Summary of MSc Dissertation: **Exploring the Impact of Targeted Screening for the Control of Chlamydia Infections**

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1 Introduction

Within the United Kingdom, chlamydia remains the most prevalent STI particularly within the 16-25 age cohort [1]. Despite infection being easily treated with a single dose of Azithromycin, untreated chlamydia can cause severe health complications including infertility, ectopic pregnancies Pelvic Inflammatory Disease (PID) [2]. As a highly asymptomatic infection, detection is often only possible through healthcare interventions. This has resulted in screening programmes developed to detect infections opportunistically by testing individuals within a subset of the population. There has been some evidence that individuals who become infected with chlamydia once may be at a higher risk of re-infection [3]. This project considers that by introducing targeted re-screening of previously infected individuals combined with the current National Chlamydia Screening Programme, greater reductions in infection may be seen.

Chlamydia infection is caused by the bacteria *Chlamydia trachomatis* infecting the epithelial cells within the cervix, urethra, rectum, conjunctiva or pharynx [4]. Common ailments resulting from chlamydia infection include urethritis, Proctitis and *Lymphogranuloma venereum* in both men and women [4]. Chlamydial infection can also lead to epididymitis (exclusive to men), cervictis, of which chlamydia is responsible for approximately 40% infections worldwide, endometritis and PID (exclusive to females) [5].

These consequences mean that chlamydia has become a serious health concern, with many governments annually expending vast resources and wealth trying to control and reduce the number of infected individuals. Within the UK the National Chlamydia Screening Programme (NCSP) was launched in 2003, in an attempt to combat the rise of chlamydial infections, particularly in those aged between 16-25. It is estimated that between 2008-2009, £42 million was spent on the programme [6].

Testing for chlamydia in an individual is a simple process. The most common test used is that of a nucleic acid amplification test (NAAT), which uses a small sample of urine or a urinary swab (taken by either a healthcare professional or the patient) to detect the presence of the *C. trachomatis* bacteria. Using the NAAT test, the NCSP currently aims to screen 17% of men and women aged 15-24 [7]. With the goal to enhance the control of chlamydia infection, we explore the potential of a screening programme split between opportunistic screening at the population level with targeted screening of previously infected individuals.

There has been a large collection of models for the epidemiology of chlamydia, taking a variety of approaches and using an array of different techniques. Due to the late identification of chlamydia, and it's similarities with gonorrhoea, many early mathematical models of chlamydia originate from models for gonorrhoea infection. The majority of mathematical models used for the study of chlamydia epidemiology fall into three approaches.

Deterministic models compartmentalise the population by infection status, with the most basic models dividing individuals into those who are susceptible to infection, or those who are already infected. Compartments are modelled explicitly using systems of Ordinary Differential Equations (ODE's) over time to represent the current infection levels within a population [8].

Individual-based and network models explicitly represent each individual and their partnerships through different stages of infection. They allow for increased detail in terms of pair formations, dissolutions, behaviour, spatial distancing, and individual characteristics such as age, gender, preferred number of partners, preferred duration of partnerships and infection status [9]. Since they monitor each individual contact tracing can be easily implemented, however they are computationally intense.

Pair-wise approximation models allow for a middle ground between deterministic and individual/network approaches by capturing any influence that network structure may have on the spread of infection, without explicitly modelling each individual [10]. Both infection compartments and pair connections are modelled explicitly using systems of ODE's, however become increasingly complex with the inclusion of additional compartments.

In terms of modelling chlamydia, pairwise approximation models allow for the inclusion of partner notification at the cost of complexity. However, this project is concerned with exploring the impact of a potential new strategy, targeted re-screening, not partner notification. Therefore we will make use of a deterministic approach to build a compartmental model of ten distinct compartments.

2 Model Formation

We develop the model based on previous work into the area starting with a simple $SITS$[1] model which has been used extensively to simulate the impact of different control strategies on chlamydial infections [11] [12]. The population is assumed to be a constant size N, as although chlamydia can lead to many severe complications, few of these are fatal within the time frame of 3 years, of which model examines [4]. This population consists only of those between 16-25 years of age; individuals may enter or exit the system by maturing into or out of the 16-25 age group, though it is done at the same rate α. Individuals within the population mix randomly and show no preferential mixing when choosing sexual partners. The population is equally mixed between male and female however the model is not gender divided. All individuals have the same number of potential partners k at any point in time. As the model does not differentiate between male or female, it allows for both heterosexual and homosexual partnerships, and assumes no difference in regards to infection and recovery rates between sexual orientations.

[1] Susceptible→Infectious→Treatment→Susceptible

Transmission of infection occurs between two individuals of classes S (susceptible) and I (infectious) at rate β and requires direct sexual contact. Infected individuals may recover naturally at a rate r moving themselves back into the susceptible class S, develop symptoms of infection at a rate d moving themselves into the treatment class T, or be screened in infection at a rate g, again moving into the treatment class. Treatment is easily available and individuals seeking treatment recover at a rate a back to the susceptible class S.

