Transmission dynamics of *Chlamydia trachomatis* affect the impact of screening programmes

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Abstract

To assess the impact of screening programmes in reducing the prevalence of *Chlamydia trachomatis*, mathematical and computational models are used as a guideline for decision support. Unfortunately, large uncertainties exist about the parameters that determine the transmission dynamics of *C. trachomatis*. Here, we use a SEIRS (susceptible-exposed-infected-recovered-susceptible) model to critically analyze the turnover of *C. trachomatis* in a population and the impact of a screening programme. We perform a sensitivity analysis on the most important steps during an infection with *C. trachomatis*. Varying the fraction of the infections becoming symptomatic as well as the duration of the symptomatic period within the range of previously used parameter estimates has little effect on the transmission dynamics. However, uncertainties in the duration of temporary immunity and the asymptomatic period can result in large differences in the predicted impact of a screening programme. We therefore analyze previously published data on the persistence of asymptomatic *C. trachomatis* infection in women and estimate the mean duration of the asymptomatic period to be longer than anticipated so far, namely 433 days (95% CI: 420–447 days). Our study shows that a longer duration of the asymptomatic period results in a more pronounced impact of a screening programme. However, due to the slower turnover of the infection, a substantial reduction in prevalence can only be achieved after screening for several years or decades.

Introduction

Infection with *Chlamydia trachomatis* is the most common bacterial sexually transmitted disease in many developed countries (World Health Organization, 2001). In women, infection can lead to pelvic inflammatory disease (PID) which can result in chronic pelvic pain, ectopic pregnancy or infertility (Cates and Wasserheit, 1991). Whilst acute infection can cause urethral discharge and pain on urination in men and symptoms such as vaginal discharge in women, most infections are asymptomatic and therefore remain undiagnosed. Screening and treatment of young adult women (Centers for Disease Control and Prevention, 2006) or women and men (Department of Health, 2004) is widely promoted as an intervention to reduce the duration of infection and thus lower the prevalence of *C. trachomatis* and reduce the incidence of possible sequelae.

Mathematical and computational models that describe the transmission of *C. trachomatis* have been applied to inform and guide public health decisions about screening programmes (Kretzschmar et al., 1996, 2001; Turner et al., 2006a; Low et al., 2007; Regan et al., 2008). Other models have been used to investigate aspects of immunity (Brunham et al., 2005), to assess the potential impact of vaccines (Gray et al., 2009) or to gain general insights into the transmission dynamics of *C. trachomatis* (Sharomi and Gumel, 2009). Since transmission occurs through sexual contact and screening strategies can be targeted to women only, women and men or specific core groups, many models incorporate detailed descriptions of contact patterns between people. However, there are great uncertainties about the parameters that describe sexual behavior and the values used for disease-specific parameters. These have led to conflicting results about the potential impact of screening programmes (Kretzschmar et al., 2009). It is therefore essential to critically investigate the impact of different parameter assumptions in order to quantify the transmission dynamics of *C. trachomatis* and the potential impact of public health interventions.

In a simple epidemiological model, the basic reproductive number, R_0, determines the endemic prevalence of an infection. R_0 can be defined as the product of the duration of an infection and the rate at which an infected individual transmits the disease to a susceptible. Whereas the first is a disease-specific parameter, the latter is also influenced by behavioral parameters that describe contacts between people. Hence, for a given prevalence of *C. trachomatis* within the population, the overall turnover of the infection is simply determined by the duration of the infection, i.e., is given by disease-specific parameters only. By treating the rate at which individuals engage in sexual contacts as a function of the endemic prevalence, we can analyze carefully the parameters that characterize the transitions through an infection and their influence on the predicted impact of a screening programme. Generally, the longer a person is infected, the more likely it is that they will be reached by a screening programme and will receive treatment. *C. trachomatis* infection is indeed characterized by a long asymptomatic period (Molano et al., 2005), but the duration of this period is not known. In addition, it is unclear what fraction of infections will cause symptoms that prompt treatment seeking behavior (Korenromp et al., 2002), or whether natural clearance is followed by a period of temporary immunity (Brunham and Rey-Ladino, 2005). Previous studies have investigated the impact of disease-specific parameters on the impact of different screening strategies (Hu et al., 2006; Regan et al., 2008). Unfortunately, due to the complexity of these models, it is difficult to perform sensitivity analysis over a wide range of parameter values.

