

Exploring the Impact of Targeted Screening for the Control of Chlamydia Infections

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Exploring the Impact of Targeted Screening for the Control of Chlamydia Infections

submitted by

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Signature of Author.....

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Abstract

Within the United Kingdom, chlamydia remains the most prevalent STI particularly within the 16-25 age cohort. Despite infection being easily treated, untreated chlamydia can cause severe health complications including infertility, ectopic pregnancies and Pelvic Inflammatory Disease. 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. This dissertation 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.

The project explores the impact of such a strategy by building a deterministic compartmental model allowing for targeted re-screening on recently recovered individuals. Previous models used in investigating the epidemiology of chlamydia are discussed and assessed in terms of their benefit in exploring the new strategy. The model is used to analyse the potential impact of the strategy in a healthcare setting by using a number of analytical methods and a published costings tool currently in use by healthcare professionals.

The dissertation concludes that by actively recalling previously infected individuals for further screening, population prevalence and incidence can be reduced to new levels without the need for increased screening coverage. However the largest reductions are seen with the current NSCP and targeted re-screening used tandem, both working at the highest available levels. The project is left open by suggesting that targeted re-screening is likely a viable and cost effective new strategy, ultimately depending on the costs required to increase screening coverage through awareness campaigns. Finally it is highlighted that further mathematical and clinical research is recommended in order to improve model accuracy and understanding of the chlamydia infection.

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Chapter 1

Background

Sexually transmitted infections (STI's) are infections transmitted mainly, though not explicitly, through direct physical sexual contact. Sexually transmitted infections are a growing problem in many areas of the world [1]; the AIDS epidemic that began in 1981 continues to increase, and throughout the last decade there has been a substantial rise in other STI's, many of which can cause serious health risks including Pelvic Inflammatory Disease, infertility and ectopic pregnancies [1].

Within the United Kingdom, chlamydia remains the most prevalent STI, in part due predominantly being a highly asymptomatic infection [2]. Asymptomatic infections pose a challenge for public health considerations, as detection is only possible through healthcare interventions. This has resulted in screening programmes developed to detect infections opportunistically by testing individuals within a population group. There has been some evidence that individuals who become infected with chlamydia once may be at a higher risk of re-infection [3]. With the goal to enhance the control of infection, this dissertation will explore the potential of a screening programme split between opportunistic screening at the population level with targeted screening of previously infected individuals.

1.1 Chlamydia

Chlamydia infection is a prevalent STI within humans, caused by the bacteria *Chlamydia trachomatis* infecting the cells within the cervix, urethra, rectum, conjunctiva or pharynx. It is the most prevalent STI within the UK [2], and the most commonly reported in many developed countries [4]. In 2010, 1.3 million case of chlamydial infections were officially reported within the U.S alone, however it has been estimated that the true figure (including unreported cases) lies closer to 2.8 million annual infections [5]. Furthermore, chlamydia has been found to be highly concentrated within 16-24 year olds, and tends to be unevenly distributed towards females [6]. In 2011,

183,561 people tested positive in England, of which 146,277 (79.7%) were aged 24 or younger, and 107,994 (58.8%) were female [6].

This bias in gender can in part be attributed to the rate at which symptoms occur. Chlamydia is commonly referred to as a silent infection¹, as research has shown that with males 50% of infection is asymptomatic, whilst in females this rate is increased to 70%-80% [7]. However, in symptomatic cases the genital symptoms can occur as epididymitis, urethritis and urethral discharge in males; or as urethritis, cystitis, urethral discharge, dyspareunia, abdominal pain and heavy bleeding, both during and between menstrual cycles, in females. Although less frequent, the symptoms of rectal infection can occur as discharge, discomfort and bleeding in both males and females; whilst in cases of ocular infection symptoms may appear as irritation, discomfort and discharge similar to conjunctivitis. Whilst it is possible for the infection to be contracted within the throat, symptoms rarely occur as more than soreness [7].

1.1.1 Chlamydia Trachomatis

In 1907, Halberstaedter and von Prowazek [8] first identified the cytoplasmic inclusion bodies in conjunctiva smears from trachoma infected Orangutans; naming them *Chlamydozoa* [9]. However it was not for a further 50 years, in 1957, that the trachoma agent was isolated and cultured in the yolk sacs of hen eggs [10]. It took another 9 years, in 1966, before it was correctly recognised as a bacteria that infects certain epithelial cells in humans (whilst *C. trachomatis* only infects humans, there do exist separate species of the bacterium, in particular *C. muridarum* and *C. suis* which infect the mauridae and swine families respectively) [11].

Prior to 1966 *Chlamydia trachomatis* was incorrectly identified as a virus; partly due to its virus-like dependence on molecules from a host organism. *C. trachomatis* cannot survive outside the epithelial cells, as it requires ATP², an energy molecule, to reproduce. The bacteria infects a host cell, changing it to a reticulate body and uses the cell's ATP to make replicates inside the cell. The reticulate bodies grow, divide, metabolize, and once there are enough copies, turn back into elementary bodies, burst the cell open and escape to infect new cells [12].

During the release of the infectious elementary bodies, these bodies may pass onto a new individual through the sharing of bodily fluids in the infected areas, transmitting the *C. trachomatis* bacteria.

¹It is such a “silent” infection that the name chlamydia is derived from the greek word for cloak, χλαμύδα

²Adenosine Triphosphate

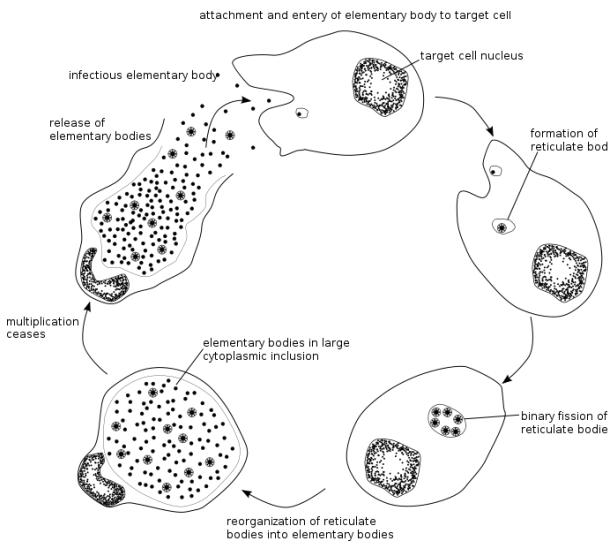


Figure 1.1: The life cycle of *C. trachomatis* [13]

1.1.2 Importance and Severity of the Chlamydia Infection

Despite being easily treatable, the chlamydia infection poses some severe health complications, particularly in long term infection. Due to the high rate of asymptomatic infection, many cases are left untreated and allow the infection to propagate through the host body. Within both males and females, a common ailment as a result of contracting the chlamydia infection is urethritis, an inflammation of the urethra. There are many causes of urethritis with chlamydia infection being the most common however urethritis is a mild condition, usually resulting in merely discomfort and dysuria. Rectal chlamydia infections also account for approximately 20% of cases of Proctitis, an inflammation of the rectal lining, causing severe discomfort and hematochezia [14]. Within both sexes, chlamydia has been shown to cause LGV, *Lymphogranuloma venereum*, an STI that infects the lymphatics and lymph nodes. LGV causes abscesses to form and in long term affliction, systematic spread may occur resulting in arthritis, pneumonitis and hepatitis [14]. Chlamydia has also been shown to have a strong correlation with that of reactive arthritis, previously known as Reiter's syndrome, an autoimmune response to an infection in another part of the body. However it has been shown that 75% of those with the reactive arthritis also test positive for the genetic marker HLA-B27, suggesting that individuals may be genetically predisposed to Reiter's syndrome, and the chlamydia infection merely initiates the underlying problem [14].

Within males, genital infection can progress and cause epididymitis, an inflammation of the epididymis³, which if left untreated can lead to reduced fertility. It has been

³Tube connecting the ducts of the testes to the ejaculatory ducts, used for storage and maturation of sperm

estimated that approximately 5% of men with untreated genital chlamydia will go on to develop epididymitis [15]. Although a rare occurrence, chlamydia has also been known to be common cause of acute Prostatitis in men, a serious infection of the prostate gland. If untreated this may result in sepsis, a potentially deadly spread of bacteria into the bloodstream [14].

Within females the complications caused by chlamydia tend to be of a higher severity than males, with some afflictions liable to pass onto the foetus if pregnant. Approximately 40% of cases of cervicitis, a mild inflammation of the cervix, are annually attributed to chlamydia [16]. Whilst easily treatable, if untreated this can progress into mucopurulent cervicitis, which may persist despite repeated courses of antimicrobial therapy. Nearly 50% of patients that contract chlamydial cervicitis will also have endometritis, an infection of the inner lining of the uterus [14]. Endometritis is characterised by heavy irregular bleeding, however is easily treated with antibiotics. Although more commonly associated with gonococcal infections, chlamydia can also cause bartholinitis, a blocking of the Bartholins duct in the labia minora, resulting in local discomfort and an abscess, which may be managed with antibiotic therapy or in more extreme cases, surgical treatment [14].

However, the most severe complication of chlamydial infection in females is PID, Pelvic Inflammatory Disease. PID is often used synonymously with salpingitis, an infection and inflammation of the fallopian tubes, however PID can also include endometritis, as previously discussed. It has been estimated that up to 80% of PID cases worldwide are due to STI's, of which chlamydia infection is the cause of at least 60% [14]. Due to the invasive techniques used to diagnose PID, data on the frequency of PID is difficult to interpret however it has been suggested that between 10%-40% of female genital chlamydial infections will develop PID [17]. PID causes adhesions and scar tissue to form on the local areas, severely damaging the fallopian tubes and causing an enhanced chance of infertility. Between 8%-20% of PID infections will cause tubal factor infertility in primary infections. This sharply rises and for females that have contracted PID on three separate occasions, the chance of infertility lies close to 60% [18]. Due to the damage caused to the lining of the fallopian tubes PID also increases the risk of miscarriage and ectopic pregnancies, which if undetected can be fatal. It has been estimated that 10% of deaths in England that occur as a complication of pregnancy, childbirth or puerperium⁴, are due to ectopic pregnancies, of which those who have contracted PID are 7-10 times more susceptible to this condition [14].

In regards to the infection from which *C. trachomatis* takes its namesake, trachoma is

⁴The 6 week period after giving birth, whereby the body returns to its non-pregnant state

the leading cause of premature blindness worldwide [19]. Trachoma causes a roughening of the inner surface of the eyelids, and eyelash follicles to become inflamed. It has been estimated that 21.4 million people suffer from the infection of which 2.2 million are visually impaired and 1.2 million are blind as a result [19]. Despite *C. trachomatis* only being identified in early 1907 [8], trachoma itself dates back as far as 1500 B.C., giving us an idea of how long the chlamydia infection may have truly existed for [20]. Furthermore, up to 50% of chlamydia infected expectant mothers are likely to pass on the chlamydia infections to their newborns, often showing in the form of trachoma and conjunctivitis, for which children are more susceptible [19].

Lastly, it has been suggested that there exists a connection between HIV, the Human Immunodeficiency Virus, and Chlamydia. Untreated Chlamydia can increase the viral load of HIV in genital fluids, making an individual with both infections up to five times more infectious. Similarly, Chlamydia can make it more likely for those suffering from it to contract the HIV virus, if they are exposed [21], due to a reduced immune response.

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 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 [22]. Such costs warrant further theoretical study, both at the microbiological level and at the population level, in order to enhance control strategies.

1.1.3 Combating the Spread of Chlamydia

With many governing bodies recognising the increased risks of the chlamydia infection, there has been a substantial rise in control and awareness campaigns. Immunisation against chlamydia is not currently possible and so avoidance remains the only way to be 100% effective in preventing the acquisition of the infection. This can be achieved through abstinence of sexual practices or by partnering with a monogamous uninfected individual. However this is unrealistic, so public health trusts try to minimise the spread of chlamydia. This has been attempted via two distinct methods, preventive educational awareness campaigns and opportunistic interventions.

Educational campaigns have focused on giving widespread information regarding safe sex and male condom use, which significantly reduces the chance of transmission between infected and uninfected individuals. Educational campaigns have been shown to be successful to a degree, such as the case of the Western Australian Department

of Health's 2005 chlamydia campaign. Using viral marketing techniques such as the internet, posters and magazine advertisement, television and radio; testing increased during the campaign period by 21% in females and 29% in males [23].

Opportunistic intervention on the other hand, focuses on locating and treating infected individuals via screening and partner tracing. Due to the high rate of asymptomatic cases associated with chlamydia, it becomes difficult to screen many of the infected population, who are unaware of their infection. As such many screening programmes advocate screening of certain subgroups of the population over others, for example screening 16-25's over the 65+ age groups. However once a positive individual has been identified, it is then possible to trace other potentially positive individuals through the original's history of sexual partners.

Within chlamydia susceptible populations re-infection remains a major cause for concern. Unlike many viral infections, having a previous chlamydial infection does not infer any future immunity, and returns treated individuals back to the susceptible population. This plays a key role in the differing prevalence and incidence rates associated with the infection, with incidence measuring only new infections and prevalence measuring total infections.

Diagnosis and Treatment

Testing for chlamydia in an individual is a simple process. The most common test used is that of a nucleic acid amplification test (NAAT). Using a small sample of urine or a urinary swab (taken by either a healthcare professional or the patient), the test detects any *C. trachomatis* bacteria present. NAATs are currently the best diagnostic tool available, having significantly higher sensitivity than the previously used DNA probes and antigen-based assays. Despite higher costs than DNA probes or enzyme immunoassay's (EIAs, the most common antigen-based assays), NAATs are in general preferred by both patients and clinicians due to their less invasive specimen collection, transport stability and ability to test for both *C. trachomatis* and *N. gonorrhoeae* (the bacteria responsible for the STI Gonorrhoea). However, due to the high level of sensitivity and method in which they amplify DNA, NAATs have been known to give false positive results [14]. A positive test result can be seen in Figure 1.2.