We now introduce the concept of 'observed classes' S_2, I_2 in a similar vein to the frailty classes used by Rodrigues *et al.*, with the previous $SITS$ system described now being given the subscript 1 to designate the standard classes [13]. Observed classes can only be entered as a result of previous chlamydial infection, and mirror the counterpart standard system in terms of events such as transmission of infection β_2, natural recovery r_2, symptoms appearing d_2, or national screening g. Whilst in the observed classes individuals may be actively recalled by clinics for secondary testing at a rate $\hat{g}\gamma$, however due to the resources required, observation is only for a limited time after initial infection and subsequent treatment, and individuals may move back into the standard susceptible class at a rate μ, if no infection is detected.

A schematic of the model can be seen in figure 1, the ODE system in (2.1)-(2.6), and parameter estimations in table 2.1.

The full model is then divided into core/non-core groups akin to the work of Hethcote and Yorke [8], where the core represents 10% of the population, which can be seen in appendix A.

$$\dot{S}_1 = \alpha N + r_1 I_1 + \mu S_2 - S_1 \left(\alpha + k \sum_{i=1}^{2} \beta_i \frac{I_i}{N} \right) \qquad S_1(0) = S_{1\,0} > 0 \tag{2.1}$$

$$\dot{I}_1 = k S_1 \sum_{i=1}^{2} \beta_i \frac{I_i}{N} - (\alpha + r_1 + g + d_1) I_1 \qquad I_1(0) = I_{1\,0} > 0 \tag{2.2}$$

$$\dot{T} = g (I_1 + (1+\varepsilon) I_2) - (\alpha + a) T + \sum_{i=1}^{2} d_i I_i \qquad T(0) = T_0 \geq 0 \tag{2.3}$$

$$\dot{S}_2 = aT + r_2 I_2 - S_2 \left(\alpha + \mu + k \sum_{i=1}^{2} \beta_i \frac{I_i}{N} \right) \qquad S_2(0) = S_{2\,0} \geq 0 \tag{2.4}$$

$$\dot{I}_2 = k S_2 \sum_{i=1}^{2} \beta_i \frac{I_i}{N} - (\alpha + r_2 + g(1+\varepsilon) + d_2) I_2 \qquad I_2(0) = I_{2\,0} \geq 0 \tag{2.5}$$

$$\begin{aligned} N(t) &= S(t) + I(t) + T(t) \\ &= S_1(t) + S_2(t) + I_1(t) + I_2(t) + T(t) \end{aligned} \qquad N(0) = N_0 > 0 \tag{2.6}$$

Where $\varepsilon = \frac{\hat{g}\gamma}{g}$.

It has been suggested by previous studies that parameters β_2, r_2, d_2 relating to the observed classes may differ slightly from the standard class parameters β_1, r_1, d_1, due to increases in viral load between primary and repeat infections [3, 22, 23]. Sensitivity analysis was performed and found that changes to β_2, r_2, d_2 by $\pm 20\%$ had little effect on equilibrium levels, however to minimise any unseen implications, β_2, r_2, d_2 were chosen to

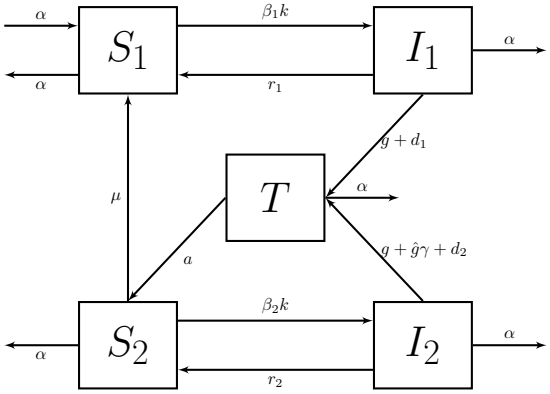


Figure 1: *Extended deterministic SITS model with national screening and targeted re-screening*

Parameter	Value	Range	Description	Source
α	2.74×10^{-4} $days^{-1}$	N/A	Maturity rate	$\frac{1}{365\times10}$
k	2.07	[1.66,5.76]	N$^{o.}$ of partners/individual	[14] [15]
r_i	0.0023 $days^{-1}$	[0.0021,0.0025]	Natural recovery rate	[16]
g	4.77×10^{-4} $days^{-1}$	N/A	Screening rate	[17] [18]
d_i	0.0067 $days^{-1}$	[0.0060,0.0073]	Rate of developing symptoms	[16] [12] [19]
a	0.0714 $days^{-1}$	[0.0476,0.1429]	Rate of treatment	[4] [20]
β_i	0.0051 $days^{-1}$	N/A	Transmission rate	Set for 8% prevalence
$\hat{g}$	0.5	[0,1]	Re-screening attendance	[18]
γ	0.0082 $days^{-1}$	[0.0056,0.0111]	Duration of observation	[21]
μ	0.0055 $days^{-1}$	[0.0027,0.0110]	Clearance from observation	[21]
N	10000	N/A	Population size	Arbitrarily chosen

Table 2.1: *Baseline Parameter Estimates*

be at only a 10% increase on the baseline values β_1, r_1, d_1.