The objective of this paper is to perform a sensitivity analysis of disease-specific parameters on the predicted impact of a screening programme. To this end, we devise a basic epidemiological model of *C. trachomatis* transmission dynamics that describes the overall turnover of the infection within a general population. In addition, we also derive a new estimate of the duration of the asymptomatic period by reanalyzing previously published data on the persistence of *C. trachomatis* in asymptomatically infected women. We discuss the implications of our results, which highlight the importance of continued evaluation of parameter estimates for mathematical and computational models that aim to assess the impact of screening programmes.

Methods

SEIRS model

We used a SEIRS (susceptible-exposed-infected-recovered-susceptible) model, which is widely used in the infectious disease modeling literature (Anderson and May, 1991; Diekmann and Heesterbeek, 2000; Keeling and Rohani, 2008), to devise a simple mathematical model of *C. trachomatis* transmission that takes into account the major transitions of infected people during an infection.

We assume a closed population where susceptibles, S, may become infected with *C. trachomatis*. They move through an incubation time, E, of the pathogen to become either asymptomatically, I_a, or symptomatically infected, I_s. Asymptomatic people that recover naturally, R, may develop temporary immunity against re-infection. Symptomatically infected people have a shorter period of infection that can be ascribed to treatment seeking due to symptoms. Both asymptomatically and symptomatically infected people can get screened and directly treated (Fig. 1). Although most infections with *C. trachomatis* happen through sexual contacts between women and men, we strictly assume a homogeneous population where both genders become infected and pass through the infected stages at equal rates. This is a valid assumption because, even though differences in gender-specific parameters of *C. trachomatis* infection have been observed, the purpose of our study is a sensitivity analysis over a broad range of parameter estimates which is wider than the gender-specific differences. We also do not assume separate risk groups that exhibit different sexual behavior but we illustrate in the *Appendix* that a stochastic implementation of our model exhibits a realistic amount of heterogeneity (see also *Discussion*). The model can be described by the following set of ordinary differential equations:

$$\frac{dS}{dt} = -\beta(I_a + I_s)S + cI_a + (r_s + c)I_s + \mu R, \tag{1}$$

$$\frac{dE}{dt} = \beta(I_a + I_s)S - \gamma E, \tag{2}$$

$$\frac{dI_a}{dt} = f\gamma E - (r_a + c)I_a, \tag{3}$$

$$\frac{dI_s}{dt} = (1 - f)\gamma E - (r_s + c)I_s, \tag{4}$$

$$\frac{dR}{dt} = r_a I_a - \mu R. \tag{5}$$

There is a wide range of published estimates for the duration of the incubation time, $1/\gamma$, the fraction of infections becoming asymptomatic, f, and the duration of the asymptomatic and symptomatic period, $1/r_a$ and $1/r_s$, respectively (Table 1). Based on observations from studies in mice, it has been suggested that natural clearance may be followed by temporary immunity of length $1/\mu$ (Brunham and Rey-Ladino, 2005). The parameter c denotes the effect of screening the population where asymptomatically or symptomatically infected people are diagnosed and treated so that they immediately become susceptible again. The rate at which susceptible people have contact with infected people and in which such contact results in transmission of *C. trachomatis* is not known. In our model, this rate is given by the parameter β, where $\lambda = \beta(I_a + I_s)$ can be described as the 'force of infection'. Since it is exceedingly difficult to get a direct estimate of β or λ, we adjust the rate at which people make a potentially infectious contact, β, to obtain a given prevalence of the infection in the total population.

Assuming the prevalence of *C. trachomatis* to be in a steady-state, the derivatives of Eq. (1) – (5) can be set to zero. Since we assume a closed population, we can set the total population size to $S + E + I_a + I_s + R = 1$, which allows us to express all compartments as fractions of the total population. By solving the system of equations for the prevalence $p = I_a + I_s$, we obtain

$$p = \frac{\gamma\mu(\beta - a - b)}{\beta(\gamma\mu + a\gamma + a\mu + b\mu)}, \tag{6}$$

where

$$a = \frac{f r_a (r_s + c)}{f r_s + (1-f) r_a + c} \qquad \text{and} \qquad b = \frac{(r_a + c)(1-f) r_s}{f r_s + (1-f) r_a + c} + c. \tag{7}$$

The expression for the prevalence p as a function of a and b can be explained by a simpler SEIRS model that does not distinguish between symptomatic and asymptomatic states. In such a model, a denotes the rate at which infected people recover and develop temporary immunity and b the rate at which infected people become directly susceptible again. The steady-state prevalence, p, of this simpler model is directly given by Eq. (6). The necessary 'infection rate' β to obtain a given prevalence p is:

$$\beta = \frac{\gamma\mu(a+b)}{(1-p)\gamma\mu - p(a\gamma + a\mu + b\mu)}. \tag{8}$$

By choosing a and b as in Eq. (7), we can distinguish between symptomatically and asymptomatically infected individuals as described in the full model from Eq. (1) – (5).