Once detected chlamydia is easily treatable via a course of antibiotics, most commonly a single dose of Azithromycin or a twice daily dose of Doxycycline for 7 days; alternatively Amoxicillin is generally used if the patient is currently pregnant. Studies have shown treatment via Azithromycin, Doxycycline and a variety of other tetracyclines and macrolides to be at least 97% effective in eradicating the bacteria from the urethra [14].

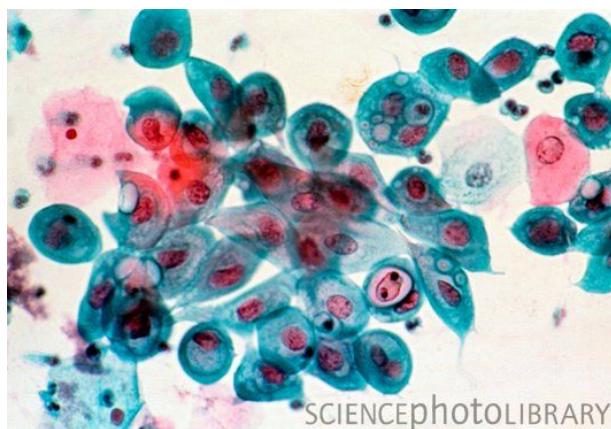


Figure 1.2: Light micrograph of a cervical smear showing *C. trachomatis* (dark pink) inside the epithelial cells (light pink and light blue) [24]

Due to the high propensity for reinfection, patients are asked to abstain from sexual encounters, especially with untested partners, for at least the duration of the treatment and until symptoms have disappeared. Ideally however an additional week of abstinence after treatment has finished is recommended.

National Chlamydia Screening Programme

In an attempt to decrease the amount of undiagnosed cases, in 2003 the UK saw the launch of the National Chlamydia Screening Programme (NCSP). Established by the Department of Health, with aims to “*prevent and control chlamydia through early detection and treatment of asymptomatic infection, reduce onward transmission to sexual partners, and prevent the consequences of untreated infection*” [25]. Using the NAAT test previously mentioned, the 2008/09 NCSP target aimed to screen 17% of men and women aged 15-24 (both in healthcare and non healthcare settings), however as of 2012 the currently achieved screen rate is closer to 16% [25]. Modelling studies have suggested that to see a significant reduction in prevalence, screening rates will have to rise to at least 35%, and the longer term aim of the NCSP is to achieve between 35%-50% per cent coverage nationwide [26]. Furthermore, if screening coverage did increase to 43%, prevalence has been estimated to reduce by 40% after 1 year, 79% after 5 years and 89% after 10 years [27]. Currently the NCSP do not re-invite patients for further screening, however they do actively seek out potentially infected partners via contact tracing.

Contact Tracing and Partner Notification

Along with screening, partner notification has been an integral part in the management of bacterial STI's. By recording details of sexual contacts from infected individuals over

the last 3-6 months, partner notification aims to identify and treat many often asymptomatic cases [14]. Contact tracing and partner notification has shown to be highly successful in identifying asymptomatic individuals linked by common sexual contacts. In 2008/09, within the UK 16-24 age gap 50% of contacted partners, per index case, agreed to a Chlamydia test, of which 65% tested positive for infection [28]. However whilst effective, notification proves to be time consuming, expensive, and not always a fruitful endeavour (as seen in 2008/09 where 50%, per index case, of contact partners refused testing) [28].

Partner notification is heavily reliant on data given from patients. In the UK patients are encouraged to co-operate and give as much data as possible, however their participation is voluntary. Despite partner notification being anonymous, many patients do not wish to divulge their sexual history. In 2008/09, within the UK 16-24 group, only 64% of patients were willing to provide details of partnerships in the last 6 months [28]. The approach to partner notification differs in many countries. A more extreme case exists in Sweden whereby in order to increase efficiency of partner notification, patients are legally obliged to name partners, and contacts have a legal requirement to be tested [14]. While this seems ideal, this approach may have unknown detrimental consequences on clinic attendance and acceptance of symptoms. If individuals are aware that by testing positive for chlamydia they will be legally required to divulge their own sexual history and past partners, an act that many may find embarrassing, they may not accept minor symptoms indicating chlamydia and instead delay treatment.

1.2 Models for the Spread of Chlamydia

The study of epidemics has a long history involving a variety of models and explanations for the spread and cause of outbreaks. Not only is it important to understand how an infectious disease works within a host, but in order to successfully apply treatments and vaccines it is imperative to understand how different infections move through target populations. Great importance has been put on creating accurate and rigorous mathematical models, particularly those which can simulate and predict disease trajectory, and potential treatment campaigns prior to distribution.

The earliest recognised use of a mathematical model for the study of epidemiology was that of Bernoulli in 1760, who considered the effect of cow-pox vaccine on the spread of smallpox, using non-linear ordinary differential equations. It is likely to be the first time that a mathematical model was used to assess a vaccination control programme [29]. Since this early attempt, mathematical models have proven to be increasingly useful in both bacterial and viral disease, particularly, as Bernoulli demonstrated, in assessing

and predicting vaccination potential.

There is a large collection of models for the epidemiology of chlamydia, taking a variety of approaches and using an array of different techniques. Some models have used a simple *SIS*⁵ framework, whilst others have explored the dynamics of certain aspects through subdivisions of the population. Due to the late identification of chlamydia, and its similarities with gonorrhoea, which was correctly identified and cultured 78 years prior to chlamydia, many early mathematical models of chlamydia originate from gonorrhoea models. They will be discussed as precursors, particularly the seminal work of Hethcote and Yorke [30].

1.2.1 Compartmental Models

Standard infection models compartmentalise the population by infection status. The simplest of these classifies individuals as either susceptible, infected or recovered and models a population moving between those classes using systems of ordinary differential equations. In the case of chlamydia, since no immunity is conferred through previous infection, individuals can be placed into either a susceptible or infected compartment of the population, as represented in figure 1.3. This makes a number of assumptions in relation to both the infection and the population at risk. This simple SIS model assumes:

- a closed constant population N
- that the incubation period of the chlamydia infection is short enough to be negligible, and any susceptible who contracts the disease becomes infective instantly
- individuals are uniformly mixed and have equal chance of pairing with any other individual regardless of infection status.

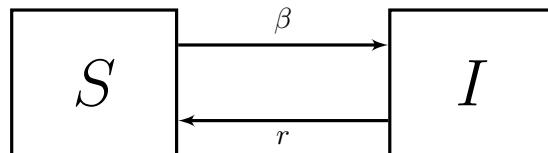


Figure 1.3: A simple closed Susceptible→Infectious→Susceptible model

By assigning values to aspects of the infection (transmission and recovery), it is possible to give adequate form to the dynamics of the population. In figure 1.3 β represents the infectious contact rate, taking into account the transmission probability from an infectious individual I to a susceptible S and rate of contact between two individuals.

⁵Susceptible→Infectious→Susceptible

r denotes the recovery rate moving individuals from the infected class I back to the susceptible class S . In this simple model r accounts for all modes of recovery, both natural and treatment enhanced. This SIS framework can then be expressed as a system of ordinary differential equation with initial value conditions (S_0, I_0) as given by (1.1)-(1.3).

$$\frac{dS}{dt} = -\beta SI + rI \quad S(0) = S_0 > 0 \quad (1.1)$$

$$\frac{dI}{dt} = \beta SI - rI \quad I(0) = I_0 > 0 \quad (1.2)$$

$$N(t) = S(t) + I(t) \quad N(0) = N \quad (1.3)$$

While the majority of STI's conform to this SIS framework, the simple classification into either susceptible S or infected I limits the amount of information able to be gathered about the at risk population. It fails to give insight into the differences in infection between genders, symptomatic or asymptomatic state, or heterogeneity. With chlamydia this demographic information is crucial, as the characteristics of chlamydia differ between sexes (female's subject to higher asymptomatic rates, as mentioned in §1.1), symptomatic states (symptomatic individuals tend to seek treatment and hence recover faster than asymptomatics), and heterogeneity (the behaviour and sexual attitudes of individuals will dictate how often they partner with other individuals). In order to try and encompass these characteristics into a workable model, many studies have subdivided the standard SIS model further at the cost of increased complexity [30].

By Gender

In order to account for differences in chlamydial infections between sexes, the standard SIS model can be subdivided into male SIS and female SIS models. As noted by Hethcote and Yorke, there is little transmission between homosexual and heterosexual populations [30], and hence only the heterosexual population is modelled. The flow diagram for this model can be seen in figure 1.4. As seen in figure 1.4, subdividing the population into male and female compartments increases the complexity twofold, however it becomes far more accurate and applicable to the real world situation than the standard SIS model. In terms of a system of ODE's this can be represented as seen in (1.4)-(1.8), where β and r hold their same meaning as before.

$$\frac{dS_m}{dt} = -\beta_{fm}S_mI_f + r_mI_m \quad \frac{dI_m}{dt} = \beta_{fm}S_mI_f - r_mI_m \quad (1.4)$$

$$S_m(0) = S_{m0} > 0 \quad I_m(0) = I_{m0} > 0 \quad (1.5)$$

$$\frac{dS_f}{dt} = -\beta_{mf}S_fI_m + r_fI_f \quad \frac{dI_f}{dt} = \beta_{mf}S_fI_m - r_fI_f \quad (1.6)$$

$$S_f(0) = S_{f0} > 0 \quad I_f(0) = I_{f0} > 0 \quad (1.7)$$

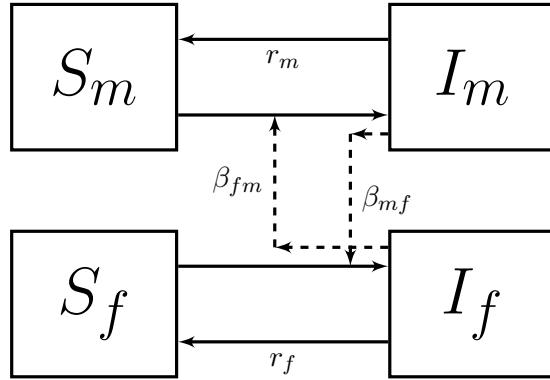


Figure 1.4: A closed male/female heterosexual Susceptible→Infectious→Susceptible model

$$N(t) = N_m(t) + N_f(t) = S_m(t) + I_m(t) + S_f(t) + I_f(t) \quad (1.8)$$

Compared to the original SIS model, figure 1.3, rather than having a single value β for the population, there are now values β_{fm} and β_{mf} for the infectious contact rate from female to male, and male to female. This allows the model to incorporate both differing transmission characteristics as well as differing recovery rates, illustrated with the use of r_m and r_f , between sexes. In terms of modelling chlamydial infections, this approach is beneficial as data has shown that recovery time from infection can greatly differ between sexes when averaging symptomatic and asymptomatic cases [30]. Models of this variety have been used to consider the effect of screening men and women separately as a control procedure, and studies have shown that screening only women is more effective than screening both men and women due to the longer infection associated with female infection, as a result of higher asymptomatic rates [30].

However as with all mathematical models, the increased complexity not only results in an increase of parameters, but also in that of assumptions. For this male/female SIS model to hold, there has been an extra assumption in addition to original SIS assumptions. It assumes the male:female ratio within the population, which many studies on large populations assume to be approximately the same, that is $N_m(t) \approx N_f(t)$. Whilst this is the standard assumption for most large male/female SIS models, this can easily be changed to suit a situation where $N_m(t) \neq N_f(t)$ by setting the initial values (S_{m0} , S_{f0}) to either $S_{m0} > S_{f0}$ or $S_{m0} < S_{f0}$ depending on the gender division.

Whilst this model assumes free uniform mixing between heterosexuals, it does not allow for homosexual partnering. An extension of this model would be to include homosexual mixing, without necessarily subdividing further. This can easily be achieved with the introduction of infectious contact rates from male to male, β_{mm} into (1.4), and from female to female, β_{ff} into (1.6).