3 Model Analysis

By simulating populations for 3 years, it was shown that by introducing re-screening we would see a reduction in overall infection levels, however the most interesting feature was an initial increase in treatment cases T, before settling on a lower equilibria state.

As predicted, figure 2 shows that for all levels of re-screening, clinics will initially see a sharp intake of new cases into the treatment class T, before dropping to lower levels due to a reduction of infection. This drop below the baseline 0% re-attendance happens after 130-150 days of increased re-screening, depending on the level of attendance. Whilst over longer timespans this minor increase could be ignored as negligible in comparison to the greater following reductions, due to the clinical setting of which this model aims to impact, an increase in treatment cases lasting 150 days must not be overlooked. For

If re-screening were to be taken on in a clinical setting, where national screen had previously been implemented and the system allowed to reach equilibrium, then it is likely to see a sharp surge in new cases before dropping to the new equilibrium. This can be seen in figure 2 where the standard SITS model with national screening at 16% is simulated for 3 years, at which point re-screening is introduced to varying degrees and simulated for an additional 3 years.

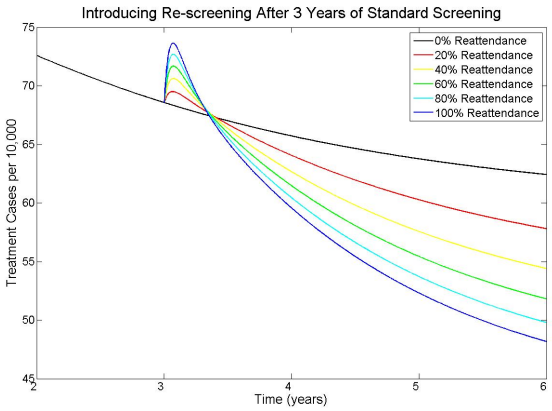


Figure 2: *Impact of introducing re-screening into an established population on number of treated cases per 10,000*

this reason it is important to know how long it would take for each level of re-screening to compensate for the increased screening, and clinics would see an overall reduction since implementing the new procedure. By calculating the absolute area under each curve minus the baseline 0% curve it is possible to find the exact number of increased treatments, and the time taken to compensate for them, as can be seen in table 3.1.

Attendance of re-screening (%)	**Number of additional cases seen (per 10,000)**	**Time when cases drop below baseline (days)**	**Time taken to compensate (days)**
20%	30.67	150	395
40%	113.92	143	410
60%	184.58	138	408
80%	245.27	133	402
100%	297.89	129	396

Table 3.1: *Numerical results for figure 2 including time taken (from time=1096 days, 3 years) to compensate for initial increase.*

Interestingly, table 3.1 shows that the fastest strategies to compensate for the initial increase in treatment cases are at the extreme ends of re-screening, when attendance is at 20% and 100%, with the strategies closest to 50% taking longest. In the case of attendance at 20% this is due to the low amount of additional initial cases (30.67 compared with 297.89 per 10,000 for 100% attendance), resulting in few cases to compensate for, whilst in the case of 100% this is due to the rapid decrease in cases after the intersection point.

Using the core/non-core model, (A.1)-(A.12), it is also possible to explore the dynamics of the population divided by sexual activity. The core group represents 10% of the population N and has on average 4.8× more sexual partners than the non-core group. Modelling this at the same values as before (screening at 16% and re-screening at 50%) allows insight into the change in com-

position of the core/non-core divide over the 3 year timespan, which is most pronounced in the infectious classes. Examining population levels after 3 years shows the core group to be responsible for approximately 32% of infection, despite only representing 10% of the population. Figure 3 shows the infectious class I_1, I_2 in terms of a core/non-core divide over time.

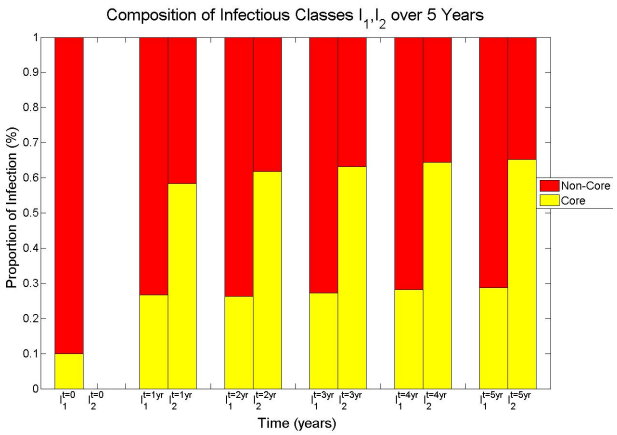


Figure 3: *Composition of* (I_1, I_2) *over time with regard to core/non-core groups (national screening at 16%, targeted re-screening at 50%)*

After the initial rise of cases into the previously empty I_2 class, figure 3 shows a slow yet steady rise of infectious cases moving into the core group, with the I_2 class being composed of 65.3% core individuals compared to the I_1 class being composed of 28.7% core individuals. Again, this is due to the increased sexual activity rate of core members. Because of this, a greater positivity of screening will be seen, resulting in a larger proportion of core individuals moving into the observation classes S_2, I_2, as seen in figure 3.

