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## **Original article**

# Direct and indirect effects of screening for *Chlamydia trachomatis* on the prevention of pelvic inflammatory disease: mathematical modeling study

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Direct and indirect effects of screening for *Chlamydia trachomatis* on the prevention of pelvic inflammatory disease: mathematical modeling study ABSTRACT

**Background:** Pelvic inflammatory disease (PID) results from the ascending spread of microorganisms, including *Chlamydia trachomatis*, to the upper genital tract. Screening could work by identifying and treating chlamydial infections before they progress to PID (direct effect) and/or reducing chlamydia transmission (indirect effect).

**Methods:** We developed a compartmental model that represents a hypothetical heterosexual population and explicitly incorporates progression from chlamydia to clinical PID. Chlamydia screening was introduced, with coverage increasing each year for ten years. We estimated the separate contributions of the direct and indirect effects of screening on PID cases prevented per 100,000 women. We explored the influence of varying the time point at which clinical PID could occur and of increasing the risk of PID after repeated chlamydial infections.

**Results:** The probability of PID at baseline was 3.1% by age 25 years. After five years, the intervention scenario prevented 187 PID cases per 100,000 women and after 10 years 956 PID cases per 100,000 women. At the start of screening, most PID cases were prevented by the direct effect. The indirect effect produced a small net increase in PID cases, which was outweighed by the effect of reduced chlamydia transmission after 2.2 years. The later that progression to PID occurs, the greater the contribution of the direct effect. Increasing the risk of PID with repeated chlamydial infection increases the number of PID cases prevented.

**Conclusions:** This study contributes to understanding the mechanisms of chlamydia screening programs by showing the separate roles of direct and indirect PID prevention and potential harms, which could not have been observed by empirical studies.

**Keywords:** Chlamydia infections, pelvic inflammatory disease, screening program, mathematical model, compartmental model

**Word counts:** Abstract, 261 words; main text, 4203 words; 2 tables; 4 figures; 42 references; 1 supplementary digital file.

#### BACKGROUND

Pelvic inflammatory disease (PID) is a clinical syndrome, which results from the ascending spread of microorganisms from the vagina and endocervix to the upper genital tract.<sup>1</sup> Inflammation in the fallopian tubes and contiguous structures can cause scarring, leading to infertility and ectopic pregnancy.<sup>2</sup> *Chlamydia trachomatis* (chlamydia) is present in the endocervix at the time of diagnosis of about 30% of PID cases<sup>2,3</sup> and is the most common bacterial sexually transmitted infection in many developed countries.<sup>4</sup> Repeated diagnosis of chlamydia has been associated with an increased risk of PID and ectopic pregnancy.<sup>5</sup> Given that chlamydia is curable, but is usually asymptomatic<sup>6</sup> and has an estimated mean duration of more than one year,<sup>7</sup> screening to detect and treat asymptomatic chlamydia is recommended as a public health intervention to prevent PID.<sup>8,9</sup>

Chlamydia screening can prevent PID in two different ways.<sup>10,11</sup> Direct prevention occurs if endocervical infections are detected through screening or diagnostic tests and treated with antibiotics before they progress to clinical PID. Indirect effects may be beneficial or harmful. Indirect prevention occurs if screening lowers chlamydia prevalence and incidence, so that the risk of becoming infected in the first place is reduced. On the other hand, women who have been treated for chlamydia are at risk of re-infection and PID. Disentangling the relative contributions of these effects could help to understand the balance between the potential benefits and harms of chlamydia screening programs.<sup>12</sup>

The impact of chlamydia screening recommendations on the incidence of PID is difficult to measure empirically. Reported numbers of PID diagnoses in the USA and Europe have fallen substantially in the past 30 years, but much of the decrease occurred before chlamydia screening

recommendations were established.<sup>13–15</sup> Trends in PID incidence from routine data sources are difficult to interpret because clinical diagnosis is non-specific and patterns of care, diagnostic criteria, antibiotic treatment options and the spectrum of causative microorganisms have all changed over time.<sup>2</sup> Randomized controlled trials (RCTs) have observed reductions of 35-50% in clinical PID diagnoses from all causes one year after a single round of chlamydia screening.<sup>16–18</sup> These trials show evidence of the direct effect of screening because randomization of individuals in a large population would not affect transmission of infection at the population level. One biological factor affecting trial effect size is the time between acquiring chlamydia and the development of PID; the longer the interval, the greater the opportunity for screening and treatment to prevent PID cases. There is no consensus about the length of this interval and it cannot be observed directly in humans for ethical reasons.<sup>19</sup>