By Symptomatic State

As with highly asymptomatic infections such as chlamydia, large differences, particularly in respect to recovery time, can occur between different symptomatic states. It has been shown that individuals who display symptoms tend to seek outside treatment, whilst asymptomatic do not, resulting in symptomatic cases often being associated with a reduced duration of infection [31]. The SIS model (1.1)-(1.3) shown in figure 1.3 can be extended to allow for multiple infection classes I_A , I_S representing the differing symptomatic states. This framework can be seen in figure 1.5 Where r_A and r_S rep-

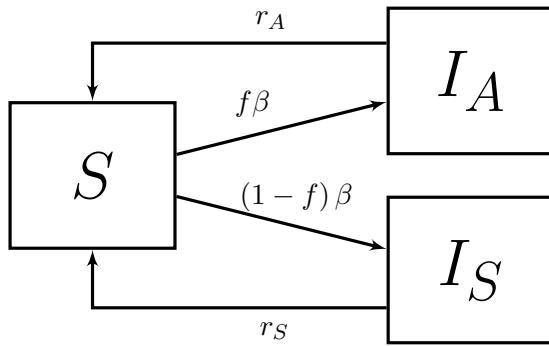


Figure 1.5: A closed symptomatic/asymptomatic Susceptible→Infectious→Susceptible model

resent the recovery rates for asymptomatic and symptomatic individuals respectively. Furthermore f is defined to be the fraction of infections that become asymptomatic. This takes the explicit ODE form (1.11)-(1.12).

$$\frac{dS}{dt} = -\beta S (f I_A + (1 - f) I_S) + r_A I_A + r_S I_S \quad S(0) = S_0 > 0 \quad (1.9)$$

$$\frac{dI_A}{dt} = f \beta S I_A - r_A I_A \quad I_A(0) = I_{A0} > 0 \quad (1.10)$$

$$\frac{dI_S}{dt} = (1 - f) \beta S I_S - r_S I_S \quad I_S(0) = I_{S0} > 0 \quad (1.11)$$

$$N(t) = S(t) + I_A(t) + I_S(t) \quad N(0) = N \quad (1.12)$$

This framework allows for the exploration of differing characteristics between symptomatic and asymptomatic cases. As mentioned previously, with chlamydial infection approximately 50%-70% of reported cases are asymptomatic. In the standard SIS model (1.1)-(1.3) this cannot be accounted for, however in the SIS model divided by symptomatic state (1.9)-(1.12), this is represented explicitly by the f parameter. Similarly, the inclusion of individual recovery rates r_A and r_S from the respective classes I_A and I_S , allows for increased accuracy over the standard recovery rate r from the SIS model (1.1)-(1.3). This is beneficial as recovery time from chlamydial infection differs vastly for different symptomatic states, with symptomatic infections lasting on average

14-28 days, and asymptomatic infections lasting 180-420 days [31].

Models conforming to this framework are often used to explore the impact of screening programmes. This is due to screening programmes relying on clinic attendance and hence often only pick up symptomatic cases. A similar approach was used by Regan *et al.* [32] to show that duration of asymptomatic infection had little effect on the impact of screening.

By Sexual Activity

In the models looked at so far, there has been a common theme of uniform mixing. Whilst this is appropriate for many airborne disease models, it is unrealistic to assume the same holds for STIs. Mixing patterns are unique for each individual, and in order to account for this SIS models are frequently divided, similar to the male/female SIS model (1.4)-(1.8), into smaller interacting populations dependant on the level of sexual activity. The first use of this approach was Lajmanovich and Yorke, 1976, who proposed and analysed an 8-group model based on sexual activity levels [33]. Unlike the male/female divided SIS model (1.4)-(1.8) where there is an explicit limit to the number of divisions that can be made (two, male and female), models divided by sexual activity can be divided any number of times as long as there is a clear definition between the divisions. The simplest of these would be to divide the standard SIS model into two categories, *high* or *low*. Defining the *high* category to be those who average more than a certain number of sexual partners at any single point in time, this takes the form seen in figure 1.6.

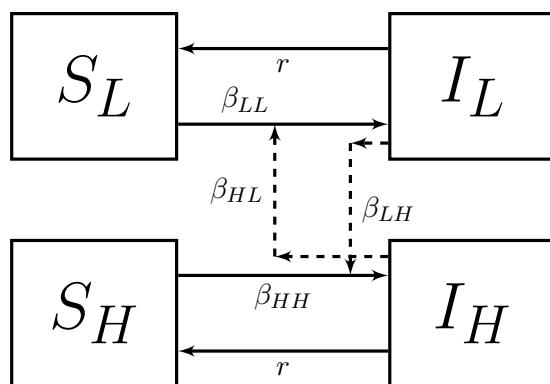


Figure 1.6: A simple closed low/high sexual activity Susceptible→Infectious→Susceptible model

In this form the sexual activity divided SIS model appears similar to the male/female SIS model (1.4)-(1.8), however as mentioned, unlike the male/female model, the sexual

activity model is able to be further divided into more categories to account for differing levels of sexual activity at the cost of increased complexity. Using this type of model allows to investigate the transmission and mixing dynamics of a disease across several sub-populations. It would make little sense to have a constant β for all interactions and hence each β_{ij} has its own unique value to represent transmission from population i to population j . This gives the explicit ODE form seen in (1.13)-(1.17).

$$\frac{dS_L}{dt} = -\beta_{LL}S_L I_L - \beta_{HL}S_L I_H + rI_L \quad \frac{dI_L}{dt} = \beta_{LL}S_L I_L + \beta_{HL}S_L I_H - rI_L \quad (1.13)$$

$$S_L(0) = S_{L0} > 0 \quad I_L(0) = I_{L0} > 0 \quad (1.14)$$

$$\frac{dS_H}{dt} = -\beta_{HH}S_H I_H - \beta_{LH}S_H I_L + rI_H \quad \frac{dI_H}{dt} = \beta_{HH}S_H I_H + \beta_{LH}S_H I_L - rI_H \quad (1.15)$$

$$S_H(0) = S_{H0} > 0 \quad I_H(0) = I_{H0} > 0 \quad (1.16)$$

$$N(t) = N_L(t) + N_H(t) = S_L(t) + I_L(t) + S_H(t) + I_H(t) \quad (1.17)$$

In this simple two category SIS model, rather than having the singular β seen in the original SIS model (1.1)-(1.3), there are now four transmission parameters. These are often described via a transmission matrix, termed the WAIFW⁶ matrix, seen in (1.18).

$$\beta = \begin{pmatrix} \beta_{LL} & \beta_{HL} \\ \beta_{LH} & \beta_{HH} \end{pmatrix} \quad (1.18)$$

With a small number of divisions, the values for the WAIFW matrix can be easily observed, however with more divisions the matrix soon grows at a rate of n^2 entries for n sub-populations, and obtaining these values through observation is unrealistic. Instead, additional assumptions about the mixing patterns can be made, such as proportional or assortative mixing. It has been shown that assortative mixing (individuals actively seek out other individuals with whom they share similar physical and behavioural traits, in particular, sexual attitudes) is an adequate mixing preference that gives the closest representation of many real world populations [34]. Assortative mixing in nature can be observed not only in terms of age and physical attributes, but also in such areas as shared religious beliefs, socio-economic status, intelligence, and political ideology [34]. Anderson *et al.* took this idea of assortative mixing when exploring the influence of mixing matrices on the pattern of AIDS within a male homosexual community, and

⁶Who Acquires Infection From Whom

expressed it in the rigorous mathematical form seen in (1.19).

$$\beta_{ij} = \frac{A_i A_j N_i}{(\sum_{i=1}^n A_i N_i) \sum_{i=1}^n \left(\frac{A_i A_j N_i}{\sum_{i=1}^n A_i N_i} \right)} \quad [34] \quad (1.19)$$

Where A_i is the activity level of group i , the average number of encounters per person per unit time; N_i is the total population of group i ; and n is the number of groups. Using this approach, Anderson *et al.* concluded that “*completely assortative mixing is shown to generate the most rapid growth of incidence in the early stages, while complete disassortativity is shown to generate the largest magnitude of prevalence over a long period.*”, showing that mixing preferences between members of different sub-groups can have a large impact on population incidence and prevalence [34]. In terms of using this approach to investigate the impact of treatment campaigns on bacterial STIs, Hethcote and Yorke applied a similar framework to gonorrhoea transmission [30]. Using a simple SIS model, divided into eight distinct groups (divide once by gender, and four times by sexual activity), the authors simulated six different control methods. They went on to identify the concept of a “*core group*”, a concentrated group of individuals responsible for a high percentage of incidence, and found this core group to be responsible for 21.6% of cases in the local county and 29.4% of cases in the local clinic, despite only representing 6.7% of the population [30]. The core group consisted entirely of women in the highest sexual activity group and the authors determined that targeting this core group would be “*a more efficient prevention strategy than targeting whole populations*”.

An extension of the sexual activity SIS model (1.13)-(1.17) is that of the risk structured SIS model. The premise here being almost identical to that of the sexual activity model, however instead of dividing the populations by number of sexual partners, the divide is chosen as the potential risk an individual has of interacting with the STI. Taking the simple two sub-group model (1.13)-(1.17), instead of denoting *Low* and *High* to represent the average number of partners, let it denote the potential risk individuals in each group have of interacting with the infection. In this scenario the low risk individuals might include those in long term partnerships, the elderly, and those who abstain from sexual interactions; whilst high risk individuals could include those living a promiscuous lifestyle (high numbers of new partners), intravenous drug users (in the case of viral STI's who may frequently share tainted needles) and individuals within the sex industry.

Metapopulations

The compartmental approaches mentioned should not be taken as only being able to be used in the way presented here. Many studies into STI epidemiology have taken aspects from some, if not all, of the concepts presented here and unified them into a single

model. Metapopulations are based around the concept of a population composed of several local sub-populations, that are in some way linked to each other. Metapopulations were perhaps demonstrated best by Chen *et al.* on the spread of gonorrhoea. The authors suggested that metapopulations could be beneficial in modelling populations such as Greater London, which could be seen as composed of smaller sub-populations defined by geographical and socio-demographic features [35]. They envisioned this metapopulation as seen in figure 1.7. Within each sub-population the model was divided by both gender and sexual activity, and by allowing for associative mixing, sexual partnerships were formed more frequently between members of the same sub-population than between members of different sub-populations. The sub-populations can be thought of as representing the demographic, social, cultural and geographical boundaries [35].

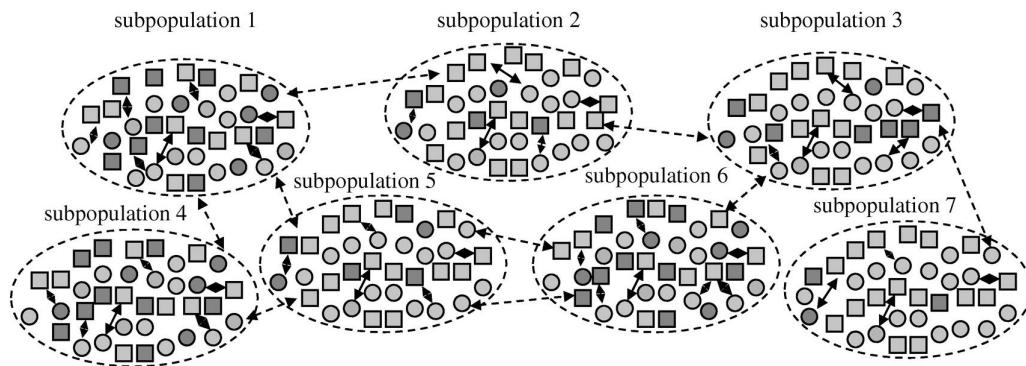


Figure 1.7: A metapopulation where squares/circles represent male/female, dark/light grey represents high/low sexual activity and solid/dashed arrows represent partnerships within/between sub-populations [35]

Despite the beneficial uses of compartmental models for the study of STI transmission, there are drawbacks to epidemiological models that follow this framework. The inability to differentiate between individuals makes incorporating individual level contact tracing and partner notification troublesome, in particular Regan *et al.* stated that “models of this type are not suitable for addressing circumstances for which there are only a ‘handful’ of individuals or when individual-level intervention strategies (such as contact tracing) or interactions (e.g. partner concurrency) are the focus for investigation” [32]. As Regan *et al.* pointed out, partner concurrency is another issue that compartmental models fail to address. Few individuals move instantaneously from partnership to partnership, Chen *et al.* explored this limitation and considered that a single relationship cycle consisted of ending a partnership, a gap of time spent between partnerships, followed by the initiation of a new partnership, which were not accurately accounted for in standard compartmental models [36]. A relationship cycle could take several forms, seen in figure 1.8, which could greatly influence rates of reinfection and

transmission.

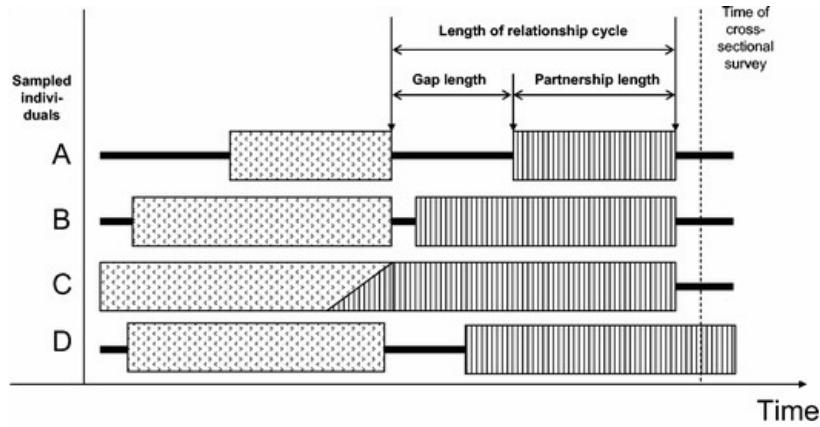


Figure 1.8: A, B, C, D represent different individuals progressing through 2 partnerships [36]

In order to overcome the shortcomings of compartmental models and to incorporate overlooked factors in individuals, as characterised by Regan *et al.* [32], a different type of model must be considered; those of individual based models.

1.2.2 Individual Based Models

Compared to the deterministic compartmental models, §1.2.1, individual based models are stochastic and explicitly represent each individual and their partnerships through different stages of infection. This allows greater flexibility and detail in terms of pair formations, dissolutions, and behaviour, than deterministic models due to the individual scale of the model. Individuals within an STI model system are categorised by a set of characteristics that generally include age, gender, preferred number of partners, preferred duration of partnerships and infection status [37]. Sexual partnership networks are then generated by simulating the formation and dissolution of partnerships in a small closed population over time; and infection is introduced. Using this approach, Ghani *et al.* explored the role of heterosexual partnerships on gonorrhoea, their network can be seen in figure 1.9 [38].