As quantities of interest to public health, prevalence, incidence and positivity are widely used by health authorities to assess effectiveness of potential control methods. They examine not only the amount of infection within the population, but also the rate of growth and disease turnover.

3.1 Prevalence

Prevalence was calculated as $\frac{I+T}{N}(t)$ for a range national screening coverages [10%,50%] representing any values for PCT's (Primary Care Trusts) who do not currently meet the average 16%, up to the target coverage suggested by Turner *et al.* of 43% [9]. Whilst for re-screening attendance, a range of [0%,100%] was chosen to signify the limits of no re-screening up to every individual is re-screened at 3 months after clearing initial infection via treatment. Prevalence was looked at for both the standard model, (2.1)-(2.6), and the core/non-core model, (A.1)-(A.12), with the core/non-core model under the additional assertion that re-screening attendance for core members is greater than re-screening attendance for non-core members, though it averages to the same attendance used in the standard model. This gives figure 4.

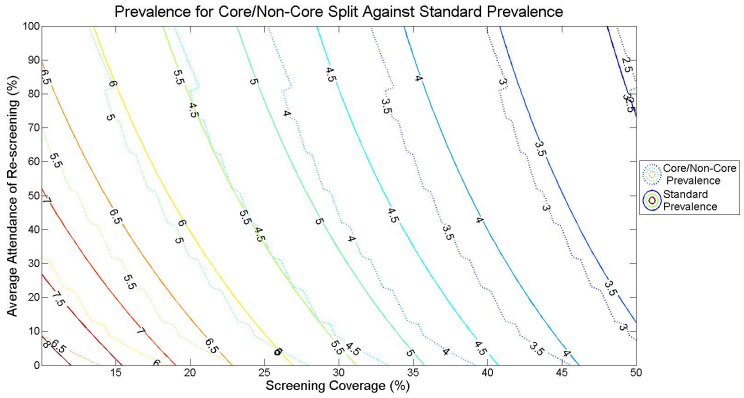


Figure 4: *Prevalence when $\hat{g}_c > \hat{g}_{nc}$ against standard prevalence. Dashed lines denote when $\hat{g}_c > \hat{g}_{nc}$, solid lines represent standard prevalence.*

The somewhat jagged nature of the core/non-core contour plot is due to the calculations of $\hat{g}_c$ and $\hat{g}_{nc}$. Attendance $\hat{g}$ is entered for all $\hat{g} \in [0, 1]$ representing re-screening attendance between 0%-100%, however since $\hat{g}_c$ and $\hat{g}_{nc}$ must abide by equation (**??**) they cannot be fixed to any value. Therefore, $\hat{g}_c$ and $\hat{g}_{nc}$ are calculated by a pseudo shooting method, using the inbuilt MATLAB function `fzero`.

Figure 4 shows that lowest rates of prevalence are achieved at the highest levels of screening coverage (50%) and re-screening attendance (100%), allowing an unprecedented reduction to 3% prevalence. However, considering that currently the NCSP averages 16% national screening coverage across the UK, of which many PCT's fall below, it seems unlikely that national screening coverage will be able to increase to the suggested 43% coverage in the close future. Therefore, figure 4 proves useful by providing an alternative with targeted re-screening. If high levels of national screening are unable to be reached, what combined levels of national screening and targeted re-screening will result in the same levels of reduction? Figure 4 shows that instead of increasing screening coverage to unattainable values, the same reductions may be seen with lower national screening values working in tandem with targeted re-screening.

Taking a reduction to 5% as an example. To reach prevalence values of 5% with only standard national screening procedures in place would take 3 years of screening coverage at approximately 36%. Conversely, by implementing targeted re-screening at 100%, national screening can drop to approximately 24% coverage. Although it is unlikely to see an attendance rate of 100% for re-screening, the model provides an alternative to simply increasing standard national screening. However the question now becomes whether either of the increases to achieve 5% prevalence are likely? In terms of standard national screening, this would require a jump from the current 16% to 36%, a 2.25 fold increase, compared to a jump from 16% to 24%, a 1.5 fold increase. Health authorities have already shown difficulty in increasing national screening above the current level, and to reach a coverage of 36% would require vast additional resources and is likely to take several years. Furthermore, it would require 2.25× the current number of individuals who participate in screening, of

which finding new individuals who are willing to participate can prove difficult. However, those who are eligible for re-screening would have already been screened at least once, and may be more receptive to additional screening. Therefore despite the larger increase required in re-screening, the individuals required may be more willing, resulting in fewer resources being spent, than those required to increase national coverage.