Mathematical models are a tool for understanding processes that cannot be observed empirically and for examining different factors that affect the same endpoint. In this study we used a mathematical model of a hypothetical heterosexual population, based on UK data, to investigate the incidence of clinical PID under different assumptions about the timing of development after chlamydial infection. We then examined the effect of introducing a chlamydia screening program and explored the influence on PID prevention of the direct and indirect effects of screening and of an increase in the risk of PID with multiple chlamydial infections.

#### **METHODS**

#### **Dynamic transmission model**

We developed a compartmental model that explicitly incorporates progression from chlamydia to clinical PID using a Susceptible-Infected-Susceptible (SIS) framework for the infection process

(Figure 1). Table 1 summarizes the model parameters. The model represents a hypothetical heterosexual population aged 16 to 25 years with equal proportions of women and men. Each sex was stratified into two risk classes.<sup>20,21</sup> The percentage of people in each risk class (94.6% low risk and 5.4% high risk)<sup>22</sup> and partner change rates were obtained from Britain's second National Survey of Sexual Attitudes and Lifestyles (Natsal-2), a population-based probability sample survey conducted between 1999-2001 (Table 1).<sup>23</sup> Mixing between women and men in high-risk and low-risk classes is described in the eAppendix (section 1.3). In brief, mixing could vary from fully assortative mixing to fully proportional mixing. The baseline value corresponds to almost fully proportional mixing.

The chlamydial infection process is the same for both risk classes. The risk classes only differ in their partner change rates. An individual enters the risk class, indicated by superscript *g*, as a susceptible (S) who can become infected (I) at rate  $\lambda_w^g$  and  $\lambda_m^g$  (force of infection) for women and men, respectively. The time dependent force of infection parameters are calculated, taking into account mixing between the risk groups, the number of infected people of the opposite sex and the transmission probability per partnership (eAppendix, section 1.3). Both men and women can clear the infection naturally at rate *r*. We assumed that the mean duration of infection is exponentially distributed taking into account that some individuals will clear the infection rapidly, while others may remain infected for substantially longer periods.<sup>7,24</sup> Women and men can receive screening and are successfully treated at rate  $\alpha_w$  and  $\alpha_m$ , respectively. Using the baseline parameter values (Table 1), the transmission probability per partnership is calibrated to the chlamydia prevalence<sup>25</sup> in the presence of a constant background chlamydia testing uptake; we refer to this as the baseline scenario. Women and men can leave the system at any stage due to cessation of sexual activity (rate  $\mu$ ) and are replaced by new susceptibles.

Chlamydial infection in women was separated into two stages, allowing us to adjust the time point after infection  $(1/\gamma)$  at which clinical PID can develop (described in detail below). There are three 'layers' of the model for women (Figure 1A), which represent the number of repeated infections a woman has had ( $k=0, 1 \text{ or } \ge 2$ ). These layers enabled us to increase the fraction of infected women who progressed to PID ( $f_k$ ) amongst women with repeated chlamydial infections. The ordinary differential equations describing the system are shown in the eAppendix (section 1.2).

#### **Progression to clinical PID**

Disease progression from chlamydial infection to PID was the same for both risk classes. The natural history of chlamydial infection and progression to clinical PID were incorporated as follows (Figure 1B). In the first infected stage  $(I_x^g)$  in each layer women have chlamydia and can avoid PID by clearing the infection naturally or by getting screened and treated. We assumed that PID development becomes possible at a single timepoint after infection with chlamydia (time point of possible PID occurrence).<sup>26</sup> Those who do not clear the infection before the time point of possible PID occurrence are at risk of developing PID when they enter the second stage  $(I_y^g)$  are at risk of developing PID when they enter the stage. The second infection stage consists of infected women who experienced a clinical PID episode and those who did not.