Due to the stochastic nature, events occur in discrete time. At each timestep, three events could occur:

- formation of a new heterosexual partnership
- dissolution of an existing partnership
- transmission of infection from an infected individual to a susceptible one via a partnership,

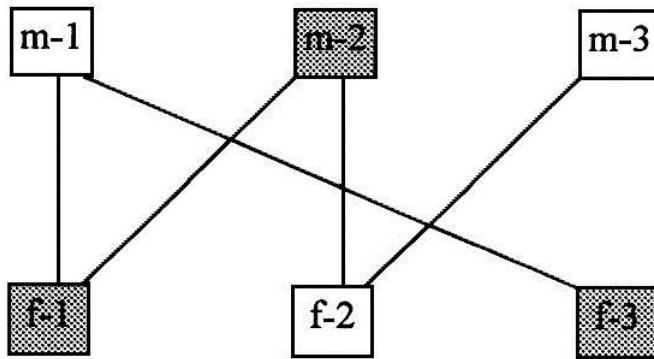


Figure 1.9: A sexual partnership network for an individual based model, where a square represents an individual, m/f represents gender, connecting lines denotes partnership, and a shaded square denotes an infected individual [38]

or any combination of the above.

Turner *et al.* later extended this model to incorporate chlamydia intervention schemes on individuals between 16-44 years of age. Individuals were now additionally categorised by identity of current and past partners, whether, if infected, an individual would actively seek treatment, and “*other clinical characteristics such as number of screens and results*” [37]. Furthermore, at each timestep five additional events could occur:

- an infected individual may recover from infection
- an individual may ‘age out’ of the age group and subsequently get replaced by new individual of the same sex but at the start of the age group
- an individual may be screened for infection
- an infected individual may receive treatment
- an individual may be notified of a recent partners infection,

of which the probability of any events occurring depends on each individual’s characteristics. The occurrence of an event also changes the characteristics of the individual for the next timestep, such as a change in infection or partnership status.

Individual based models clearly demonstrate an increased amount of detail on each individual. Compared to the deterministic models of §1.2.1, each individual in an individual based model can differ from the rest due to the wide set of characteristics able to be assigned to them. This allows for a greater inclusion of sexual behaviour such as preferred partnership length, which standard compartmental model’s fail to do. The

inclusion of partnership length is of particular importance, as with individual based models, transmission is dependent on current partnership status of individuals and not the average levels of infection within the population, as is the case with compartmental models. Furthermore, individual based models allow exact tracing of infection through individuals [37]. In relation to chlamydia intervention schemes this means that contact tracing and partner notification can be easily incorporated into the model. This is a clear advantage as contact tracing has been shown to significantly reduce levels of prevalence within a population.

However at the cost of this increasingly detailed model is an progressively large number of parameters, more so than any compartmental model, which have to be either estimated or observed. For both Ghani's and Turner's models the authors made use of the NATSAL⁷ 2000 data for parameter estimation, a 'stratified probability sample survey' of 12,110 people aged 16-44 that recorded individual sexual attitudes and infection status after a simple urine test for *C. trachomatis* [39]. Due to the increased complexity with larger population sizes, the original model by Ghani *et al.* chose to only simulate for population sizes of 200, 500, and 1000; though when Turner *et al.* later expanded upon this model they were able to simulate for a larger population size of 40,000 [38] [37]. Compartmental models have shown to be superior in this regard, as population size is rarely limited by parameter estimation due to the lack of individual data associated with them.

1.2.3 Network Models

In §1.2.2 the concept of an individual based model was discussed. Individual based models have shown to be effective in exploring the epidemiology of chlamydia however as seen in figure 1.9 they are based upon the notion of random partnerships, where no individual shows any sexual preference when seeking a partner. As previously discussed in §1.2.1 this does not accurately represent the real life scenario where partnerships are formed associatively between acquaintances and those sharing common ideologies. Network models attempt to solve this by using the concepts of an individual based model, but applying similar sexual mixing preferences as those used in compartmental models.

Networks are powerful tools for understanding infection transmission through sexual contact, particularly in populations where each individual is in direct contact with only a small proportion of the population [40]. Within a network two individuals are linked if they have sufficient contact to allow the infection to pass between them, in the case of chlamydia the network link is defined as undirected, as infection can pass in both

⁷National Surveys of Sexual Attitudes and Lifestyles

directions across an partnership [40]. Several types of network structure are possible, each differing in amount of heterogeneity, clustering and average path length [40].

Random Networks

Random networks allow individuals to make connections at random with each individual having the same number of contacts. The network shows little heterogeneity, appears highly uniform, and lacks any true clustering [40]. Random networks associate with a low average path length as many long distance connections exist between individuals of large spatial distance, resulting in the infection being able to traverse from one ‘side’ of the population to the other in few steps.

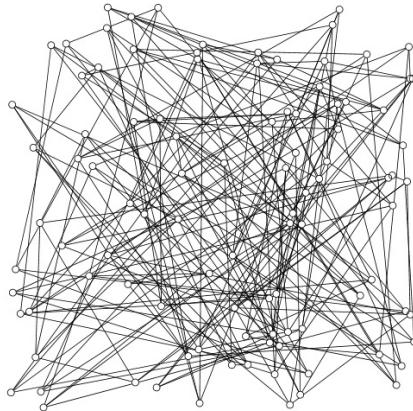


Figure 1.10: A random network where nodes represent individuals and edges represent contacts, all individuals have 4 contacts [40]

Random networks have been successfully used to monitor the spread of gonorrhoea, as in the case of Ghani *et al.*, who used random networks to conclude “*establishment of infection is most sensitive to the proportion of nonmonogamous pairs*” [38]. However, many individuals will tend to form connections at a higher rate with other ‘close by’ individuals, which random networks do not account for.

Spatial Networks

Spatial networks use a kernel to calculate the probability of two individuals forming a connection, with close proximity individuals having an increased chance, and individuals having differing numbers of connections [40]. Spatial networks generally show high degrees of heterogeneity and clustering and are characterised by a high average path length, since the connection kernel preferentially links neighbouring individuals, infection will be forced to go through numerous individuals in order to traverse the network.

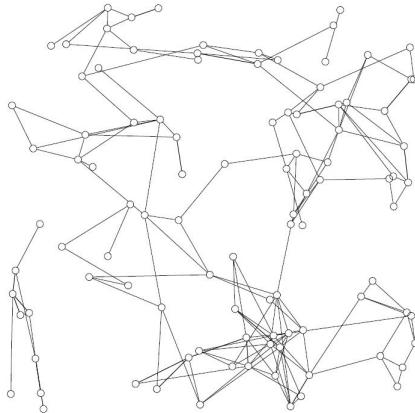


Figure 1.11: A spatial network where nodes represent individuals and edges represent contacts, with an average of 4 contacts per individual [40]

De *et al.* used spatial networking to exploring an outbreak of gonorrhoea within Alberta, Canada, finding the heaviest clustering to be located close to a local motel bar, with 34% of infected individuals admitting to being frequent patrons [41]. This emphasised that “*the notion that social venues, may be essential and, in this case, the only factor defining individuals at risk of infection*”, suggesting that geographical proximity to not only other individuals, but also to social mixing venues may be as important in STI transmission [41].

Scale-Free Networks

In sexual networks the majority of the population will maintain a single monogamous relationship, with a few individuals having large numbers of concurrent partners. Scale-free networks emulate this with most individuals having few contacts and a small number of individuals having many [40]. Individuals are added to the network one by one, with new individuals preferentially connecting to other highly connected individuals, despite spatial distance. They are characterised by high levels of heterogeneity and strong clustering, however have low average path distance since connections ignore spatial distance.

Keeling and Rohani compared this approach to “*everyone wanting to be friends of the most popular people*” [40], and this may mirror many sexual settings whereby a few individuals may form short partnerships with other promiscuous individuals, if they are known as being receptive to sexual advances; whilst other individuals seeking monogamous partnerships may avoid connecting with such individuals.

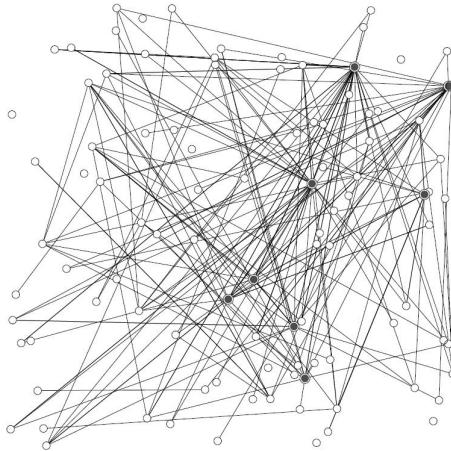


Figure 1.12: A scale-free network where nodes represent individuals, edges represent contacts, shaded nodes represent high numbers of contacts; with an average of 4 contacts per individual [40]

Lattices

With lattices individuals are mapped as a regular grid of contacts where each individual has a fixed number of contacts. Connections are either active or inactive and infection can only pass through active ones. Lattices show little heterogeneity, highly uniform clustering, and since all connections are local are characterised by an extremely high average path length [40].

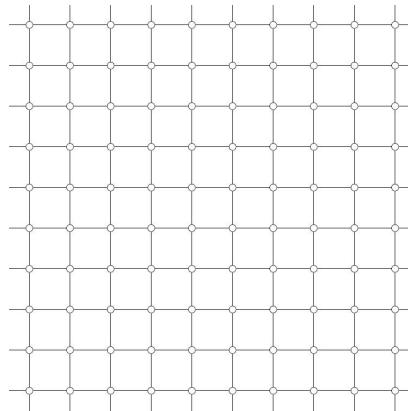


Figure 1.13: A 10×10 lattice where nodes represent individuals, edges represent contacts; with 4 contacts per individual [40]

Lattices were used when examining the effect of concurrency on the rate of HIV spread, with the authors finding that “concurrent partnerships may be as important as multiple partners or cofactor infections in amplifying the spread of HIV” [42]. Whilst a lattice may not accurately represent a sexual population, in terms of public health it allowed

the authors to conclude that awareness campaigns promoting messages of ‘one partner at a time’ are as important as messages promoting fewer overall partners [42].

Small World Networks

Small world networks take the premise of a lattice and introduce a small number of long range connections [40]. They are highly clustered, show little heterogeneity, however due to the presence of long range connections, are characterised by a higher degree of average path length [40].

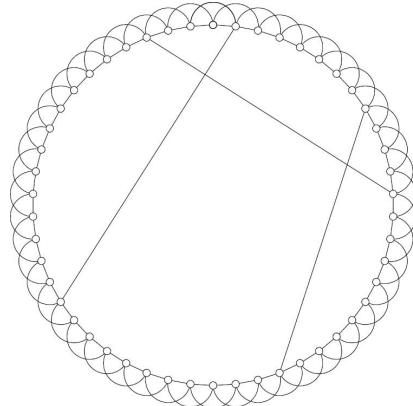


Figure 1.14: A small world network where nodes represent individuals, edges represent contacts; with an average 4 contacts per individual [40]

This concept was used to explore the impact of the ‘small world effect’ on chlamydia control schemes [43]. The authors denoted individuals who made long range connections as ‘spatial bridgers’ (approximately 8% of the population), and found the prevalence of these ‘spatial bridgers’ to have a serious effect on the spread of STIs [43]. To reduce the speed at which chlamydia is spread through populations of different levels of incidence, the authors recommended that an effective intervention approach would be the removal of these ‘spatial bridgers’ through awareness campaigns [43].

Whilst network models are far more accurate than the deterministic models seen in §1.2.1, they become computationally intense with larger networks. As network models must keep track of both every individual, or node, and every contact, the level of complexity will increase with every individual, though at what rate depends on the type of network. Therefore network models are often left with few choices, either keep the size of the network small and manageable (seen in Ghani *et al.*), use complex algorithms to construct larger networks at the cost of computational time, or to use network approximation models, such as pair-wise approximation models.

1.2.4 Pair-Wise Approximation Models

Pair-wise approximation models offer the chance to understand the processes involved in disease transmission of network models, seen in §1.2.3, by regaining some of the robustness from deterministic models, §1.2.1, that had been previously lost [40]. These models aim to capture any influence that network structure may have on the spread of infection, however without explicitly modelling each individual. Pair models are constructed similar to the deterministic SIS model seen in §1.2.1, however transmission is only between active connected pairs. By formulating ordinary differential equations for the number of connected pairs rather than just the number of individuals, pair-wise models link individual behaviour to population level dynamics. As with deterministic models, individuals can be placed into classes based upon their infectious state. Considering an extension of the SIS model discussed earlier, the SITS⁸ model allows infectious individuals to move into a separate class whereby they undergo treatment for the infection, before moving back into the susceptible class. SITS models have been used extensively in deterministic and pairwise models for sexually transmitted infections, due to their ease in incorporating opportunistic intervention campaigns, such as random screening and contact tracing. Eames and Keeling took the approach of a pair-wise SITS model to explore the effect of contact tracing on disease control within STIs, of which the model can be seen in figure 1.15 [44].