For any given combination of disease-specific parameters, we wish to calculate the expected prevalence of *C. trachomatis* in a population that receives screening at a rate c. To this end, we first assume a prevalence p_0 in absence of screening and denote the corresponding 'infection rate' β_0 which is given by Eq. (8) for $c = 0$. We then calculate the new steady-state prevalence in the presence of screening ($c > 0$) by Eq. (6) with β_0 as the 'infection rate'. This scenario is considered to reflect the long-term impact of opportunistic screening, where a relatively small proportion of the total population is tested in health care settings. In contrast to opportunistic screening, an organized screening programme aims to reduce the prevalence of the infection by targeting a larger proportion of the population at regular intervals. Further, the reduction in prevalence will now depend on the time that has passed since the organized screening programme was introduced. To contrast this with the first scenario, we also perform numerical simulations starting at the pre-screening steady-state, p_0, to calculate the reduction in prevalence after an organized screening programme ($c > 0$) has been active for a certain number of years.

Since we can express β_0 as a function of the disease-specific parameters and the pre-screening prevalence, we can analyze the impact of screening over a wide range of parameters. To express the uncertainties of previously used estimates, we use the upper and lower bounds of disease-specific parameters that have been used in various models of *C. trachomatis* transmission dynamics (Kretzschmar et al., 1996; Brunham et al., 2005; Turner et al., 2006a; Low et al., 2007; Regan et al., 2008; Gray et al., 2009; Sharomi and Gumel, 2009). As baseline parameters, we use the mean value of the respective ranges (Table 1). Since the upper bound for the duration of temporary immunity ($1/\mu$) is life long, we cannot provide the mean value of the range and therefore set the baseline duration of immunity arbitrarily to 90 days.

Analytical results were derived in Mathematica (Wolfram Research, Inc., 2008) and numerical integrations were performed in C using the routine odeint (Runge-Kutta with adaptive stepsize control) from Numerical Recipes (Press et al., 1992). Code files can be obtained freely on request from the authors.

Parameter estimation

To estimate the natural clearance rate of *C. trachomatis*, we used data from a previously published study. Molano et al. (2005) analyzed data from women who had endocervical specimens taken every 6–9 months for up to 5 years during a follow-up study about human papillomavirus infection. After the end of the study, stored specimens were also tested for *C. trachomatis* from which a survival function of the persistence of *C. trachomatis* infection could be derived. The date of chlamydia clearance was defined as the midpoint between the last positive test and a negative test. Data about antibiotic treatment for chlamydia and sexual partner change that might have resulted in a new infection were not collected but both were thought to be rare. We devise a mathematical model that describes the persistence of *C. trachomatis* in asymptomatically infected women:

$$\frac{dI_a}{dt} = -r_a I_a + \alpha S, \tag{9}$$

$$\frac{dS}{dt} = r_a I_a - \alpha S. \tag{10}$$

Here, asymptomatically infected women, I_a, can clear the infection at a rate r_a. Being susceptible again, they are at risk of re-infection at a rate α. Molano et al. (2005) provide data on 82 women, all of whom are infected with *C. trachomatis* at the beginning, so we can set $I_a(0) = 1$ and $S(0) = 0$ and solve for I_a(t):

$$I_a(t) = \frac{\alpha + r_a e^{-(r_a+\alpha)t}}{\alpha + r_a}. \tag{11}$$

The natural clearance rate and the re-infection rate can now be estimated by fitting Eq. (11) to the data from figure 1 in Molano et al. (2005). The data were digitized using Plot Digitizer (http://plotdigitizer.sourceforge.net) and we excluded time points within the first 4.5 months to ensure that all women have been tested at least once during the follow-up period. The model was fitted using the FindFit routine that minimizes the sum of squared residuals (SSR) from the software package Mathematica (Wolfram Research, Inc., 2008).