In the absence of any screening uptake ( $\alpha_w = 0$ ), a certain fraction ( $f_k$ ) develops PID. We incorporated the possibility of varying the mean time until the time point of possible PID occurrence because it is not known when in the course of infection PID develops. For a given value of  $f_k$ , we introduce a second fraction  $\tilde{f}_k$ , which allows for the fact that the chlamydial infection in women might clear naturally before the time point at which women are at risk of

developing PID (see Figure 1B). The fraction  $f_k$  relates to all women entering  $I_x^g$ , whereas  $\tilde{f}_k$  applies only to those entering  $I_y^g$  in layer k. When the mean time until PID occurrence is short  $\tilde{f}_k$  will be similar to  $f_k$ . With an increasing mean time  $\tilde{f}_k$  has to increase as more women are able to clear their infection before they were at risk of developing PID. Both fractions can increase with repeat chlamydial infections but do not increase further after the second repeat infection (eAppendix section 3.1 and eFigure A4).

The mean time until possible PID occurrence  $(1/\gamma)$  is exponentially distributed and can be varied by multiplying the mean duration of infection by a scaling factor *J*, *i.e.*  $\frac{1}{\gamma} = J \frac{1}{r}$ . For example, the baseline value *J*=0.5 means that the mean time until the point of possible PID occurrence is half the mean duration of infection (eAppendix section 3.1 and eFigure A3).

#### **Screening intervention**

Every individual was eligible to receive screening using a test with 100% sensitivity and specificity and, if infected, would be successfully treated. The baseline scenario assumed constant coverage of background chlamydia testing for ten years in women of 4.5%<sup>27</sup> and in men 2.25% (Table 1). For the intervention scenario we estimated screening uptake using reports from the National Chlamydia Screening Programme in England for women and men aged 15 to 24 in 2010/11 (Table 1).<sup>28</sup> We assumed a yearly stepwise increase over ten years from the baseline scenario to the 2010/11 estimates, with the same screening uptake in low and high risk groups (eFigure A2).

#### Direct and indirect effects of chlamydia screening on PID incidence

The incidence of PID in each layer for risk group *g* is  $\tilde{f}_k \gamma I_x^{g,k}$ . The number of PID cases directly prevented by treatment was derived by tracking how many women who left the first infection stage through screening would have developed PID in the absence of the intervention scenario. The total number of prevented PID cases was determined by the difference in the cumulative number of PID cases in the intervention scenario compared to the baseline scenario (see eAppendix section 3.2 for the corresponding differential equations). Indirectly prevented PID cases were obtained by subtracting directly prevented cases from the total number of prevented PID cases.

#### Analysis

First, we used baseline values for all parameters (Table 1) in the presence of the baseline scenario to derive the probabilities that a woman would experience 0, 1, 2 or  $\geq$ 3 PID episodes by age 25 years (eAppendix section 3.3 and eFigure A5). Second, we described the incidence of PID in a hypothetical cohort of women who experienced their first chlamydia episode at the same time as each other. For this analysis we assumed no screening uptake, using baseline values for all other parameters (Table 1). We determined the number of days after the start of infection by which half of the expected PID cases occurred, using different assumptions about the timing of PID development. Third, we determined the total numbers of PID cases prevented after five and ten years of the intervention scenario and those prevented by direct and indirect effects, using baseline values for all other parameters (Table 1). We obtained the time point at which the numbers of directly and indirectly prevented PID cases were equal and at which the net number of PID cases prevented indirectly was greater than zero.