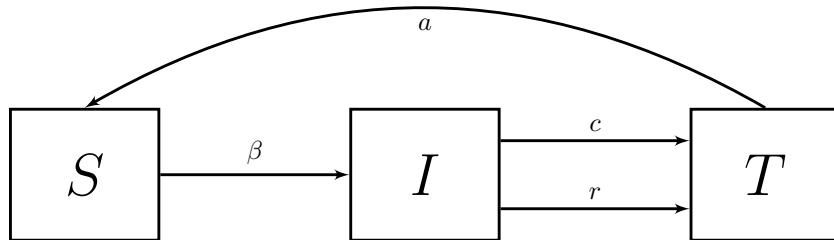


Figure 1.15: A simple closed pair-wise Susceptible→Infectious→Treatment→Susceptible model used by Eames and Keeling [44]

In keeping with previous notation, β denotes the rate of transmission across a partnership, r denotes natural recovery rate in absence of tracing, c the rate of contact tracing, and a the rate at which individuals move out of the treatment class, typically the average length of treatment. Allowing $[AB]$ to denote the number of total partnerships within the network connecting an individual of class A and another of class B , gives

⁸Susceptible→Infectious→Treatment→Susceptible

rise to the model system (1.20)-(1.22).

$$[\dot{S}] = -\beta [SI] + a [T] \quad S(0) = S_0 > 0 \quad (1.20)$$

$$[\dot{I}] = \beta [SI] - r [I] - c [IT] \quad I(0) = I_0 > 0 \quad (1.21)$$

$$[\dot{T}] = r [I] + c [IT] - a [T] \quad T(0) = I_0 \geq 0 \quad (1.22)$$

However, unlike deterministic models, in order to solve these equations the behaviour of connected pairs of individuals, representing sexual partnerships, also needs to be modelled [44]. These pair equations require the inclusion of triples, to allow for concurrency in partnerships. To close the system pair-wise models approximate these triples in terms of pairs and singles, by assuming that pairs are independently binomially distributed [45]. Letting k represent the number of partnerships per individual at any time allows a triplet $[ABC]$ to be expressed as seen in (1.23), commonly referred to as ‘moment-closure approximation’ [40].

$$[ABC] = \frac{k-1}{k} \frac{[AB][BC]}{[B]} \quad (1.23)$$

Using this moment-closure approximation, it is possible to model all combinations of pairs and close the system, as seen in (1.24)-(1.29).

$$[\dot{SS}] = -2\beta [SSI] + 2a [ST] \quad (1.24)$$

$$[\dot{SI}] = \beta ([SSI] - [ISI] - [SI]) - c [SIT] + a [IT] - r [SI] \quad (1.25)$$

$$[\dot{ST}] = r [SI] + a [TT] - \beta [TSI] + c [SIT] - a [ST] \quad (1.26)$$

$$[\dot{II}] = 2\beta ([SI] + [ISI]) - 2c [IIT] - 2r [II] \quad (1.27)$$

$$[\dot{IT}] = c ([IIT] - [IT] - [TIT]) - (r + a) [IT] + \beta [TSI] + r [II] \quad (1.28)$$

$$[\dot{TT}] = 2(c + r) [IT] + 2c [TIT] - 2a [TT] \quad (1.29)$$

Here equations for pairs of same class individuals (such as an $[AA]$ pair) contain factors of two, as pairs represent contacts in both directions across the partnership. However equations for individuals of differing classes (such as an $[AB]$ pair) represent only one direction ($A \rightarrow B$), however their counterparts have not been explicitly modelled as they “*evolve in exactly the same way*” [45]. Models of this approach allow for deterministic modelling of partnerships over time, as a $[SS]$ partnership may evolve into a $[SI]$ when one individual becomes infected, which could then either evolve directly into a $[ST]$ partnership if the infected individual seeks treatment before infecting their partner, or into a $[II]$ partnership if the infected individual infects their partner.

Eames and Keeling used this model to explore the effects of contact tracing in sexual mixing networks on a generic STI [44]. They found that “*contact tracing is favoured*

when infection is globally rare but locally common within connected areas of the network" suggesting that the effectiveness of contact tracing is directly proportional to local network density [44].

Pair-wise approximation are able to provide a deterministic approximation for pair dynamics of connected individuals in a network. They can account for network clustering of local correlations however are most accurate with low clustering networks, such as the random networks discussed in §1.2.3 [40]. It has been shown that there is excellent congruity between stochastic network simulations and deterministic pair-wise approximations, however pair-wise models have the advantage of easier complexity and are in general less computationally intense [40].

As seen with compartmental models, §1.2.1, increased compartment often result in an increased complexity, and pair-wise approximation models are no different. The simple SITS model, (1.20)-(1.22), was able to be explicitly represented by three ODE's, however by included the pair-wise approximations this quickly grows to a system of twelve ODE's (including equations for both directions over a partnership). This grows at an increasing rate of $n(n + 1)$ ODE's for an n class system and hence pair-wise models may not always be the best choice when modelling a complex system.

1.2.5 Model Comparison

There is clearly a wide variety of approaches to chose from when forming a mathematical model to explore chlamydia epidemiology. None of these approaches are truly 'better' than the next, as each model has its own set of advantages and disadvantages to contend with. Deterministic compartmental models provide the simplest approach, are easily manageable, and allow for population wide infection dynamics, such as the application of national screening, to be assessed. However mixing is generally homogeneous, with only models divided by sexual activity or metapopulations providing limited heterogeneity, and while simple models remain easy to analyse, larger models with numerous compartments quickly become mathematically complex [30]. Furthermore, few involve spatial aspects and since compartmental models only keep tract of how many individuals rather than which ones are in each compartment, they provide no accurate way of measuring contact tracing.

Individual based and network models are able to overcome the lack of individual traceability by modelling each individual. This provides a more accurate model, are able to include spatial aspects, track individual movement through the system, and allow for population heterogeneity [37]. Unlike deterministic models, individuals control strategies such as contact tracing can be included, however due to the amount of data needed

on each individual, are frequently computationally intense and difficult to parameterise.

Pair-wise approximation models allow for a middle ground between compartmental/metapopulation and individual/network approaches. The model can capture any influence that network structure may have on the spread of infection, without explicitly modelling each individual. Forming in a similar way to deterministic models, by modelling not only the compartments but also the connected pairs, they provide a model more accurate than deterministic ones, yet not as accurate as individual or network models. Pair-wise approximation models allow for both population level (national screening) and individually targeted (contact tracing) control strategies to be explicitly modelled, however increase in complexity faster than deterministic models with the addition of extra compartments [40]. They do not allow for population heterogeneity.

In terms of modelling chlamydia, pair-wise 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 the model formed in this dissertation will start with a basic deterministic SIT model. By adding additional infection classes the model will eventually become a deterministic compartmental model of ten distinct compartments, (2.11)-(2.22), comparable to a random network. Although a pair-wise model provides additional accuracy by including spatial dynamics, this would cause the model to become far too complex for the scope provided here.

Chapter 2

Model Formation

Following the early work of Hethcote and Yorke, it is possible to formulate a simple yet accurate deterministic model for chlamydia epidemiology, that includes opportunistic screening as used by the NCSP [30]. By explicitly modelling changes in levels of national screening, as well as the introduction of targeted repeat screening, the model aims to explore both the impact and costs of opportunistic screening in a public health setting.

2.1 A Deterministic SITS Model Incorporating Opportunistic Screening and Targeted Re-screening

In order to explore opportunistic screening as a control strategy, the model builds on the previous SITS¹ framework, which has been used extensively to simulate the impact of different control strategies on chlamydial infections [44] [45]. As mentioned in §1.1.3, previous chlamydia infections confer no immunity towards future infection, resulting in individuals becoming susceptible to re-infection once treatment has ceased. This gives rise to three infection categories within the larger population.

S	Susceptible
I	Infectious
T	Undergoing Treatment
N	Total Population

Table 2.1: *Infection class categories*

¹Susceptible→Infected→Treatment→Susceptible

2.1.1 A Deterministic SITS Model with Opportunistic Screening

Assumptions

As with all mathematical models, before this system can be explicitly modelled, it is necessary to assert a number of biological and mathematical assumptions. These assumptions are:

- **A constant population N :** The first assumption is that the population N is fixed. There is no migration in or out of the system, nor is there any birth or death present. While chlamydia can lead to many severe complications, §1.1.2, few of these are fatal and in the case of those that are, even less will go undetected. Similarly, although some complications resulting from chlamydia such as Trachoma may be passed to newborns, there has been few recorded cases of newborns showing full chlamydial infection to warrant inclusion in this model.
- **The 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 such that when an individual matures to 26 and exits the system (at any infection category), they are immediately replaced by an individual of 16, who has matured into the susceptible category. As mentioned in §1.1, the highest rates of chlamydia prevalence are seen within the 16-25 age range, which was responsible for 79.7% of infections in England in 2011 [6]. For this reason the 16-25 group is seen as cause for concern by many health authorities, and the model shall focus on infection within this age range [28]. Furthermore, individuals can mature out of the system at any state of infection however individuals that mature into the system enter strictly into the susceptible category. This is taken to represent the real world situation where few individuals under 16 are sexually active and those that are do not frequently associate with chlamydia at the same infection levels as the 16-25 group.
- **Individuals mix randomly:** Within the larger population N , individuals 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.

- **Transmission of infection requires direct sexual contact:** Transmission of chlamydia infection can only occur between two individuals engaging in a direct sexual partnership, originating from an infected individual I and transmitting to a susceptible S at a rate β . The model does not distinguish between infection via different sexual practises (oral, vaginal, anal) and infected individuals who partner with other infected individuals do not acquire an increased viral load. Whilst it has been shown that certain sexual acts (vaginal and anal) have higher chance of transmitting the infection than others (oral), the model does not account for this as the majority of sexual partnerships will involve multiple sexual practises.
- **Infected individuals may recover naturally:** Infected individuals, particularly asymptomatic ones, may experience a natural recovery from infection I back into susceptibility S at a rate r , without the assistance of antibiotics or clinical diagnosis. The individual may or may not be aware of their previous status as ‘infected’, and similarly healthcare authorities are not made aware of the infection.
- **Infected individuals may experience symptoms:** Infected individuals may become symptomatic and display symptoms indicating infection at a rate d . The model assumes all symptomatic individuals will seek clinical treatment and move from the infected category I to the treatment category T .
- **Susceptible and infectious individuals undergo national screening:** All individuals except those currently undergoing treatment for chlamydia infection may be screened for infection at a rate g . Positively identified cases of infection moves individuals from the infection category I to the treatment category T .
- **Treatment is easily available:** Individuals who are positively identified as infected move from the infected category I to the treatment category T . Treatment is assumed to be quickly available and effective at curing infection, as is the real world case [14]. During treatment individuals are assumed to abstain from sexual intercourse, in line with advice from health care professionals [14]. Following treatment, treated individuals move from the treatment category T to the susceptible category S at a rate a .

It is important to keep in mind that whilst the system may accurately represent a real world setting, any and all results from the models presented should be taken to hold only under these assumptions. Despite this, the model may be able to indicate

real world population dynamics and responses to changes in control strategies, though values, particularly those of population size, may differ.

Parameters

From these assumptions the model parameters can now be easily summarised in table 2.2, values for which will be estimated in table 2.4.

Parameter	Description
α	Rate of maturity in/out of 16-25 age range
β	Rate of infection from an infected individual
k	Average number of sexual partners per individual
r	Rate of asymptomatic natural recovery
g	National screening rate
d	Rate of developing symptoms naturally
a	Recovery rate via treatment

Table 2.2: Basic model parameters

Using these parameters, a schematic of the model can now be built to show how individuals move between the different infection classes, as shown in figure 2.1.

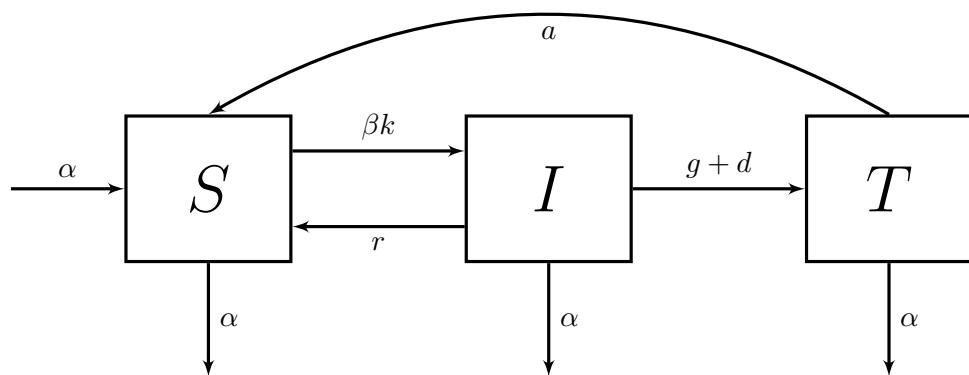


Figure 2.1: Base deterministic SITS model with national screening

From table 2.2 and figure 2.1 it is now possible to explicitly derive the system of equations for the model.

Derivation of equations

Looking at the class of susceptible individual S in figure 2.1 it is clear to see a number of possible events taking place:

- maturity into the 16-25 age cohort,

2.1. A Deterministic SITS Model Incorporating Opportunistic Screening and Targeted Re-screening

- maturity out of the 16-25 age cohort,
- infection from an infected individual via sexual contact,
- natural recovery of an infected individual,
- recovery via treatment of an infected individual.