Results

Impact of an organized screening programme

To investigate the impact of organized screening in the general population, we first assume the pre-screening prevalence of *C. trachomatis* in the population to be 5%. This roughly corresponds to the prevalence observed in sexually active young adults (Fenton et al., 2001). Now, we can follow the decrease in prevalence after the introduction of three different organized screening programmes (Fig. 2). Screening the population randomly at a rate of 0.05 per year (i.e., every individual is screened once every 20 year on average) reduces the prevalence of infection only slightly (solid line). Increasing the screening rate to 0.25 per year (individuals are screened once every 4 years on average, dashed line) or even 0.5 per year (individuals are screened once every 2 years on average, dotted line) results in a pronounced impact within 5 to 10 years of screening. Clearly, the longer a screening programme is in place, the more pronounced is the reduction in prevalence. The new steady-state prevalence that will be approached in the presence of a screening programme will therefore be further reduced. In this model, screening the population at a rate higher than 0.1 per year would eventually be sufficient to eradicate the infection from the population (Fig. 3, dashed line). However, the slow decline in prevalence after introducing a screening programme (Fig. 2) illustrates that such a state can only be achieved after screening for several decades. The impact of a screening programme implemented for 5 years (Fig. 3, dotted line) or 10 years (Fig. 3, solid line) is less pronounced, highlighting the difficulties in reducing the prevalence of an infection that exhibits a slow turnover within a reasonable time span.

Parameter sensitivity on the impact of screening

Due to the large uncertainties of disease-specific parameters that determine the transmission dynamics of *C. trachomatis* (Table 1), it is essential to perform a sensitivity analysis if one wants to assess the impact of screening the general population. We have shown above that it is important to distinguish between the effects of a screening programme over different time spans. Both, the temporal impact of screening during a given time period and the expected long-term prevalence if screening is prolonged give important insights into screening strategies. For our sensitivity analysis, we thus consider two different screening scenarios; an organized screening programme with a screening rate of 0.25 per year implemented for 10 years, and opportunistic screening at a rate of 0.05 per year, in which the new steady-state prevalence is shown after long-term implementation.

Arguably the most critical steps during an infection with *C. trachomatis* are the fraction of infections that become asymptomatic (f) and the durations of the asymptomatic and symptomatic period, $1/r_a$ and $1/r_s$, respectively. During these stages *C. trachomatis* is assumed to be infectious so changes in these values should determine the overall transmission within a population. Varying the fraction of infections becoming asymptomatic at levels greater than 20%, however, has little effect on the predicted outcome of a screening programme (Fig. 4A, gray area). As long as the asymptomatic period is substantially longer than the symptomatic period, the screening intervention detects mostly asymptomatically infected people and only a small proportion of transmission events is caused by symptomatic individuals. Similarly, changing the duration of the symptomatic period hardly affects the impact of screening (Fig. 4B). If the duration is short, little transmission is caused by symptomatics. As the duration of the symptomatic period increases, it becomes more likely that symptomatically infected individuals are also detected by the screening programme. A different picture arises when we vary the duration of the asymptomatic period (Fig. 4C). Here, the predicted long-term impact of screening is much more pronounced if the asymptomatic period is at the upper bound of the previously used parameter range (gray area). This property also holds if, for example, the fraction of infections that becomes asymptomatic is varied at the same time (see two-way sensitivity analysis in the *Appendix*). Interestingly, the impact of screening for 10 years is much less affected. This is because increasing the duration of the asymptomatic period results in a slower turnover of *C. trachomatis* within the population, which will decelerate the effect of screening. We performed the same analysis for different pre-screening prevalences of *C. trachomatis* which can be found in different risk groups (1% – 15%, results not shown). Higher pre-screening prevalences of *C. trachomatis* imply an elevated turnover of the infection. While this does not affect the qualitative results of the sensitivity analysis for a long-term screening intervention, the effect of screening for 10 years changes. Due to the elevated turnover, the impact of screening for 10 years becomes effective earlier and more closely resembles the effect of a long-term screening programme. Thus, different durations of the asymptomatic period can result in a substantially different impact of screening during an intervention period of a few years.