#### **Uncertainty analysis**

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We examined the effect of repeated chlamydial infections on model predictions by increasing the risk of PID by 50% for each repeated chlamydia episode, using baseline values for all other parameters. We also did a univariable uncertainty analysis for the mean time until the point of possible PID occurrence. We then did a multivariable uncertainty analysis by sampling 3,000 times from the distributions in Table 1. Of those, 2,727 parameter combinations were selected based on the constraints that the transmission probability per partnership cannot be higher than one and that the infection exists in both risk groups. For every parameter set, we varied the scaling factor for the mean time until the point of possible PID occurrence, from immediate progression ( $J=10^{-5}$ ) to an average of twice the mean duration of infection (J=2). We obtained the median and interquartile range (IQR) within the ten years of the intervention scenario for the time points at which the direct and indirect effects were equal and the net number of PID cases prevented was greater than zero.

Numerical solutions were obtained in R.<sup>29</sup> Code files can be obtained from the authors on request.

#### RESULTS

The overall probability of any PID episode was 3.1% by age 25 years in the presence of the baseline scenario, 2.1% in low risk women and 20.3% in high risk women (Table 2). Overall, 92% of women with PID had only one episode (98% of low risk and 82% of high risk women). These probabilities were almost the same as in the absence of screening (eTable A3).

The cumulative incidence of PID for three different mean times until the point of possible PID development is shown in Figure 2 as a function of time since infection, assuming that 10% of women with chlamydia will develop PID (f=10%) in the absence of any screening uptake. The

time taken for half of the expected PID cases to accumulate increases with increasing mean time until PID development and higher values for the fraction  $\tilde{f}$  are needed. If PID develops almost immediately after the start of chlamydial infection, half of the PID cases accrue by 0 days and  $\tilde{f}$ =10%; with a mean time to PID development of 6 months it takes 82 days for half the cases to accrue ( $\tilde{f}$ =15.5%); and with a mean time of two years it takes 159 days ( $\tilde{f}$ =32%).

The implementation of the intervention scenario reduced chlamydia prevalence from 3.0% to 1.0% after ten years (eFigure A6). The prevalence in the high risk group decreased from 22.1% to 7.9% and in the low risk group from 1.9% to 0.6%. The intervention scenario also resulted in a continuous increase in the number of prevented PID cases (Figure 3). In the baseline scenario, the cumulative incidence was 1,685 PID cases per 100,000 women after five years. The intervention scenario reduced this to 1,498 PID cases per 100,000 women. Of the 187 prevented PID cases per 100,000 women, 122 per 100,000 were in the low risk group and 65 per 100,000 in the high risk group. After ten years, the cumulative incidence was 3,370 PID cases per 100,000 women in the baseline scenario. The intervention scenario reduced the cumulative incidence to 2,414 PID cases per 100,000 women. Of the 956 prevented PID cases per 100,000 women, 610 per 100,000 were in the low risk group.

At the start of the intervention scenario, most of the prevented PID cases result from the direct effect that prevents the development of PID as a result of timely antibiotic treatment (Figure 3). Using baseline values, the direct and indirect effects prevent equal numbers of PID cases 4.4 years after the introduction of screening, after which the indirect effect contributes the majority of prevented PID cases as a result of reduced *C. trachomatis* transmission. In women in the high risk group, the time at which direct and indirect effects contribute equally to PID prevention occurs later than in low risk women (eFigure A7).

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The indirect effect of screening produces a net increase in PID cases at the beginning of the intervention scenario (Figure 3). This is because chlamydia-infected women who passed the time point of possible PID occurrence without developing PID become susceptible after screening and treatment; these women can become infected again and are again at risk of developing PID. The effect is small, with a maximum of 5 additional PID cases per 100,000 women, and is outweighed by reduced chlamydia transmission after about 2 years. The net increase in PID cases resulting from the indirect effect of screening is larger and lasts longer in women in the high risk group compared to the low risk group (eFigure A7).

#### Uncertainty analysis

Increasing the risk of PID by 50% per chlamydia episode (10%, 15%, and 22.5% risk of PID for 0, 1, and  $\geq$ 2 repeated chlamydial infections) increased the number of cases of PID prevented by the intervention scenario by 31%; after five years there were 246 PID cases prevented per 100,000 women (135 in the low risk group, 11% more than in the baseline scenario and 111 in the high risk group, 71% more). In this scenario, the time until the direct and indirect effects contributed equally to prevented PID cases (4.6 years) and the time until indirectly prevented PID cases exceeded zero (2.3 years) were similar to those obtained with baseline values.