Therefore the change in the class of susceptible individuals S can be represented as:

$$\text{Change in susceptibles} = \frac{\text{Mature into age group}}{\text{Mature out of age group}} - \frac{\text{Become infected}}{\text{Natural recovery}} + \frac{\text{Recovery via treatment}}{}$$

As discussed in §2.1.1 and table 2.2, individuals from the larger population N mature into the 16-25 age gap at a rate α , whilst individuals within each infection class may mature out of the 16-25 age gap at the same rate α . Susceptible individuals S may also become infected at a rate β when partnering with an infected individual I , with each individual having k number of partners, moving them from the S to I infection classes. Infectious individuals may then return to the susceptible class through either natural recovery at a rate r , or by moving into the treatment class T and then into the susceptible class S at a rate a . This results in the differential equation:

$$\frac{dS}{dt} = \alpha N - \alpha S - \beta k S \frac{I}{N} + r I + a T$$

which neatens to

$$\dot{S} = \alpha N + r I + a T - S \left(\alpha + \beta k \frac{I}{N} \right)$$

The infected class I and treatment class T can be similarly expressed as:

$$\text{Change in infecteds} = \frac{\text{Become infected}}{\text{Natural recovery}} - \frac{\text{Mature out of age group}}{\text{Develop symptoms}} - \frac{\text{Develop symptoms}}{\text{Screened for infection}} - \frac{\text{Screened for infection}}{\text{infection}}$$

$$\text{Change in treatment} = \frac{\text{Screened for infection}}{\text{infection}} + \frac{\text{Develop symptoms}}{\text{symptoms}} - \frac{\text{Mature out of age group}}{\text{age group}} - \frac{\text{Recovery via treatment}}{}$$

Leading to the differential equations:

$$\begin{aligned}\dot{I} &= \beta k S \frac{I}{N} - (\alpha + r + g + d) I \\ \dot{T} &= (g + d) I - (\alpha + a) T\end{aligned}$$

Which forms the system (2.1)-(2.4):

$$\dot{S} = \alpha N + rI + aT - S \left(\alpha + \beta k \frac{I}{N} \right) \quad S(0) = S_0 > 0 \quad (2.1)$$

$$\dot{I} = \beta k S \frac{I}{N} - (\alpha + r + g + d) I \quad I(0) = I_0 > 0 \quad (2.2)$$

$$\dot{T} = (g + d) I - (\alpha + a) T \quad T(0) = T_0 \geq 0 \quad (2.3)$$

$$N(t) = S(t) + I(t) + T(t) \quad N(0) = N_0 > 0 \quad (2.4)$$

While this model system can capture the impact of national screening on chlamydia infection of a susceptible population, it does not cater for the goal of this dissertation, whether targeted re-screening can impact chlamydia infection.

2.1.2 Extending the Model to Include Targeted Re-screening

It was suggested by Turner and Adams that to see a significant drop in prevalence, national screening would have to increase from the current aim of 16% to a target 43% of the population per year [37]. However many PCT's² fail to meet the current aim and this project hypothesises that the same reductions seen by increasing national screening, may be seen with smaller increases combined with re-screening of previously infected individuals. Taking inspiration from the work of Rodrigues *et al.*, who used a standard SIRI³ model but introduced iterative frailty classes for repeat infections, the model includes additional infection classes of which targeted re-screening can assess for chlamydial infection [46]. These classes take the form of observed classes which an individual can only enter as a result of previous chlamydial infection. The additional infection classes are observed susceptible's and observed infectious, denoted as $S_2(t)$ and $I_2(t)$ respectively.

Additional assumptions

With the introduction of re-screening, and the target classes S_2 and I_2 , the extended model will require additional assumptions on top of the ones previously stated.

- **Individuals may be re-screened:** Individuals who have shown a positive initial screen may be re-tested at a rate $\hat{g}\gamma$. Rather than simply returning immediately to the susceptible class S , individuals treated for infection move into the observed $S_2I_2TS_2$ system at a rate a , allowing for targeted re-screening. Individuals within the observed classes are still able to be nationally screened for the infection.

²Primary Care Trusts

³Susceptible→Infected→Recovered→Infected

- **Observed classes mirror their counterparts:** Individuals in the observed classes S_2 and I_2 may experience the same events as those in the standard S and I classes, which from here on out shall be renamed to S_1 and I_1 classes, that is to say infection (β), natural recovery (r), national screening (g) or developing symptoms (d). However values between standard and observed classes may differ. Furthermore, the overall classes S, I may be regained by combining the standard S_1, I_1 classes and the observed S_2, I_2 classes such that $S = S_1 + S_2$ and $I = I_1 + I_2$.
- **Observation is only for a limited time:** Due to the increased resources required for re-screening, individuals may return to the standard classes if no infection is detected through screening (national or re-screening) at a rate μ . In terms of resource management, this allows for resources not to be wasted on constantly re-screening individuals who may only contract the infection once within their time in the system.

Additional parameters

As with the introduction of re-screening causing addition assumptions to be made, it also causes a number of extra parameters to surface. These are given in table 2.3.

Parameter	Description
\hat{g}	Attendance of individuals for re-screens
γ	Rate of re-screening
μ	Rate of clearance from observed to standard classes

Table 2.3: Additional parameters

In addition to the extra parameters introduced in table 2.3, the parameters (β, r, d) previously introduced in table 2.2 shall have subscripts of either 1 or 2 to represent the same event (infection, natural recovery, development of symptoms) but in relation to either the standard or observed classes in the extended model. This now leads to a new schematic of the model as shown in figure 2.2.

Derivation of equations

In a similar manner as before, it is now possible to explicitly describe changes in class sizes via different events taking place at each stage. This allows the infection classes to be expressed by the ODE system (2.5)-(2.10).

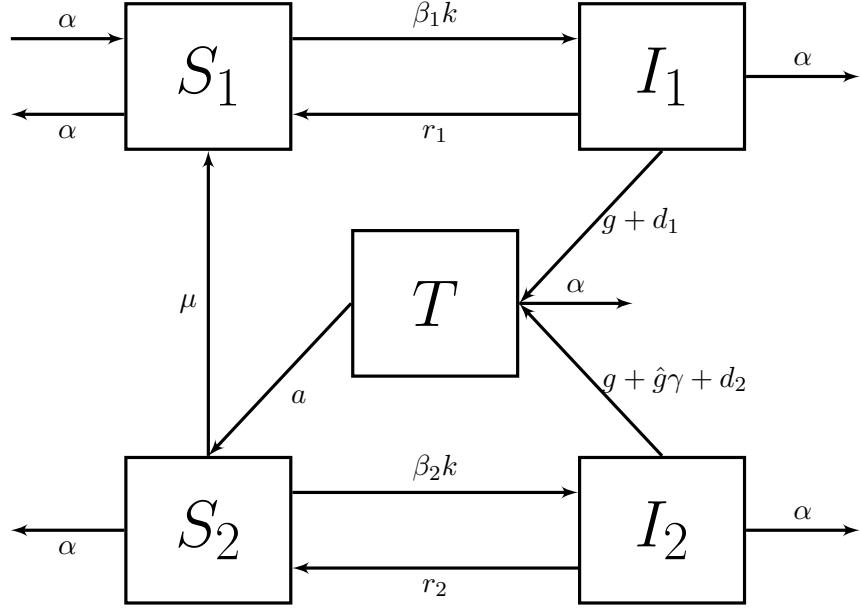


Figure 2.2: Extended deterministic SITS model with national screening and targeted re-screening

$$\dot{S}_1 = \alpha N + r_1 I_1 + \mu S_2 - S_1 \left(\alpha + k \sum_{i=1}^2 \beta_i \frac{I_i}{N} \right) \quad S_1(0) = S_{10} > 0 \quad (2.5)$$

$$\dot{I}_1 = k S_1 \sum_{i=1}^2 \beta_i \frac{I_i}{N} - (\alpha + r_1 + g + d_1) I_1 \quad I_1(0) = I_{10} > 0 \quad (2.6)$$

$$\dot{T} = g (I_1 + (1 + \varepsilon) I_2) - (\alpha + a) T + \sum_{i=1}^2 d_i I_i \quad T(0) = T_0 \geq 0 \quad (2.7)$$

$$\dot{S}_2 = a T + r_2 I_2 - S_2 \left(\alpha + \mu + k \sum_{i=1}^2 \beta_i \frac{I_i}{N} \right) \quad S_2(0) = S_{20} \geq 0 \quad (2.8)$$

$$\dot{I}_2 = k S_2 \sum_{i=1}^2 \beta_i \frac{I_i}{N} - (\alpha + r_2 + g (1 + \varepsilon) + d_2) I_2 \quad I_2(0) = I_{20} \geq 0 \quad (2.9)$$

$$\begin{aligned} N(t) &= S(t) + I(t) + T(t) \\ &= S_1(t) + S_2(t) + I_1(t) + I_2(t) + T(t) \end{aligned} \quad N(0) = N_0 > 0 \quad (2.10)$$

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

This model now allows for the impact of targeted re-screening on a chlamydia susceptible population to be explored in terms of prevalence, positivity, incidence, cost and cost effectiveness, as can be seen in §3.

2.1.3 Dividing into Core/Non-Core groups

As discussed in §1.2.1, subdividing models for the spread of chlamydia by sexual activity has proven to be useful in exploring opportunistic prevention strategies [30]. Furthermore this has lead to the concept of core and non-core groups. Dividing the system (2.5)-(2.10) by sexual activity level yield two systems, the core (2.11)-(2.16) and non-core (2.17)-(2.22), with the only difference between the two being the average number of sexual contacts per individual, k_1 for core and k_2 for non-core, allowing for some heterogeneity. To denote classes representing either core or non-core individuals the model uses superscript notation of c or nc for core or non-core, as can be seen in figure 2.3. Furthermore, by adding the core, (2.11)-(2.16), and non-core equations, (2.17)-(2.22), the original extended system, (2.5)-(2.10), can be regained.

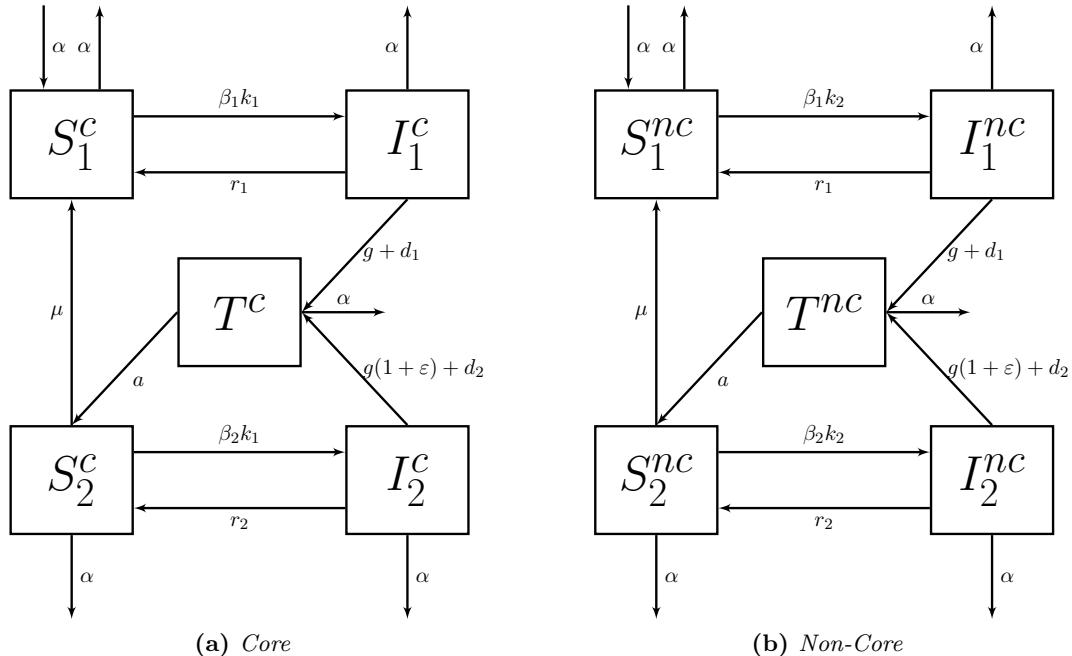


Figure 2.3: Core/Non-Core deterministic SITS model with national screening and targeted re-screening

Core

$$\dot{S}_1^c = \alpha N^c + r_1 I_1^c + \mu S_2^c - S_1^c \left(\alpha + k_1 \sum_{i=1}^2 \beta_i \frac{I_i}{N} \right) \quad S_1^c(0) = S_{10}^c > 0 \quad (2.11)$$

$$\dot{I}_1^c = k_1 S_1^c \sum_{i=1}^2 \beta_i \frac{I_i}{N} - (\alpha + r_1 + g + d_1) I_1^c \quad I_1^c(0) = I_{10}^c > 0 \quad (2.12)$$

$$\dot{T}^c = g (I_1^c + (1 + \varepsilon) I_2^c) - (\alpha + a) T^c + \sum_{i=1}^2 d_i I_i^c \quad T^c(0) = T_0^c \geq 0 \quad (2.13)$$

$$\dot{S}_2^c = a T^c + r_2 I_2^c - S_2^c \left(\alpha + \mu + k_1 \sum_{i=1}^2 \beta_i \frac{I_i}{N} \right) \quad S_2^c(0) = S_{20}^c \geq 0 \quad (2.14)$$

$$\dot{I}_2^c = k_1 S_2^c \sum_{i=1}^2 \beta_i \frac{I_i}{N} - (\alpha + r_2 + g (1 + \varepsilon) + d_2) I_2^c \quad I_2^c(0) = I_{20}^c \geq 0 \quad (2.15)$$

$$\begin{aligned} N^c(t) &= S^c(t) + I^c(t) + T^c(t) \\ &= S_1^c(t) + S_2^c(t) + I_1^c(t) + I_2^c(t) + T^c(t) \end{aligned} \quad N^c(0) = N_0^c > 0 \quad (2.16)$$