Despite the irregularity of the core/non-core curves, they show a similar pattern to the standard prevalence curves, though at reduced levels. This suggests that by ensuring those individuals with higher sexual activity levels return for re-screening at higher rate than those with lower sexual activity levels, overall prevalence can be further reduced, compared to uniform attendance across both core and non-core individuals. In a clinical setting this could be achieved by stressing the importance of re-screening, and by taking data of average number of sexual partners, additional appointment reminders could be made to core members to maximise attendance.

3.2 Incidence

Incidence was calculated as the number of new cases per 10000 person-years, using $\int_{t_i}^{t_{i+1}} \sum_{j=1,2} \beta_j k_j S_j^{c+nc} \frac{I^{c+nc}}{N}$. Incidence was calculated for discrete levels of screening coverage $15\%, 25\%, 35\%, 45\%$ and re-screening attendance $0\%, 50\%, 100\%$ after years $0, 1, 2, 3$. This resulted in figure 5 which was then compared to real world data. Baseline vales for 15% screening coverage with 0% re-screening attendance at year 0 (2825 per 10000 person-years) showed close values to those reported by both Kretzschmar *et al.*, with average values slightly higher than those of the HPA model, yet lower than those of the ClaSS model, and by Batteiger *et al.* who found real world incidence to be approximately 3400 cases per 10000 person-years [19, 24].

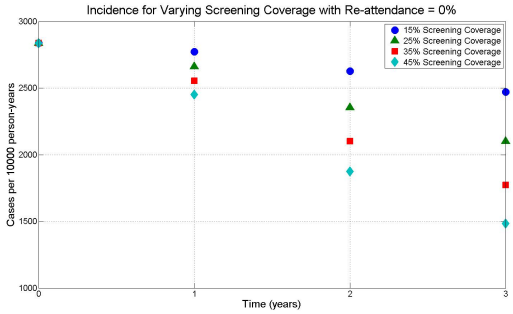
Incidence levels with targeted re-screening in effect were also able to be compared to recently published data on the re-screening of previously infected 16-25 year olds [25]. For 60% re-screening attendance 3 months after initial screening (at 16% screening coverage), the Woodhall *et al.* found incidence of new cases to be 1840 per 10000 person-years [25]. Comparatively, the model here predicts that for 16% screening coverage and 60% re-screening attendance, incidence to be 2046 cases per 10000 person-years. These values show a clear synergy between the compartmental model in use here, and real world data, suggesting the compartmental model accurately represents chlamydial dynamics and potential risk of contracting the infection.

3.3 Positivity

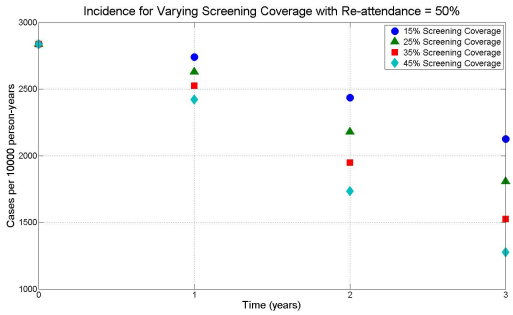
Positivity was calculated for both screening and re-screening separately using $Pos_{NS} = \frac{1}{365} \int_{t_i}^{t_{i+1}} \frac{I_1^{c+nc} + I_2^{c+nc}}{S_1^{c+nc} + S_2^{c+nc} + I_1^{c+nc} + I_2^{c+nc}} dt$ and $Pos_{TR} = \frac{1}{365} \int_{t_i}^{t_{i+1}} \frac{I_2^{c+nc}}{S_2^{c+nc} + I_2^{c+nc}} dt$ respectively.

Comparing positivity for the two measures shows that positivity levels for re-screening are less sensitive to changes in both national screening and targeted re-screening. Furthermore, figure 6 shows that as prevalence decreases, the effectiveness of national screening also decreases. However for targeted re-screening, whilst initial reductions in prevalence reduces effectiveness, for further reductions in prevalence, effectiveness is not significantly affected, though it does sit at lower overall levels of positivity than that of national screening. Re-screening positivity also appears

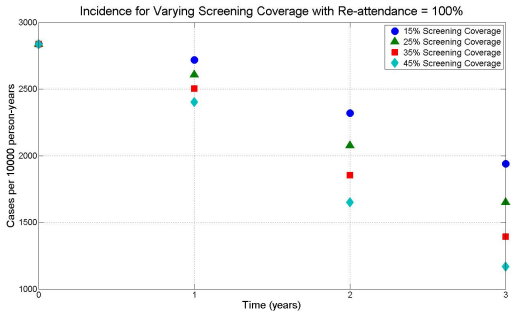
to be largely unaffected by changes in national screening coverage, whilst screening positivity is significantly affected by changes in both national screening coverage and targeted re-screening attendance.