In addition, we perform a sensitivity analysis on the parameters that describe the stages of an infection which are not infectious, i.e., the period of temporary immunity after natural clearance of an asymptomatic infection ($1/\mu$) and the incubation time ($1/\gamma$). Although the incubation time is generally assumed to be short (gray area), the sensitivity analysis illustrates that changing this parameter over a wider range of values can affect the predicted impact of a screening programme (Fig. 5A). For a longer duration of the incubation time, more infected people will be screened during the time when the infection is assumed not to be detectable or infectious yet. Hence, the impact of screening the general population at a certain rate diminishes slightly. Assuming temporary immunity also results in a less pronounced impact of screening. Increasing the duration of temporary immunity decreases the impact of screening even more (Fig. 5B). Regarding the wide range of immunity that has been used in different models so far (gray area), this effect becomes especially strong in the long-term. Here, screening and treating asymptomatically infected people prevents the development of temporary immunity and renders them susceptible immediately. This somewhat counterbalances the otherwise strong impact of screening.

Estimating the duration of the asymptomatic period

We have shown that the long-term outcome of a screening programme is most sensitive to the duration of the asymptomatic period. In the modeling literature of *C. trachomatis* transmission dynamics, values for this parameter range from 180 to 420 days, emphasizing the uncertainty. A recent study that followed a large number of asymptomatic chlamydia-infected women indicated that the infection can persist for several years (Molano et al., 2005). However, it was mentioned that repeated infections from an untreated male sex partner might have biased the data in such a way that the estimated duration of the asymptomatic period only serves as an upper limit. In order to test the assumption of re-infection and to provide a robust estimate of the natural clearance rate in asymptomatically infected women, we fit a mathematical model to the data (Fig. 6). The estimated re-infection rate is low (0.01 per year; 95% CI: -0.01–0.03 per year) which indicates that the data are mainly described by natural clearance. With an estimated clearance rate of 0.84 per year (95% CI: 0.82–0.87 per year), we obtain a mean duration of the asymptomatic period of 433 days (95% CI: 420–447 days).

Discussion

We developed a basic epidemiological model that captures the most essential transitions through an infection with *C. trachomatis* to assess the importance of disease-specific parameters on the impact of chlamydia screening programmes. Sensitivity analyses show that the duration of temporary immunity and the duration of the asymptomatic period strongly affect the long-term impact of screening. Longer periods of temporary immunity diminish the effect of screening. A longer duration of the asymptomatic period, however, results in a more pronounced impact of such a programme. Using previously published data, we estimated the average duration of the asymptomatic period at 433 days, which is substantially higher than most estimates used in mathematical and computational models. Interestingly, previous studies have indicated an even longer duration of the asymptomatic period than we estimate here (McCormack et al., 1979; Morré et al., 2002). As those studies followed a much smaller number of women than Molano et al. (2005) and did not explicitly take the effect of re-infection into account, our new estimate is likely to be more robust.

The simplicity of our model facilitates the understanding of basic properties of the transmission dynamics of *C. trachomatis*. Previous attempts to investigate *C. trachomatis* transmission and the potential impact of public health interventions have often been performed with more detailed models (Kretzschmar et al., 1996; Brunham et al., 2005; Turner et al., 2006a; Low et al., 2007; Regan et al., 2008; Gray et al., 2009; Sharomi and Gumel, 2009). However, as more complicated models can be difficult to analyze and interpret, it is sometimes reasonable 'to keep it simple' in order to address some general principles of the transmission dynamics of an infectious disease (May, 2004; Regan and Wilson, 2008). In this study, we have shown the utility of a simple epidemiological model, especially for performing a sensitivity analysis over a wide range of parameters.

In contrast to our assumption of homogeneous mixing, transmission of sexually transmitted infections (STIs) has been found to be driven by 'core groups'. This concept is especially important to describe the transmission of bacterial STIs with short infectious periods, such as gonorrhea (Hethcote and Yorke, 1984). However, *C. trachomatis* appears to be more evenly spread across subpopulations due to its longer duration of infection (Chen et al., 2009). Since we assume a homogenous population, it is worthwhile analyzing the values of the 'infection rate' β that we obtained by adjusting the pre-screening prevalence to 5%. Changing disease-specific parameters within the range that has been previously used results in values of β that are between 1.3 and 3.9 per person per year (Fig. 9). The infection rate can be expressed as the product of the sexual partner change rate and the transmission probability per partnership. Given a transmission probability of around 0.7 (Quinn et al., 1996), the sexual partner change rates are in the range of 0.9 and 2.7 per year which is in agreement with reported data from young adults in Britain (Johnson et al., 2001). Thus, it appears that our model captures the overall transmission dynamics of *C. trachomatis* reasonably well.