Increasing the time from chlamydial infection until clinical PID could occur increased the period during which the direct effect of screening prevented most PID cases (Figure 4A). If progression to PID occurs almost immediately after chlamydial infection there is no direct effect. The opportunity for direct PID prevention becomes stronger with increasing time until progression can occur, e.g. for a mean of 2 years, the direct effect dominates for 7.6 years. The time until PID

development has less effect on the length of time for which the indirect effect of screening results in an increase in the number of PID cases (Figure 4B).

The multivariable uncertainty analysis gave results that were similar to the univariable analyses. When the mean time to progression to PID was half the mean duration of infection (J=0.5), the contributions of direct and indirect screening effects were equal with a median of 5.3 years (IQR 4.5, 6.6 years) after the introduction of screening and the median duration of the period in which the indirect effect of screening resulted in an increase in the number of PID cases was 2.6 years (IQR 2.2, 3.4 years) (eFigure A8 and A9).

#### DISCUSSION

In this dynamic modeling study, we show the separate direct and indirect effects by which screening for chlamydia can prevent PID in a hypothetical population. The direct effect, achieved by antibiotic treatment of chlamydial infection in an individual woman before it causes clinical PID, accounts for PID cases that are prevented at the start of the intervention scenario. The indirect effect, which reduces *C. trachomatis* transmission at the population level, produces a small net excess of PID cases at the start of screening. The indirect effect then increases and outweighs the direct effect after a few years. The later that PID develops in the period between acquiring and clearing infection, the greater the impact of screening and the time for which the contribution of direct effects dominate. The impact of screening is also greater if the risk of PID increases after repeated chlamydial infections.

The use of a simple dynamic mathematical model was appropriate for the aim of illustrating the direct and indirect effects of chlamydia screening on the prevention of clinical PID cases. The model was not designed to make quantitative predictions but outputs related to PID were consistent with published data, if allowances are made for the well-described challenges to the accuracy of clinical PID diagnosis<sup>30</sup> and other differences between studies in age groups, definitions of sexual risk classes, healthcare setting and duration of follow up. At baseline, the incidence of chlamydial PID in women aged 16-25 years in the model is 337 cases per 100,000 women per year. Estimates of all-cause PID diagnosed in 20-24 year old women are: about 670 per 100,000 cases in primary care in England in 2000;<sup>31</sup> and 426 per 100,000 in commercial insurance plans in the US in 2001.<sup>32</sup> The probability of recurrent PID predicted by the model was 19% after 10 years amongst the high sexual activity class. In a US longitudinal study, women at high risk of sexually transmitted infections were treated for clinically diagnosed PID and followed up. <sup>33</sup> Amongst those aged  $\leq 19$  years at diagnosis, 25.1% (50/199) had a repeat episode of PID during 7 years of follow up. The model outputs cannot be directly compared with the RCTs, which have screening uptake of 64-100% and report all-cause PID.<sup>16-18</sup>

Our model predictions of changes in chlamydia prevalence should not be compared directly with published chlamydia trend data in the US,<sup>34</sup> first because of simplifying assumptions in the model and second because the model scenario does not represent a real-life situation. Model predictions likely overestimate the impact of screening on chlamydia prevalence for two reasons. First, the model structure cannot take into account the effect of re-infections within ongoing sexual partnerships, which contribute to endemicity.<sup>35</sup> The reduction predicted by this model is, however, comparable to other risk-group stratified compartmental models.<sup>36</sup> Second, we assumed that treatment was 100% effective, although failure rates of >5% after azithromycin are likely.<sup>37</sup>

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The effects of assuming equal screening uptake across risk classes in ours and other models<sup>27,36</sup> are not easily predictable and we are investigating this question in an ongoing study. Of note, the baseline scenario represents a population with no screening program so the greatest reduction in prevalence is expected at the start of the intervention. Population prevalence monitoring of chlamydial infection in the US started in 1999/2000 when screening recommendations were already in place. On the other hand, statistical uncertainty in the published estimates (19% reduction, 95% CI -57 to 57%)<sup>34</sup> does not exclude a larger reduction in chlamydia prevalence in women aged 14-25 years.