Non-Core

$$\dot{S}_1^{nc} = \alpha N^{nc} + r_1 I_1^{nc} + \mu S_2^{nc} - S_1^{nc} \left(\alpha + k_2 \sum_{i=1}^2 \beta_i \frac{I_i}{N} \right) \quad S_1^{nc}(0) = S_{10}^{nc} > 0 \quad (2.17)$$

$$\dot{I}_1^{nc} = k_2 S_1^{nc} \sum_{i=1}^2 \beta_i \frac{I_i}{N} - (\alpha + r_1 + g + d_1) I_1^{nc} \quad I_1^{nc}(0) = I_{10}^{nc} > 0 \quad (2.18)$$

$$\dot{T}^{nc} = g (I_1^{nc} + (1 + \varepsilon) I_2^{nc}) - (\alpha + a) T^{nc} + \sum_{i=1}^2 d_i I_i^{nc} \quad T^{nc}(0) = T_0^{nc} \geq 0 \quad (2.19)$$

$$\dot{S}_2^{nc} = a T^{nc} + r_2 I_2^{nc} - S_2^{nc} \left(\alpha + \mu + k_2 \sum_{i=1}^2 \beta_i \frac{I_i}{N} \right) \quad S_2^{nc}(0) = S_{20}^{nc} \geq 0 \quad (2.20)$$

$$\dot{I}_2^{nc} = k_2 S_2^{nc} \sum_{i=1}^2 \beta_i \frac{I_i}{N} - (\alpha + r_2 + g (1 + \varepsilon) + d_2) I_2^{nc} \quad I_2^{nc}(0) = I_{20}^{nc} \geq 0 \quad (2.21)$$

$$\begin{aligned} N^{nc}(t) &= S^{nc}(t) + I^{nc}(t) + T^{nc}(t) \\ &= S_1^{nc}(t) + S_2^{nc}(t) + I_1^{nc}(t) + I_2^{nc}(t) + T^{nc}(t) \end{aligned} \quad N^{nc}(0) = N_0^{nc} > 0 \quad (2.22)$$

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

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

2.2 Parameter Estimation

Having fully defined the model equations for both the deterministic model with national screening and targeted re-screening, (2.5)-(2.10), and the core/non-core deterministic model, (2.11)-(2.22), all that remains is to estimate values for the parameters used, as summarised in tables 2.2 and 2.3. As the model does not differentiate between male or female, the parameter values chosen are not gender specific and where appropriate have been taken as an average of men and women. Since this dissertation aims to advise PCT's and health authorities, the overall timespan of any simulations will not be run for longer than three years. Therefore, due to the short timespan any dimensional parameters used have been chosen to be on a per day timescale for optimum accuracy.

As described in table 2.2, α is the maturity rate into/out of the 16-25 age group. As this age gap spans ten years this gives α to be the inverse of that age gap, multiplied by the timescale:

$$\alpha = \frac{1}{10 \times 365} [\text{days}^{-1}] \approx 2.74 \times 10^{-4} [\text{days}^{-1}]$$

From table 2.2, the parameter k is representative of the average number of sexual partners per individual at any time. This has been estimated using the work of Brown *et al.* [47] who, based on data from the NATSAL 2000 [39], created an age dependent linear function for average number of sexual partners, given by:

$$z_i(a) = \begin{cases} 0.1411a, & a \leq 16 \\ 2.93 - 0.042a, & 16 < a \leq 69 \\ 0, & a > 69 \end{cases} \quad [47]$$

Since this model is only concerned with the 16-25 age group, k can be taken to be the average value of z_i over 16-25's.

$$k = \frac{0.1411 \times 16 + 9 \times 2.93 - 0.042 \sum_{a=17}^{25} a}{10} \approx 2.07$$

Based on this value, the k_1 and k_2 values for core and non-core variants can be calculated. Within core/non-core chlamydia models, core groups are often chosen to represent no larger than 10% of the sexually active population, (as mentioned in §1.2.1 Hethcote and Yorke found the core group to represent 6.7% of the population) [30]. Therefore, keeping the non-core population's k_2 close to k by setting $k_2 = 1.66$ (20%

less than k):

$$\begin{aligned} k &= k_1 \frac{N^c}{N} + k_2 \frac{N^{nc}}{N} \\ 2.07 &= k_1 \times 0.1 + 1.66 \times 0.9 \\ \Rightarrow k_1 &= 5.76 \end{aligned}$$

From table 2.2, r_i is given as the rate of asymptomatic natural recovery from the infection classes I_i to their corresponding susceptible classes S_i . In a similar manner to how α was calculated, r_i can be calculated as the inverse of the average duration of asymptomatic infection. Based on the work of Althaus *et al.* this has been estimated at 433 days with 95% confidence intervals of 420-447 days, resulting in $r_i = \frac{1}{433} \approx 0.0023[\text{days}^{-1}]$ [31].

The parameter g is representative of the rate of national screening per day. Currently in the UK the NCSP aims for 16% coverage per year, however some PCT's within each county may fall far below this [28] [26]. Assuming this 16% coverage, this value can be obtained by solving $\frac{dI}{dt} = -gI \Leftrightarrow \ln(0.84) = -365g$, giving the per day rate $g \approx 4.77 \times 10^{-4}$.

Parameter d_i is defined as the rate at which symptoms develop naturally within an infected host. With chlamydia infection, approximately 20% of infected individuals go on to be symptomatic, of which average duration of infection has been estimated to last 30 days [31] [45] [48]. Therefore d_i can be calculated as $d_i = \frac{0.2}{30} \approx 0.0067[\text{days}^{-1}]$.

In table 2.2 a is given to be the recovery rate via the treatment class. This can be directly calculated as the inverse of the average time spent in treatment. As discussed in §1.1.3 treatment has been shown to be at least 97% effective, taking an average of one week [14]. However health agencies often advise abstinence from sexual interactions for another week after treatment has finished [14] [7]. Therefore $a = \frac{1}{14} \approx 0.0714[\text{days}^{-1}]$.

Possibly the most sensitive parameter value is that of the rate of infection from an infected individual, β . Within real world scenarios chlamydia prevalence is often found at around 8% [45] [49], and is defined as;

Definition 2.1 (Prevalence):

The proportion of individuals infected within a population:

$$\frac{I^{c+nc} + T^{c+nc}}{N^{c+nc}}(t_i)$$

Using the base deterministic SITS model with national screening, (2.1)-(2.4), β can be

estimated by keeping all other parameters constant and setting β to achieve a steady state prevalence of 8%.

$$\begin{aligned} \text{At steady states } \frac{dI}{dt} = 0 &\Rightarrow 0 = \beta k S \frac{I}{N} - (\alpha + r + g + d) I \\ \text{Using } \frac{I+T}{N} = 0.08 \text{ and (2.4)} &\Rightarrow 0.92\beta k = \alpha + r + g + d \\ &\beta \approx 0.0051[\text{days}^{-1}] \end{aligned}$$

Moving onto the additional parameters, \hat{g} is defined by table 2.3 to be the attendance of individuals for re-screens. This can vary anywhere between 0 - no re-attendance, to 1 - 100% re-attendance, and shall be tested for these values in §3. However due to lack of clinical data for patient re-attendance, the baseline value becomes difficult to estimate. Instead the estimate is based on clinic attendance of those individuals invited for screening when obtained through partner notification. In 2008/09 within the UK 16-24 age gap, this was recorded as 50% of contacted partners per index case accepting an invitation for screening [28]. Therefore as a baseline value $\hat{g} = 0.5$.

The parameter γ denotes the rate of the re-screening. This is a crucial parameter in that re-screening individuals too soon after treatment for the initial infection will not give individuals time to become re-infected, resulting in wasted resources on negative screens, whilst screening too late after treatment will allow re-infected individuals to pass on the infection to numerous others. It has been suggested that the highest levels of re-infection are seen between three and six months after treatment for an initial infection, with the highest seen after four months [50]. To optimise the positivity of re-screening, this becomes the optimum time to screen, therefore $\gamma = \frac{1}{\frac{1}{3} \times 365} \approx 0.0082[\text{days}^{-1}]$.

Lastly the clearance rate from observed to the standard classes, μ , is taken by considering how long observation should last. As no health authorities currently use observation for chlamydia re-testing, there is no clinical data to suggest a value for μ . However, it can be logically considered that observation and re-testing use valuable resources. Therefore to minimise costs observation should not last much longer than the length of time between a positive initial screen and negative re-screen. Since the highest re-infection levels are seen up to six months after treatment it can be argued that observation should last six months [50], giving $\mu = \frac{1}{0.5 \times 365} \approx 0.0055[\text{days}^{-1}]$.

The parameters in this model can, and will, be altered to consider different situations. To remove national screening or targeted re-screening from the model simply set g or \hat{g} , respectively, to zero. Setting (g, \hat{g}, d) all to zero results in returning to a simple SIS model with no treatment class, allowing for only natural recovery from infection.

However, unless otherwise stated parameters shall be as defined in table 2.4.

Parameter	Value	Range	Source
α	$2.74 \times 10^{-4} \text{ days}^{-1}$	N/A	See Text
k	2.07	[1.66,5.76]	[47] [39]
r_i	0.0023 days^{-1}	[0.0021,0.0025]	[31]
g	$4.77 \times 10^{-4} \text{ days}^{-1}$	N/A	[26] [28]
d_i	0.0067 days^{-1}	[0.0060,0.0073]	[31] [45] [48]
a	0.0714 days^{-1}	[0.0476,0.1429]	[14] [7]
β_i	0.0051 days^{-1}	N/A	See Text
\hat{g}	0.5	[0,1]	[28] & See Text
γ	0.0082 days^{-1}	[0.0056,0.0111]	[50]
μ	0.0055 days^{-1}	[0.0027,0.0110]	[50]
N	10000	N/A	Arbitrarily chosen

Table 2.4: Baseline Parameter Estimates

2.2.1 Sensitivity of β_2 , r_2 , d_2 Values

While baseline parameter values have been estimated for β_i , r_i , and d_i (table 2.4), it has been suggested 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 differences in viral load between primary and repeat infections [3]. Despite limited studies in evaluating chlamydial load, several studies have found a reduction in viral load within re-infected individuals. Organism load has been found to be significantly lower for the first repeat infection compared with the initial infection, but have found little difference in load between the first and second repeat infections [3] [51] [52]. Gomes *et al.* suggested that chlamydial load could impact both rate of infection β_i and rate of natural recovery r_i . Their findings showed that the probability of being infected was 7.7 fold higher in patients with prior infection, compared to those with no history of infection, and while the host immune defense does not block entry of chlamydiae into cells, there may be an “*immunologic impact on replication*” within re-infected individuals [51]. Here this would suggest $\beta_2 > \beta_1$ and $r_2 > r_1$ though to what level remains to be seen. However, Gomes *et al.* went onto to state that “*distribution of chlamydial load among these groups suggests that load is not a major factor for transmission*”, when evaluating whether a higher load would be associated with a higher risk of transmission, making the relationship between β_1 and β_2 unclear [51]. It is worth noting that within these studies the control groups remained small and that although some associations were found, none of them were confirmed [51].

In terms of the d_2 parameter it is logical to consider that individuals who find them-

selves in the observation classes will have experienced at least one symptomatic infection. Therefore if an individual becomes infected again within a short space of time, they might be more aware of the symptoms due to recent previous infection. This would then suggest $d_2 > d_1$, however as with β_2 and r_2 there is a lack of published data to clarify this.

Before the model can progress, these values must be tested to try and obtain sensible values, though the amount they differ from their standard counterparts may be negligible. This can be achieved by examining changes in the basic reproductive ratio R_0 and steady states.

Basic Reproductive Ratio R_0

One way to consider the impact of parameters on infection dynamics is to consider the basic reproductive ratio R_0 . Defined as “*the average number of secondary cases arising from an average primary case in an entirely susceptible population*”, it is frequently cited as one of the most important quantities in epidemiology as it can be considered to represent the maximum reproductive potential for an infectious disease [40].

By combining equations (2.6) and (2.9) it is possible to regain the overall infection class I , since $I = I_1 + I_2$, giving:

$$\dot{I} = \dot{I}_1 + \dot{I}_2 = k \frac{S}{N} \sum_{i=1}^2 \beta_i I_i - (\alpha + g) I - (r_1 + d_1) I_1 - (r_2 + d_2 + g\varepsilon) I_2$$

Since R_0 is based on the impact of a single primary case of infection ($I_1 = 1$, $I_2 = 0$) in an entirely susceptible population ($\frac{S}{N} \approx 1$)

$$R_0 = \frac{k\beta_1}{\alpha + g + r_1 + d_1} \approx 1.0870$$

By definition, if $R_0 < 1$ then the infection will die out, while if $R_0 > 1$ infection is able to spread in a population, as is the case here. However whilst giving valuable insight into the infection potential, in the final stages of calculation R_0 did not depend on either β_2 , r_2 , or d_2 , failing to clarify the impact of these values.