Based on our results, we can test whether differences in the duration of the infection are able to explain the conflicting results that have been found in Kretzschmar et al. (2009). Looking at the mean duration of *C. trachomatis* infection in men, the model with the longest duration indeed predicts the largest impact of a screening programme (Turner et al., 2006a). In contrast, the model with the shortest duration of infection in men results in the smallest impact of screening (Low et al., 2007). The same pattern does not hold for the average duration of infection in women, however. Thus, it is likely that different assumptions of the underlying sexual partnership dynamics further contribute to the observed differences in the predicted impact of a screening programme.

Besides the qualitative insights of this study, we can also provide some quantitative predictions. For example, the results of our study, showing that screening the population at a rate of 0.25 – 0.5 per year over a period of 5 – 10 years can result in a pronounced decrease in the prevalence of *C. trachomatis*, are similar to those of more complicated compartmental or individual-based models (Kretzschmar et al., 2001; Turner et al., 2006b; Regan et al., 2008). Nevertheless, quantitative conclusions from our model should be interpreted cautiously. Our simplifying assumptions neglect potential effects that will counter against the effect of an organized screening programme. As mentioned above, we do not assume a core group with a higher sexual activity than the general population. High prevalences of *C. trachomatis* could persist in such core groups if they are not targeted directly. If there is ongoing transmission between the core group and the general population, this could diminish the effect of population-wide screening programmes. Further, we assume perfect screening uptake and do not explicitly consider sexual partnerships between people. Re-infection of treated cases within steady partnerships is expected to counter the desired effect of screening (Lamontagne et al., 2007; Low et al., 2009). These processes and the impact of partner notification have to be taken into account to fully evaluate the potential of different screening programmes. To investigate those questions, more sophisticated mathematical and computational models that treat people as individuals with current and previous partners are necessary.

Interestingly, our analysis contrasts somewhat with the sensitivity analysis of the study by Regan et al. (2008). There, the duration of the asymptomatic period had less influence on the impact of screening than what we found here. Also, they found that the duration of temporary immunity only affects the reduction in prevalence through screening moderately. Differences between these results can be explained, at least partly, by the narrow ranges of parameter values investigated in the sensitivity analysis of Regan et al. (2008). For example, the average time to recover from an asymptomatic infection was assumed to be between 44 to 52 weeks, i.e., 310 to 360 days. The sensitivity analyses presented here covered a much wider range of parameters and our new estimate for the average duration of the asymptomatic period in women, 433 days, exceeds their upper limit. We are also able to show the effects of a wider range of assumptions about the duration of temporary immunity and find that it can drastically diminish the effect of screening. Whether natural clearance of asymptomatic infection is followed by a period of temporary (or partial) immunity is still a matter of debate (Brunham and Rey-Ladino, 2005). In our model, we made the assumption that temporary immunity can only develop in asymptomatic individuals who clear the infection naturally. Thus, screening and treatment directly interfere with establishing immunity, causing a diminished effect of screening in our model (Brunham and Rekart, 2008). In order to fully evaluate the role of immunity on the impact of screening programmes, we need further insights about the possibility of temporary immunity to *C. trachomatis* infection in humans and the timing of its development.

To summarize, we have shown how simple epidemiological models can give important insights into the transmission dynamics of *C. trachomatis*. Our sensitivity analysis illustrates that disease-specific parameters can critically influence the impact of a screening programme. This emphasizes the importance of continued evaluation of parameter estimates for mathematical and computational models that are used to inform and guide public health decisions about chlamydia screening. Based on a new estimate for the average duration of the asymptomatic period in women, we conclude that *C. trachomatis* exhibits a slow turnover within the sexually active population and interventions that aim to reduce the prevalence will only become apparent after screening for several years or decades.

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Appendix

Heterogeneity in risk behavior

Deterministic models of infectious diseases that assume a homogenous population imply that all people are, on average, subject to the same behavior. In the case of the SEIRS model presented in *Methods*, it can be seen that everyone obeys the same 'infection rate' β. However, the time interval at which a susceptible makes potentially infectious contacts to other persons is exponentially distributed. Stochastic models can make use of this implicit variation if each process is drawn separately from such a distribution. With time, this will inevitably cause variation in peoples behavior if we could look at them on an individual level.