The results of our study confirm the hypothesis that the ratio of directly and indirectly prevented PID cases depends on assumptions about the timing of progression from chlamydial infection to PID.<sup>11</sup> The direct effects dominate for longer when it is assumed that PID develops later in the course of chlamydial infection. Although few mathematical modeling studies have explicitly investigated how the timing of progression from chlamydia to PID might affect the impact of screening interventions,<sup>19</sup> our study is in line with those that show that more PID cases are averted as the mean time between infection and PID development increases.<sup>26,38</sup> The true distribution and rate of progression to PID are not known. In our model, PID was an event that could happen at a single, variable, time point. The mean time from the start of chlamydial infection to PID occurrence followed an exponential distribution (a constant rate). Thus, even if the mean time to PID development is short, some women will only be at risk of PID late in the course of infection and if the mean time is long, some will develop PID soon after the start of infection. We think it unlikely that the assumption of an exponential distribution affected the results based on a previous modeling study in which the results were not sensitive to the shape of the distribution of PID development time.<sup>38</sup>

By distinguishing between the direct and indirect effects,<sup>10</sup> this modeling study allows the potential beneficial and harmful effects of chlamydia screening programs to be examined. There was a direct beneficial effect as soon as chlamydia screening was introduced, even though coverage increased only gradually from a low background level. The number of directly prevented PID cases dominates until screening begins to have an effect on the transmission of chlamydia. The model results also show how chlamydia screening and treatment of infected cases might result in unintended harm. In the model population infected women become susceptible to infection and PID immediately after treatment if there is no immunity. At the start of the screening intervention the number of new PID cases in newly susceptible women exceeded the number of cases prevented by screening. Although the effect was small and, with our model assumptions, was always outweighed by the direct beneficial effect at the population level, this study illustrates the balance of potential benefits and harms for individuals who take part in screening programs.<sup>12,24</sup> At the individual level it is not possible to determine which women will benefit from or be harmed by chlamydia screening. The potential harmful effect of screening would increase if there was a long period of immunity after natural clearance and no immunity after treatment of screen-detected infection.<sup>40</sup> The existence and role of immunity after chlamydial infection remain unclear<sup>11</sup> so we did not include it in our model.

Our study also suggests that if repeated chlamydial infections increase the risk of PID, women at the highest risk of infection benefit most from screening despite the increased risk of repeated infection. The strength of the association between repeated chlamydia and the risk of PID increases remains unclear.<sup>11,41</sup> Even in prospective studies, knowledge of a woman's history of chlamydial infection could affect the assignment of a diagnosis of PID, which might result in differential bias that overestimates the effect size. In our study, we assumed that the number of PID episodes did not influence the probability of future PID, the duration of chlamydial infection, or susceptibility to chlamydia. We did not find any published evidence to support or refute these assumptions but they are unlikely to affect the conclusions because PID was a rare event overall.

This study has implications for future research. Clinical research to help understand the time from chlamydial infection to clinical PID development and the role of repeated chlamydial infections is needed because these parameters influence the opportunity for strengthening direct PID prevention. Detailed longitudinal data about *C. trachomatis* genotype in women and their partners and dates of sexual partner change and onset of symptoms as proxies for the time from exposure to clinical PID diagnosis would be valuable. The findings of this study, together with other modeling studies,<sup>26,38</sup> and RCTs<sup>16–18</sup> suggest that chlamydia screening can only have a direct effect if the delay between the onset of chlamydial infection and clinical PID is several months. Further interdisciplinary efforts might determine the relative importance of cellular and immunological mechanisms of tissue damage, which might affect the delay between chlamydial infection and PID, in animal and human studies. This mathematical modeling study has made a new contribution to understanding the mechanisms of chlamydia screening programs by showing the separate contributions of direct and indirect PID prevention and potential harms, which could not have been observed by empirical studies.

