool of asymptomatic infections. These asymptomatic infections can be reduced by screening asymptomatic women.

In most settings, interventions are more feasible if they are restricted to a target population. For the baseline parameters, Figure 7 illustrates the effectiveness of targeted interventions. The results achieved rely on the highest-activity group contributing most to the prevalence of infection. However, it should be noted that for the parameters used it is the 2% of the population with the highest activity that maintains the infection. The most effective targeting reaches those that are maintaining the infection within the population and ignoring the majority whose average levels of activity are insufficient to transmit infection further.

### Discussion

How can the insights gained from this intervention model be translated into practice? The treatment options discussed,

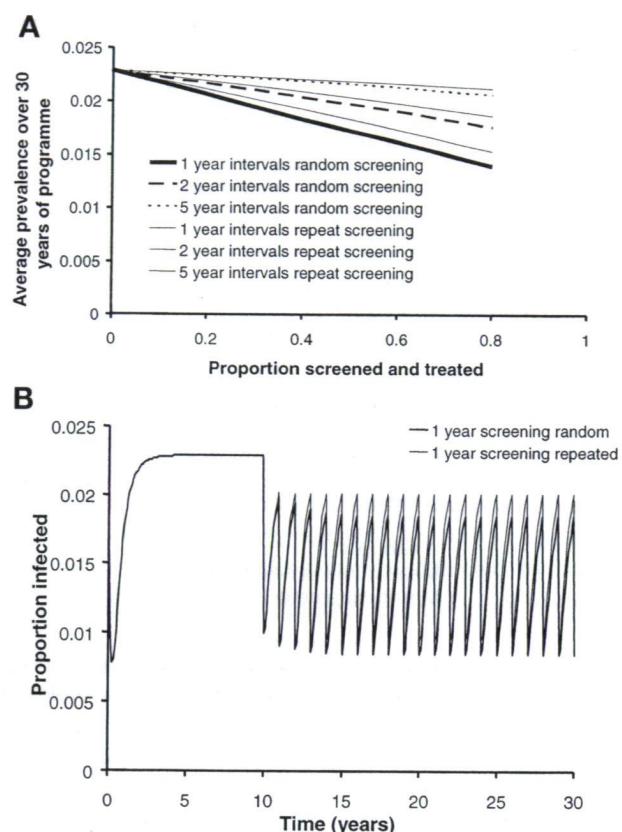


Fig. 4. The impact of intermittent mass screening and treatment (or mass treatment) of women on the prevalence of a sexually transmitted disease. Baseline parameters from Table 2 are used. **A**, The relationship between the mean prevalence of infection during the program and the fraction of the population the intervention reaches. Three frequencies of mass treatment, every year, every other year and every 5 years are illustrated. Two assumptions are made about who is reached by the program: either a random sample of the population receives care at each round or the same people are repeatedly accessed. **B**, The impact of the program is limited by the rapid return of infection, where treatment occurs each year and 80% of the population is reached either at random or with the same people repeatedly treated.

although theoretically conservative in terms of parameter assumptions, may be extremely difficult to implement in the field. Mass treatment has been shown to be logistically complex and expensive.<sup>30</sup> Even in the context of a major clinical trial, coverage of the infected population was substantially less than complete. The treatment of symptomatic disease is promoted by the World Health Organization under the banner of "syndromic management," but as we have shown coverage rates and the proportion of symptomatic infections must be high for this strategy to realize useful reductions in prevalence.

A safe and effective treatment has an immediate role in preventing disease in the individual. Beyond that, the impact of treatment on the population prevalence of an infection depends on whom is treated and how rapidly. Treatment reduces the basic reproductive number of the infection