To illustrate this effect, we implemented a stochastic version of the SEIRS model in an individual-based population. This method allows us to store all previous contacts of an individual in the memory. To keep track of all contacts of an individual (including the non-infectious ones), it is necessary that susceptibles not only make contacts to infected people but also to other susceptibles or recovered people. For simplicity, we assume that all contacts happen at the same rate β and that transmission occurs in any case if a susceptible makes a contact to an infectious individual. The individuals can now be grouped according to their past history of contacts at any given time. Further, we can calculate the prevalence of *C. trachomatis* for each specific group. We use the baseline parameters from Table 1 and run the simulation for 100 years to approach the steady-state in absence of any screening intervention. The simulations were run in the R software environment for statistical computing (R Development Core Team, 2009) using the package *Rstisim* (Althaus et al., manuscript in preparation). For the graphical representation of the contact network, we use the network package (Butts et al., 2008).

The simulation shows that people can have widely different numbers of contacts, exemplifying the intrinsic property of variation in the individuals behavior (Fig. 7A). People with no or few contacts within the last year have a lower prevalence of *C. trachomatis* than the average population (Fig. 7B). By chance, a small fraction of people will have a high number of contacts and the prevalence in those groups can be much higher than the average. Therefore, a stochastic implementation of our SEIRS model in an individual-based population illustrates that, although we assume a 'homogenous' population, such models do account for a certain variation in people's behavior.

Two-way sensitivity analysis

For reasons of clarity, we restricted our sensitivity analysis in the *Results* section to be univariate. However, it is important to analyze the combined effect of changing critical parameters. Since we found the duration of the asymptomatic period to be important, it is natural to investigate its impact together with changing the fraction of infections that become asymptomatic (Fig. 8A). It can be seen that the duration of the asymptomatic period remains a critical parameter whereas the fraction of infections that become asymptomatic has little impact within the range of parameters that has been previously used (white dashed rectangle). We also investigated the combined effect of varying the duration of the asymptomatic period together with the duration of temporary immunity (Fig. 8B). Here, both parameters strongly affect the impact of a screening programme and we observe that the predicted outcome can vary from only little reduction in prevalence (top left corner) to close to extinction of the infection (lower right corner).

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Table 1: Parameters for *C. trachomatis* transmission dynamics. The baseline values of disease-specific parameters for the SEIRS model are given as the mean values from the range of parameters that have been used in several mathematical and computational models so far (Kretzschmar et al., 1996; Brunham et al., 2005; Turner et al., 2006a; Low et al., 2007; Regan et al., 2008; Gray et al., 2009; Sharomi and Gumel, 2009). As an exception, we assume 90 days for the baseline duration of temporary immunity ($1/\mu$). Given the baseline parameter values, we obtain $\beta = 1.95$ per person per year for the infection rate and $R_0 = 1.07$ for the basic reproductive number.

Parameter	Range	Baseline value	Explanation
f	[0.25,1]	0.625	Fraction of infections becoming asymptomatic. Note that the fraction of infections being asymptomatic in a population at cross-section is given as $(fr_s)/(r_a+f(r_s-r_a))$. Assuming baseline parameters, this corresponds to 93% of infected cases.
$1/\gamma$	[0,28] days	14 days	Incubation time, i.e., the time people are infected but not yet infectious.
$1/r_a$	[180,420] days	300 days	Duration of the asymptomatic period.
$1/r_s$	[30,40] days	35 days	Duration of the symptomatic period.
$1/\mu$	[0,∞] days	90 days	Duration of temporary immunity after natural clearance of asymptomatic infection.
p_0	–	0.05	Prevalence of *C. trachomatis* in the absence of screening.
c	–	$\frac{x}{365}$ per day	Screening rate with $1/x$ being the average interval in years at which people receive screening. Note that the fraction of people that get screened at least once within a year is given by $1-e^{-x}$.

Figure 1: SEIRS model illustrating infection with *C. trachomatis* and subsequent transitions through the different stages of infection. Susceptibles, S, get infected by infected people, $I_a + I_s$, at a rate β. They then move through an incubation period (E) at a rate γ to become either asymptomatically infected (I_a) or symptomatically infected (I_s). f denotes the fraction of infections that become asymptomatic. Asymptomatically infected people recover through natural clearance at a rate r_a and develop temporary immunity to re-infection (R) for a duration of $1/\mu$. Symptomatically infected people clear the infection at a rate r_s that can be ascribed to treatment seeking due to symptoms. Both asymptomatically and symptomatically infected people get screened and directly treated at a rate c.