a: *0% re-screening*

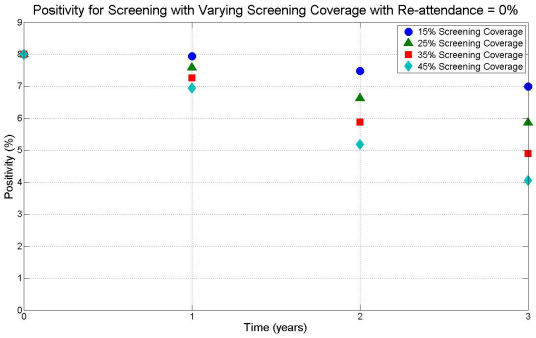


b: *50% re-screening*

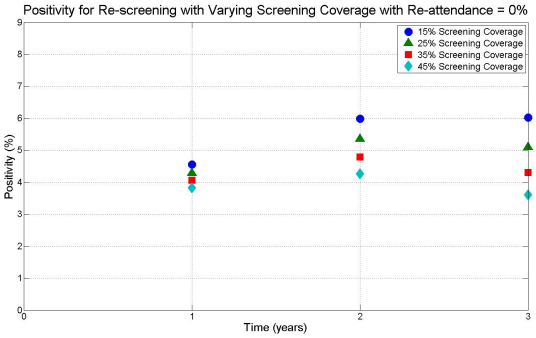


c: *100% re-screening*

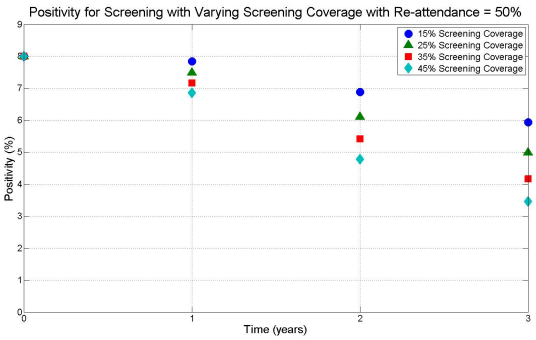
Figure 5: *Incidence levels over 3 years for varying screening coverage with* $0\%, 50\%, 100\%$ *re-screening*



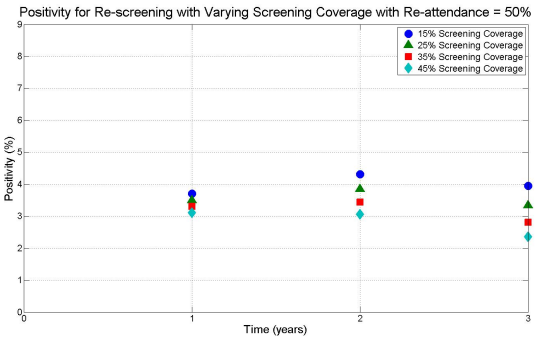
(a) *Screening Positivity*



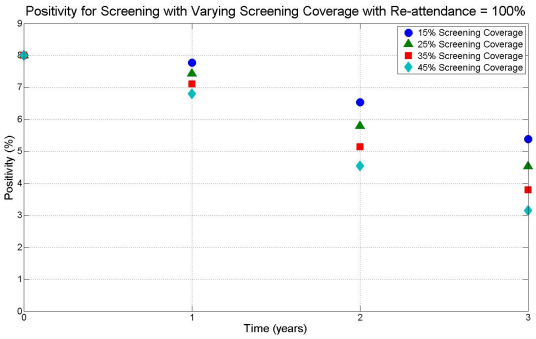
(b) *Re-screening Positivity*



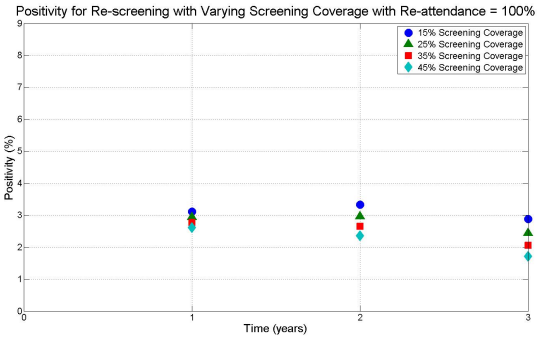
(c) *Screening Positivity*



(d) *Re-screening Positivity*



(e) *Screening Positivity*



(f) *Re-screening Positivity*

Figure 6: *Positivity for national screening and targeted re-screening*

4 Cost Analysis

Cost and cost effectiveness were analysed by making use of a previously published costings tool, currently used by healthcare proffesionals [26]. Screening costs were assigned following the costings used by Turner *et al.*, however costs for targeted re-screening had to be estimated due lack of data on how such a scheme would be used. The costings table can be seen in table 4.1.