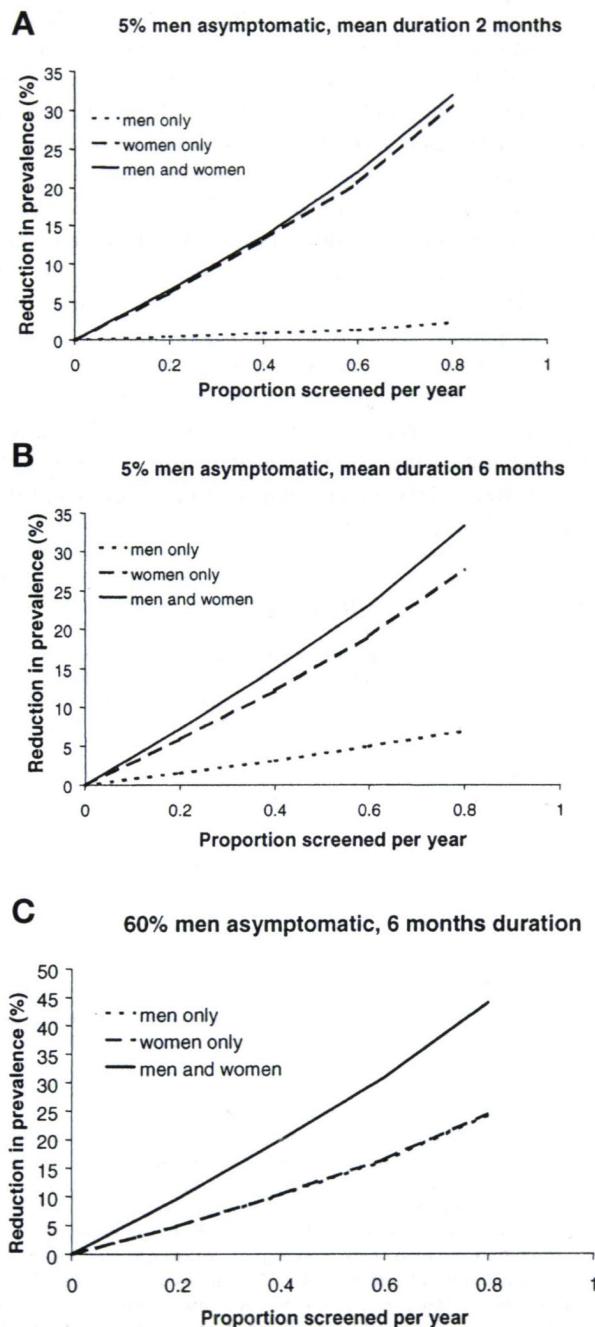


Fig. 5. The impact of screening and treating men and women. The graphs illustrate the percentage reduction in the total endemic prevalence of infection achieved by screening and treating a fraction of asymptomatic men, women, or men and women each year from a baseline determined by the parameters in Table 2 and assuming that 80% of symptomatic patients are treated each month. The additional benefits of screening and treating men for asymptomatic infection are slightly less than additive, but its contribution depends crucially on the parameters describing the natural history of infection in men. Three sets of assumptions are illustrated. **A**, Five percent of men remain asymptomatic when infected and have infections that last an average of 2 months. **B**, Five percent of men remain asymptomatic when infected and have infections which last an average of 6 months. **C**, Sixty percent of men remain asymptomatic when infected and have infections that last an average of 6 months.

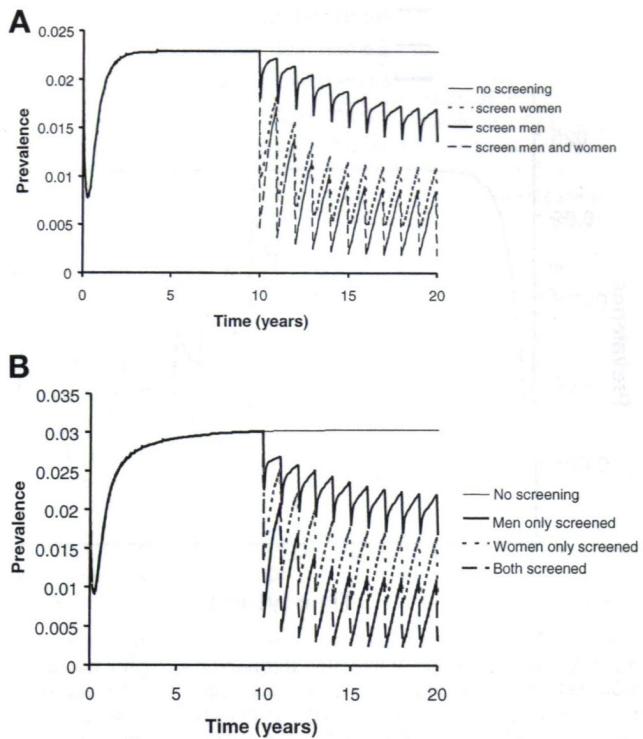


Fig. 6. The impact of heterogeneous durations of infection on the impact of repeat screening or mass treatment of men, women, or both. It is assumed that those with symptoms are already treated (80% of symptomatic cases treated per month). The prevalence of infection **A** without and **B** with 20% of men having a mean duration of asymptomatic infection of 4 years as opposed to the usual 2 months. After 10 years, 80% of men, women, or both are screened. Other parameters are those presented in Table 2.

by reducing the mean duration of infectiousness. If the basic reproductive number is reduced below one, then the infection cannot persist.<sup>6</sup> However, it is likely that there are some persons with high rates of sexual-partner change or who cannot access available care that could act as a reservoir of infection. Therefore, the impact of interventions is likely to reduce the prevalence of infection in the population rather than eliminate it.