Figure 2: Declining prevalence of *C. trachomatis* after the introduction of a screening programme. Only high screening rates can achieve a significant reduction in prevalence within a reasonable time span. Solid line, screening rate of 0.05 per year; dashed line, screening rate of 0.25 per year; dotted line, screening rate of 0.50 per year.

Figure 3: Prevalence of *C. trachomatis* as a function of the rate at which the population receives screening. In the long-term, screening more than 10% of the population would eradicate *C. trachomatis* from the population. Due to the slow decline in prevalence, however, this is only expected after screening over several decades. Dotted line, prevalence after 5 years of screening; solid line, prevalence after 10 years of screening; dashed line, new steady-state that is expected in presence of a screening programme.

Figure 4: (A) Prevalence of *C. trachomatis* as a function of the fraction of infections that become asymptomatic. For the most reasonable estimates of f, the reduction in prevalence is only slightly affected. (B) Prevalence of *C. trachomatis* as a function of the duration of the symptomatic period. The reduction in prevalence is only slightly affected by the duration of the symptomatic period. (C) Prevalence of *C. trachomatis* as a function of the duration of the asymptomatic period. Most estimates on the duration of the asymptomatic period are within 200–400 days, which results in large differences of the predicted impact of long-term screening programmes. In all graphs: Dotted line, baseline prevalence in the absence of a screening programme; dashed line, long-term prevalence if the population receives screening at a rate of 0.05 per year; solid line, prevalence after screening the population at a rate of 0.25 per year for 10 years; gray area, parameter range; black dots, baseline scenario as given in Table 1.

Figure 5: (A) Prevalence of *C. trachomatis* as a function of the duration of the incubation time, i.e., the time people are infected but not yet infectious. (B) Prevalence of *C. trachomatis* as a function of the duration of temporary immunity. In all graphs: Dotted line, baseline prevalence in the absence of a screening programme; dashed line, long-term prevalence if the population receives screening at a rate of 0.05 per year; solid line, prevalence after screening the population at a rate of 0.25 per year for 10 years; gray area, parameter range; black dots, baseline scenario as given in Table 1.

Figure 6: Persistence of *C. trachomatis* in asymptomatically infected women as given in (Molano et al., 2005). Fitting a mathematical model that includes natural clearance and re-infection (see *Methods*) results in a natural clearance rate of $r_a = 0.84$ per year (95% CI: 0.82–0.87 per year) and a re-infection rate of $\alpha = 0.01$ per year (95% CI: -0.01–0.03 per year). The low re-infection rate indicates that the data is mainly described by natural clearance and we obtain a mean duration of the asymptomatic period of 433 days (95% CI: 420–447 days).

Figure 7: Stochastic implementation of the SEIRS model in an individual-based population. (A) Contact network during a period of one year. For illustrative purposes, the population size was limited to 100 which results in higher connected components compared to larger population sizes. (B) Variation in *C. trachomatis* prevalence if the population is stratified by sexual behavior. Each bar represents a risk group with a given number of contacts within the last year. The width of the bar represents the fraction of the population that belongs to the specific risk group (see legend). The height of the bar indicates the prevalence of *C. trachomatis* within that group. The gray area within each bar corresponds to the total amount of infections within the group. The overall prevalence is given by the dashed line. Population size: 10'000.

Figure 8: Two-way sensitivity analysis of disease-specific parameters on the impact of a screening programme. The density plots describe the new steady-state prevalence of *C. trachomatis* in the presence of a screening programme ($c = 0.05$ per year). (A) Varying the duration of the asymptomatic period ($1/r_a$) together with the fractions of infections becoming asymptomatic (f). (B) Varying the duration of the asymptomatic period ($1/r_a$) together with the duration of temporary immunity ($1/\mu$). The range of parameters that have been previously used is outlined by the white dashed rectangle and the baseline scenario is given by the white dots (Table 1). The white area indicates extinction of the infection from the population.

Figure 9: Infection rate β and the mean duration of infectiousness as a function of disease-specific parameters. Changing the fractions of infections becoming asymptomatic (A), the duration of the symptomatic period (B) and the duration of the asymptomatic period (C) within the range that has been previously used (gray area) results in values of β (solid lines) that are between 1.3 and 3.9 per person per year. Taking into account symptomatic and asymptomatic infections, the mean duration of infectiousness ($f/r_a + (1-f)/r_s$, dashed lines) is in the range of 101–300 days.