Cost and cost effectiveness were then plotted for the same ranges of screening coverage and re-screening attendance as before ([10%,50%] and [0%,100%]). A prevalence contour plot was then overlaid onto the cost effectiveness surface plot giving figure 7.

Expense	Cost (£ per screen)	Applicable Groups
Screen	43.65	S_1, S_2, I_1, I_2
Administration	2.76	S_2, I_2
Text reminder	0.10	S_2, I_2
Missed re-screen notification	0.10	S_2, I_2

Table 4.1: *Costs of control strategy*

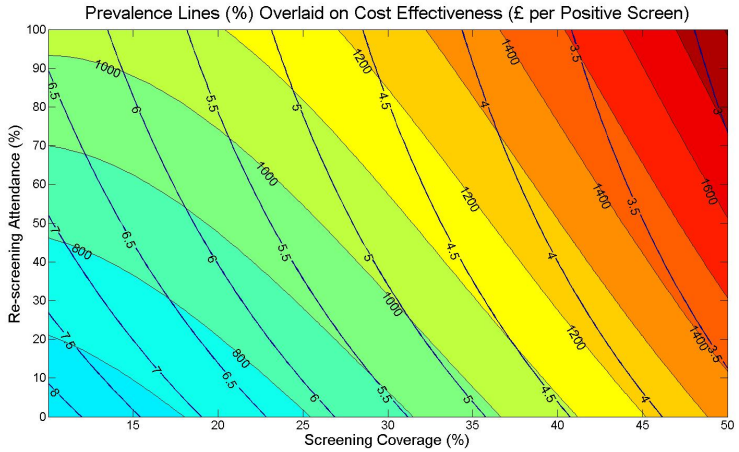


Figure 7: *Prevalence (%) (lines) overlaid onto cost effectiveness (£ per positive screen) (filled blocks) for varying screening coverage 10%-50% and re-screening attendance 0%-100%*

Figure 7 shows that for the costs assigned, prevalence has a dramatic consequence on cost effectiveness. Take a reduction to 6% prevalence as an example. This can be achieved with 27% screening coverage and 0% re-screening attendance, at a cost of approximately £825 per positive screen. The same reduction can also be achieved with 13% screening coverage and 100% re-screening attendance, at a cost of approximately £1040 per positive screen, a 1.26 fold increase per positive screen. However, this monetary increase does slow at higher levels of prevalence, for example a reduction to 3.75% prevalence. This can be achieved with combination (coverage,attendance) levels of (49%,0%) costing £1300 per positive screen or (37%,100%) costing £1420 per positive screen, a 1.09 fold increase. It is important to note that these are approximate estimates as the cost values in regards to re-screen lack any true data to base these on. However, taking the values given here, this promotes an important question. Whilst an increase to 27% coverage with 0% re-screening attendance is £215 per positive screen cheaper than a decrease to 13% coverage with 100% re-screening attendance, obtaining new individuals to increase screening coverage may required more resources than persuading currently screened individuals to return for secondary screenings. The question becomes whether extra resources to recruit new screenings is less than the saving of £215 per positive screen. If this is the case then re-screening would be unlikely to be considered for implementation in a clinical setting, however if the saving of £215 (in

the case of reductions from 8% to 6% prevalence) is smaller than that of increasing national coverage, then re-screening is likely to be considered as a possible alternative measure.

5 Discussion

From the results demonstrated by the model, it could be recommended to public health services that by incorporating targeted re-screening of previously chlamydia infected individuals, in conjunction with the already present national screening, they would likely see a substantial drop in both overall prevalence and incidence. However, this would not happen immediately and a brief rise in cases should be anticipated, before seeing reductions to previously unattainable levels.

While the greatest reductions in infection were clearly found at the highest levels of combined screening coverage and re-screening attendance, these targets may be unrealistic considering the current screening levels achieved. However, even small increases in re-screening have been shown to dramatically reduce both prevalence (figure 4) and incidence (figure 5) without the need to increase national screening. It is therefore recommended that every effort is made for both screening coverage and re-screening attendance to be maximised.

Increased coverage and attendance can be best achieved through awareness campaigns, highlighting the dangers of untreated chlamydia, especially in females. Informing the population is likely to result in individuals becoming more open to the possibility of screening and returning for additional screens, though the costs of these have not been accounted for in this model. By increasing public opinion of chlamydia screening in these ways, greater values for screening coverage and re-screen attendance may become attainable.

It was also shown that by identifying individuals with higher sexual activity levels, 'core individuals', and ensuring that re-screening attendance of these individuals is higher than those with lower sexual activity levels, further reductions in prevalence can be seen (figure 4). In a clinical setting this would be achieved through additional appointment reminders being made to those identified as core individuals.