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#### **Figure Legends**

FIGURE 1. Schematic overview of the chlamydial infection process and PID development. The model has a susceptible-infected-susceptible (SIS) structure and stratifies the population by sex (Panel A, women; Panel C, men) and by risk class (low or high) indicated by the label g in the superscript. An individual enters the risk class at rate  $\mu$  as a susceptible. Women and men can become infected with C. trachomatis at rate  $\lambda_w^g$  and  $\lambda_m^g$  (force of infection), respectively. They can clear the infection naturally (rate r), or can be screened and treated (rate  $\alpha_w$  and  $\alpha_m$ , respectively), and leave the population at rate  $\mu$ . The three layers for women (k=0, 1,  $\geq$ 2) allow us to vary the fraction progressing to PID, according to the number of repeated chlamydial infections (the third layer contains women with two or more repeated infections). Panel B, progression to clinical PID is only assumed to be possible at one time point after infection with chlamydia. The separation of the infection in women into two stages allows investigation of different time points for progression from chlamydia to PID. Women move from the first to the second stage at rate y. In each layer, a certain fraction  $f_k$  of all women who become infected will develop PID. In stage  $I_x^g$  women are infected and cannot develop PID, but those who make the transition to stage  $I_y^g$  are at risk of developing PID, i.e., upon entering  $I_x^g$  in layer k a fraction  $\tilde{f}_k$ of those women who are still infected will experience a clinical PID episode.

FIGURE 2. Influence on PID incidence of changing the time point after chlamydial infection at which clinical PID can occur. Cumulative incidence of clinical PID following a hypothetical cohort of women who become infected with *C. trachomatis* at the same time as each other for f=10%. For this analysis we assumed no screening uptake, using baseline values for all other parameters (Table 1). With almost immediate progression after the start of chlamydia (dashed line) the corresponding fraction  $\tilde{f}$ =10%; with a mean time of 6 months (solid line),  $\tilde{f}$ =15.5%; with a mean time of two years (dashed-dotted line),  $\tilde{f}$ =32%. The black dots show when half of the expected PID cases, i.e. 5%, occurred.

FIGURE 3. Cumulative incidences of clinical PID cases prevented by direct and indirect effects, using baseline values. The total number of prevented clinical PID cases per 100,000 women (solid line) is split into those prevented by direct (dashed line) and indirect (dasheddotted line) effects. The direct and indirect effects prevent the same number of clinical PID cases 4.4 years after the start of the intervention scenario (filled circle). The number of PID cases prevented exceeds the number of cases produced by the indirect effect 2.2 years after the start of the intervention scenario (filled square).

FIGURE 4. Univariable uncertainty analysis of mean time until possible occurrence of clinical PID. Panel A, influence on the time after the start of the intervention scenario until direct and indirect effects contribute equally to prevented PID cases (solid line). Direct effect dominates (white area), indirect effect dominates (gray area), filled circle shows the mean time using the baseline value. Panel B, influence on the time after the start of the intervention scenario for which the indirect effect results in a net increase in PID cases (white area) and then results in net reduction in PID cases (gray area). The filled square indicates the time using baseline value.