Treatment of syphilis, gonorrhea, and chlamydia provides a means of reducing the prevalence of these infections within host populations. Substantial initial gains in STD control may be possible simply by providing easy access to appropriate treatment for patients with disease symptoms. However, the frequency with which infections remain asymptomatic restricts the potential of such a strategy. Because asymptomatic infections have to be actively found, the rate at which such infections can be treated will always be constrained. This is particularly problematic for gonorrhea, syphilis, and chlamydia because available data suggest a high transmission probability. Consequently, in any population where mass screening or mass treatment dramatically reduces the prevalence of infection, there is the potential for it to rapidly return between rounds of treatment.

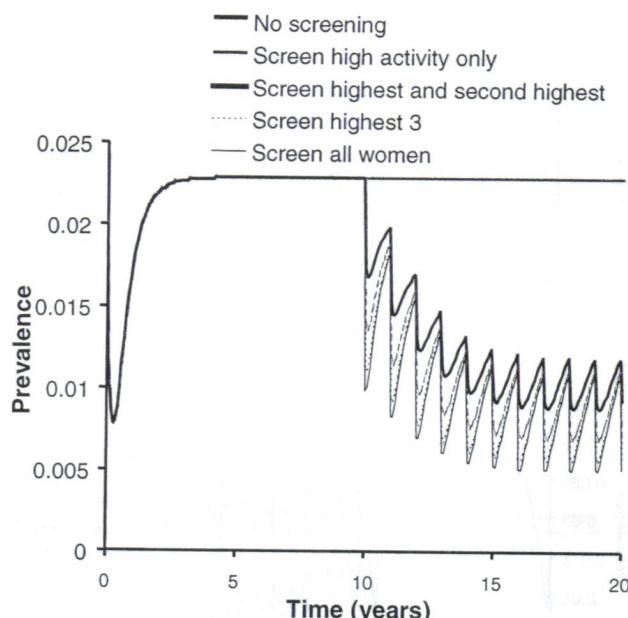


Fig. 7. The impact of targeted screening or presumptive treatment on the prevalence of infection through time. Eighty percent of women in the target population are treated each year. No screening is compared with screening the highest-activity population, the two highest-activity populations, all but the lowest-activity population, and the entire population.

This is less true of an infection such as *T vaginalis* that has a long infectious period and will take longer to return to its original prevalence. For a given endemic prevalence, a longer duration of infectiousness implies a lower transmission probability, and a lower transmission probability means that the host population will be reinvaded more slowly. Additionally, if an infection generates immunity to reinfection or the screening and treatment reduces risk behavior, screening for asymptomatic infections could have a longer-term impact.

Further reductions in prevalence are possible when asymptomatic infections are found and treated in men in addition to women. These reductions would probably be small for gonorrhea, where asymptomatic infections are uncommon in men, at least in the developed world. However, if asymptomatic infections are common in men, as appears likely for chlamydia, then the additional reduction is more substantial. Targeting treatment is almost as effective in reducing prevalence as using it generally, which has obvious implications in resource-poor settings.

The model used here is a simple modification of the one introduced by Hethcote and Yorke.<sup>2</sup> It is used in the context of a relatively high prevalence of infection in a large population, such as that observed in some developing countries. In this context, the model can still be useful in generating insights about treatment and screening. However, observed prevalences of infection for gonorrhea and syphilis in in-

dustrialized countries suggest that the infections are near the threshold where they can persist. In such circumstances, the model fails to realistically represent interventions because elimination in the model is too easy.<sup>18</sup> The explanation of why gonorrhea and syphilis have been harder to eliminate than the model would suggest may be derived from models that include spatial stratification and sex-partner network structures, or include transmission within partnerships, thereby allowing for repeated infection of the same partner.<sup>33,34</sup> However, such models necessitate the estimation of the same parameters as those used here, along with more detailed estimates of the relationship between sex acts within a partnership and the chances of transmission, and of the pattern of sex contacts within populations. As has been described, the estimation of parameter values is not straightforward. Regardless, careful marshalling of available data has allowed many insights.

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