While cost and cost effectiveness were assessed, values chosen for targeted re-screening had to be estimated on data of similar schemes, as no costings data for re-screening currently exists. Despite this, to achieve the same reductions in prevalence across all levels of screening coverage and re-screening attendance, the cost effectiveness (£ per positive screen) was shown to be marginally higher for re-screening (figure 7). However the question of whether this increased cost is less than the costs of acquiring new patients for increased coverage was highlighted. The chance of targeted re-screening being taking on in clinical settings essentially relies on this. If this extra cost is less than the costs of increasing coverage, then it is recommended that targeted re-screening becomes standard practise across all settings where national screening applies. However, to truly make this comparison, a more detailed estimation of the costs of the potential scheme would be required; which in turn relies on the publishing of an accurate costings report by the health services on how this control strategy could realistically be put into effect.

On top of a detailed costings report into the possible financial costs of running re-screening as a control strategy, it is highly

recommended that an extended clinical trial of combined national screening and targeted re-screening be undertaken. Not only would this give the required data to extensively test the model against, but would also lead to a better parameter estimation and more accurate predictive modelling, enabling a better understanding of the influence of targeted re-screening as a possible control strategy.

A Full system of equations

Core

$$\dot{S_1^c} = \alpha N^c + r_1 I_1^c + \mu S_2^c - S_1^c \left(\alpha + k_1 \sum_{i=1}^{2} \beta_i \frac{I_i}{N} \right) \qquad S_1^c(0) = S_{1\,0}^c > 0 \tag{A.1}$$

$$\dot{I_1^c} = k_1 S_1^c \sum_{i=1}^{2} \beta_i \frac{I_i}{N} - (\alpha + r_1 + g + d_1) I_1^c \qquad I_1^c(0) = I_{1\,0}^c > 0 \tag{A.2}$$

$$\dot{T^c} = g \left(I_1^c + (1+\varepsilon) I_2^c \right) - (\alpha + a) T^c + \sum_{i=1}^{2} d_i I_i^c \qquad T^c(0) = T_0^c \geq 0 \tag{A.3}$$

$$\dot{S_2^c} = a T^c + r_2 I_2^c - S_2^c \left(\alpha + \mu + k_1 \sum_{i=1}^{2} \beta_i \frac{I_i}{N} \right) \qquad S_2^c(0) = S_{2\,0}^c \geq 0 \tag{A.4}$$

$$\dot{I_2^c} = k_1 S_2^c \sum_{i=1}^{2} \beta_i \frac{I_i}{N} - (\alpha + r_2 + g(1+\varepsilon) + d_2) I_2^c \qquad I_2^c(0) = I_{2\,0}^c \geq 0 \tag{A.5}$$

$$\begin{aligned} N^c(t) &= S^c(t) + I^c(t) + T^c(t) \\ &= S_1^c(t) + S_2^c(t) + I_1^c(t) + I_2^c(t) + T^c(t) \end{aligned} \qquad N^c(0) = N_0^c > 0 \tag{A.6}$$

Non-Core

$$\dot{S_1^{nc}} = \alpha N^{nc} + r_1 I_1^{nc} + \mu S_2^{nc} - S_1^{nc} \left(\alpha + k_2 \sum_{i=1}^{2} \beta_i \frac{I_i}{N} \right) \qquad S_1^{nc}(0) = S_{1\,0}^{nc} > 0 \tag{A.7}$$

$$\dot{I_1^{nc}} = k_2 S_1^{nc} \sum_{i=1}^{2} \beta_i \frac{I_i}{N} - (\alpha + r_1 + g + d_1) I_1^{nc} \qquad I_1^{nc}(0) = I_{1\,0}^{nc} > 0 \tag{A.8}$$

$$\dot{T^{nc}} = g \left(I_1^{nc} + (1+\varepsilon) I_2^{nc} \right) - (\alpha + a) T^{nc} + \sum_{i=1}^{2} d_i I_i^{nc} \qquad T^{nc}(0) = T_0^{nc} \geq 0 \tag{A.9}$$

$$\dot{S_2^{nc}} = a T^{nc} + r_2 I_2^{nc} - S_2^{nc} \left(\alpha + \mu + k_2 \sum_{i=1}^{2} \beta_i \frac{I_i}{N} \right) \qquad S_2^{nc}(0) = S_{2\,0}^{nc} \geq 0 \tag{A.10}$$

$$\dot{I_2^{nc}} = k_2 S_2^{nc} \sum_{i=1}^{2} \beta_i \frac{I_i}{N} - (\alpha + r_2 + g(1+\varepsilon) + d_2) I_2^{nc} \qquad I_2^{nc}(0) = I_{2\,0}^{nc} \geq 0 \tag{A.11}$$

$$\begin{aligned} N^{nc}(t) &= S^{nc}(t) + I^{nc}(t) + T^{nc}(t) \\ &= S_1^{nc}(t) + S_2^{nc}(t) + I_1^{nc}(t) + I_2^{nc}(t) + T^{nc}(t) \end{aligned} \qquad N^{nc}(0) = N_0^{nc} > 0 \tag{A.12}$$

$$N(t) = N^c(t) + N^{nc}(t)$$

$$\text{where } \varepsilon = \frac{\hat{g}\gamma}{g}$$

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