# List of Supplemental Digital Content

Supplemental Digital Content 1. eAppendix.pdf

### **TABLE 1.** Parameter values describing the natural history of chlamydia infection, PID

development and the screening intervention

Parameter	<b>Baseline value</b>	Description	Uncertainty analysis	
			<b>Distribution</b> <sup>a</sup>	Parameters
Infection para	meters			
1/ <i>r</i>	365 <sup>7,35</sup>	Mean duration of infection (days)	Normal	$\mu = 365^{7,35}$
				$\sigma^2 = 75^{b}$
р	3% <sup>25</sup>	Prevalence at start	Uniform	1-5 <sup>b</sup>
β	0.36°	Transmission probability per partnership		
$\lambda_m^g$ , $\lambda_w^g$	Calculated <sup>d</sup>	Force of infection (per year) on men and		
		women in risk class $g \in \{\text{low, high}\},\$		
		respectively		
PID developm	ent parameters			
$f_k$	10% <sup>26</sup>	Fraction of all infected women who	Uniform	1-30 <sup>b</sup>
		develop clinical PID having had at least $k$		
		previous chlamydia episodes, in absence		
		of screening uptake ( $u_f=0$ )		
$1/\gamma$	Calculated <sup>e</sup>	Mean time until point of possible PID		
		occurrence		
J	0.5 <sup>b</sup>	Scaling factor for the mean time until	Uniform	10 <sup>-5</sup> -2 <sup>b</sup>
		point of possible PID occurrence		
$\tilde{f}_k$	$Calculated^{\mathrm{f}}$	Fraction of women who develop PID at		
		time point of possible PID occurrence		
		and having had at least $k$ previous		
		chlamydia episodes		
Behavioral pa	rameters			
$1/\mu$	10	Mean duration of sexual activity (years)		
ρ	5.4% <sup>22,f</sup>	Proportion of population in high risk	Normal	µ=5.363 <sup>22</sup>
		group		$\sigma^2 = 0.005^{22}$
ω	0.95 <sup>b</sup>	Parameter to change from fully	Uniform	0-1 <sup>b</sup>

		assortative mixing ( $\omega$ =0) to fully		
		proportional mixing ( $\omega$ =1) between risk		
		groups		
$c^l$	$0.6^{22,f}$	Partner change rate in low risk group	Normal	$\mu = 0.607^{22}$
		(per year)		$\sigma^2 = 0.018^{22}$
$c^h$	8.1 <sup>22,f</sup>	Partner change rate in high risk class (per	Normal	$\mu = 8.052^{22}$
		year)		$\sigma^2 = 0.357^{22}$
Screening pa	rameters			
$\alpha_m, \alpha_w$	$Calculated^h$	Screening rate (per year) for men and		
		women, respectively		
$u_m, u_w$		Coverage of screening uptake (per year)		
		for men and women, respectively <sup>i</sup>		
	2.25%, <sup>b</sup> 4.5% <sup>27</sup>	Baseline scenario		
	22.6%, <sup>28</sup> 42.7% <sup>28</sup>	Intervention scenario, yearly increase		
		from baseline scenario coverage over		
		10 years		

<sup>a</sup> Distributions in the uncertainty analysis determined by agreement among the authors. For all normal distributions, the mean equals the baseline value and  $\sigma^2$  is the variance. For all uniform distributions, the range (minimum - maximum) is given in the column parameters.

<sup>b</sup> Value(s) determined by agreement among the authors.

- <sup>c</sup> Calibrated in the presence of the baseline scenario to observe an overall chlamydia prevalence of p at steady state.
- <sup>d</sup> Calculated using the behavioral parameters (except mean duration of sexual activity) and the transmission probability per partner (eAppendix section 1.3).
- <sup>e</sup> Calculated using scaling factor  $J, \frac{1}{\gamma} = J \frac{1}{r}$ .
- <sup>f</sup> Calculated in the absence of screening (u = 0) with  $\tilde{f}_k = \frac{\gamma + r + \mu}{\gamma} f_k$ .
- <sup>g</sup> Data from Natsal-2<sup>23</sup> were stratified into two activity classes using maximum likelihood method.<sup>22</sup>
- <sup>h</sup> The coverage of screening uptake u per year is converted into a screening rate  $\alpha = -\log_e(1-u)$  per year.<sup>42</sup>
- <sup>i</sup> In the baseline scenario, chlamydia test uptake in men is assumed be half of that in women. Coverage in women is based on estimation from Turner *et al.*<sup>27</sup> for the UK in 2000. In the intervention scenario, screening

coverage is based on 15 to 24 year olds, reported by the National Chlamydia Screening Programme in England in 2010/11<sup>28</sup> (eAppendix, eFigure A2).

**TABLE 2.** Probabilities of clinical PID episodes amongst women aged 16-25 years in the

 presence of the baseline scenario, using baseline values

Risk group	<b>Probability of experiencing clinical PID episodes (%)</b>						
	None	Any	One	Two	≥3		
Low risk	97.9	2.1	2.1	0.04	<10-4		
High risk	79.7	20.3	16.5	2.3	1.5		
Overall	96.9	3.1	2.8	0.2	0.08		



B PID