Steady State Analysis

Since R_0 values were unable to clarify the impact of changes to parameters (β_2, r_2, d_2), an alternative measure is to explore and compare the steady state values produced when varying values of (β_2, r_2, d_2). Starting with the base deterministic SITS model with national screening, (2.1)-(2.4), steady states are achieved when the system reaches

equilibrium, i.e. at points where $\frac{dS}{dt} = \frac{dI}{dt} = \frac{dT}{dt} = 0$. Solving for (S, I, T) yields two steady states, the disease-free equilibrium

$$(S_0, I_0, T_0) = (N, 0, 0) \quad (2.23)$$

and the endemic equilibrium

$$(S^*, I^*, T^*) = \left(\frac{N}{R_0}, \frac{\alpha + a}{\alpha + g + d + a} N \left(1 - \frac{1}{R_0} \right), \frac{g + d}{\alpha + g + d + a} N \left(1 - \frac{1}{R_0} \right) \right) \quad (2.24)$$

Where $R_0 = \frac{\beta k}{\alpha + r + g + d}$. Using values from table 2.4 the epidemic steady state becomes

$$(S^*, I^*, T^*) = (9171.17, 754.05, 74.78) \quad (2.25)$$

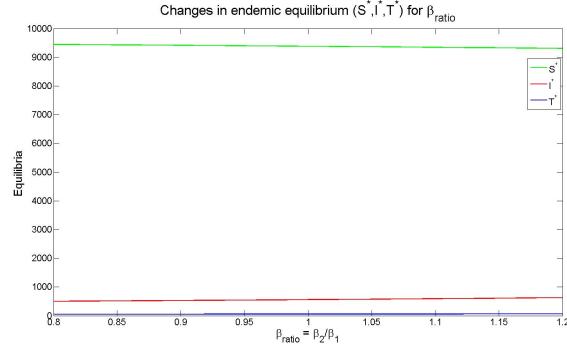
Furthermore, since $R_0 > 1$, shown in §2.2.1, the endemic equilibrium (S^*, I^*, T^*) is a stable steady state. In a similar manner, steady states for the extended model with targeted re-screening, (2.5)-(2.10), can be obtained, resulting in the disease-free equilibrium $(S_0, I_0, T_0) = (S_{10} + S_{20}, I_{10} + I_{20}, T_0) = (N, 0, 0)$, and endemic equilibrium $(S^*, I^*, T^*) = (S_1^* + S_2^*, I_1^* + I_2^*, T^*)$. Since this endemic equilibrium now relies on secondary values (β_2, r_2, d_2) , it is possible to explore the impact of changes to the baseline values.

Since the secondary values (β_2, r_2, d_2) are likely to remain close to the baseline values, it is sufficient to vary the baseline values by 20% either side and compute the ratio of these values to the baseline (β_1, r_1, d_1) , against the changes in endemic equilibrium as can be seen in figure 2.4.

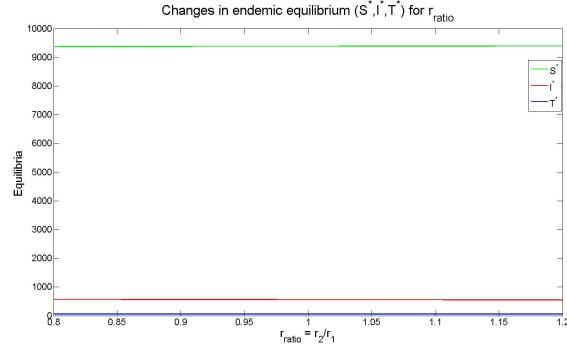
By comparing equilibrium values, figure 2.4 is able to demonstrate that despite testing for a wide range of values either side of the baseline ($\pm 20\%$), there is little significant impact on the equilibrium (S^*, I^*, T^*) . From figure 2.4 and the more detailed figures A.1-A.3, seen in appendix A.1, it is suggested that only β_2 has any true impact on equilibrium values, of which is not significantly different for the range explored. Since perturbations to the baseline values for (β_i, r_i, d_i) do not seem to have any lasting implications on the model system, it could be argued that continuing on with $\beta_2 > \beta_1$, $r_2 > r_1$ and $d_2 > d_1$ should not detriment the model, as long as values are chosen within the sensitivity displayed here ($\pm 20\%$). To minimise any potential unseen implications, secondary values for parameters β_2, r_2, d_2 shall be chosen at only a 10% increase of the baseline value, which can be seen in table 2.5.

Parameter	Value
β_2	0.0056 days ⁻¹
r_2	0.0025 days ⁻¹
d_2	0.0074 days ⁻¹

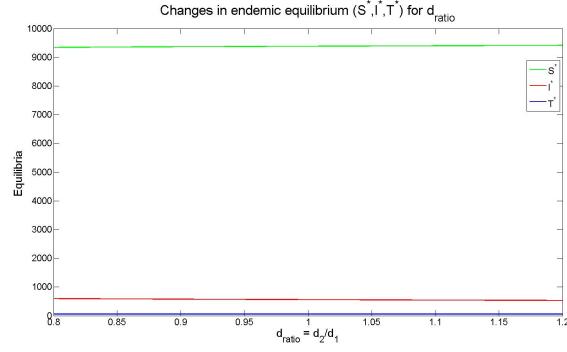
Table 2.5: Observed class estimates



(a) Varying β_2 with r_2, d_2 fixed at baseline values



(b) Varying r_2 with β_2, d_2 fixed at baseline values



(c) Varying d_2 with β_2, r_2 fixed at baseline values

Figure 2.4: Impact of varying (β_2, r_2, d_2) on endemic steady states (S^*, I^*, T^*) . The M-file can be found in appendix B.2.1

Chapter 3

Model Analysis

With the model now formulated, it is possible to explore different rates of national screening and targeted re-screening in an attempt to understand and analyse the impact of both methods of control. The model will compare the effectiveness of both methods by comparing short term disease growth, levels of prevalence and incidence, and composure of core/non-core groups within the population. The model will then assign costings to the control strategies and calculate cost effectiveness against reductions in prevalence.

3.1 Deterministic SITS Model with National Screening and Targeted Re-screening

Using the parameters set in tables 2.4 2.5, along with models (2.1)-(2.4), (2.5)-(2.10) and (2.11)-(2.22), it is possible to investigate the impact of national chlamydia screening and targeted re-screening on infection prevalence, incident and positivity. As this project aims to advise public health services (who are frequently under pressure to see quick results) on potential control methods, all simulations will be run over a time period of 3 years. Simulations will also be given the initial conditions $(S_0, I_0, T_0) = (N - I_0, 0.08N, 0)$ that is, initial infectives represent 8% of the population N , initial treatment is empty, and susceptibles S are the remainder of the population. Since N is set at 10000 individuals (table 2.4) $(S_0, I_0, T_0) = (9200, 800, 0)$. Similarly, when introducing re-screening the observation classes are assumed to be initially empty, therefore $(S_{1,0}, S_{2,0}, I_{1,0}, I_{2,0}, T) = (9200, 0, 800, 0, 0)$; while for the core/non-core model, since the core represents 10% of the overall population $(S_{1,0}^c, S_{2,0}^c, I_{1,0}^c, I_{2,0}^c, T^c) = (920, 0, 80, 0, 0)$ and $(S_{1,0}^{nc}, S_{2,0}^{nc}, I_{1,0}^{nc}, I_{2,0}^{nc}, T^{nc}) = (8280, 0, 720, 0, 0)$. The differential systems (2.1)-(2.4), (2.5)-(2.10) and (2.11)-(2.22) are solved in MATLAB using a Runge-Kutta numerical integration method and the inbuilt ordinary differential solver `ode45`.

3.1.1 National Screening at 16% Coverage

Before analysing the effect of targeted re-screening, it is important to have a baseline result which can be compared back to. Considering the base deterministic SITS model, (2.1)-(2.4), representing the system currently in use by public health agencies, and examining the infection status of individuals allows some insight into current possible levels of infection, as seen in figure 3.1.

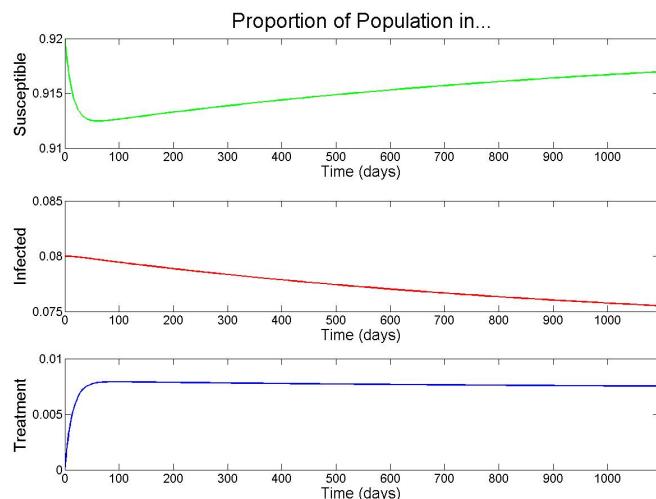


Figure 3.1: Proportion of population in (S, I, T) classes with national screening at 16%. The M-file can be found in appendix B.1.1

Figure 3.1 shows that when introducing national screening into a 92% susceptible and 8% chlamydia infected population at a rate of 16% coverage per year, an initial drop will be seen in susceptible individuals coinciding with an increased rise in ‘In Treatment’ individuals. The proportion of infected individuals also starts to decline as a result of 16% national screening however values soon start to stabilise to the endemic equilibrium (S^*, I^*, T^*), with S, I classes slightly lower their initial S_0, I_0 at (9170, 755) and the treatment class T rising from $T_0 = 0$ and stabilising almost immediately at $T = 75$. An addition graph of the population levels can be seen in figure A.4.

3.1.2 Introducing Targeted Re-screening at 50% Re-attendance

With the baseline result of figure 3.1 shown, it is now possible to introduce targeted re-screening as an additional control scheme. By assessing reduction levels in prevalence, incidence and positivity, it is possible to compare the efficiency of targeted re-screening as a potential intervention strategy. Simulating the deterministic SITS model with national screening and targeted re-screening, (2.5)-(2.10), with national screening set at 16% and re-screening at 50% results in population levels as seen in figure 3.2.

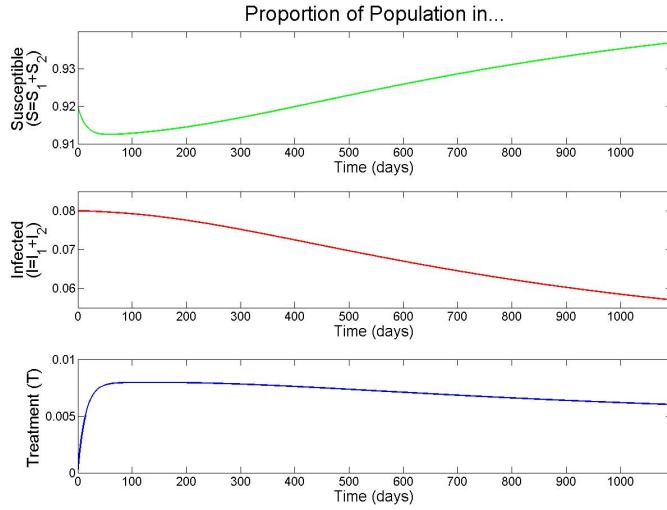


Figure 3.2: Proportion of population in (S, I, T) classes with national screening at 16% and targeted re-screening at 50%. The M-file can be found in appendix B.1.2

Figure 3.2 shows that by introducing targeted re-screening into a 92% susceptible and 8% chlamydia infected population at a rate of 50% re-attendance per year individual, i.e. half of those screening return for a second screen, the equilibrium (S^*, I^*, T^*) moves from the previous $(9170, 755, 75)$ to $(9370, 570, 60)$. This result shows that although re-screening reduces overall infection levels, it too reduces treatment levels. This is due to lower levels of infection becoming present in the population, hence there being less infection to screen for, and as a result fewer individuals move into the treatment class. Addition graphs of the population levels divided into (S_1, S_2, I_1, I_2, T) classes can be seen in figures A.5-A.6.

Perhaps the most interesting feature shown here is the initial increase in treatment cases, before settling on a lower equilibria state. In figure 3.2 the model is simulated with re-screening in use from the initial time t_0 . However 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 3.3 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.

As predicted, figure 3.3 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, see figure 3.4. This drop below the baseline 0%

3.1. Deterministic SITS Model with National Screening and Targeted Re-screening

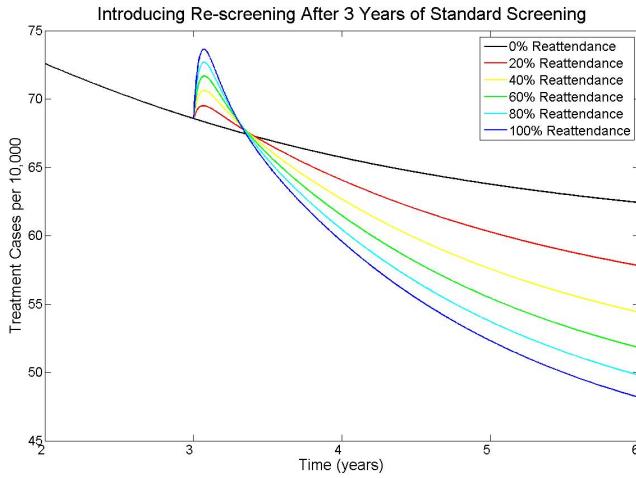


Figure 3.3: Impact of introducing re-screening into an established population on number of treated cases per 10,000. The M-file can be found in appendix B.2.2

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 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 3.3 including time taken (from time=1096 days, 3 years) to compensate for initial increase. The M-file can be found in appendix B.2.2

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 (figure 3.3).

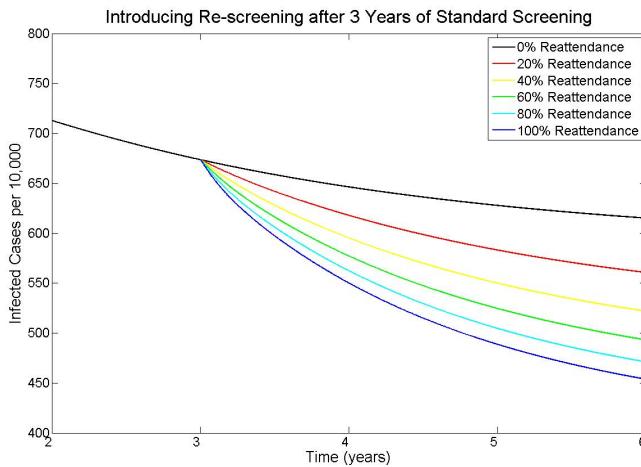


Figure 3.4: Impact of introducing re-screening into an established population on number of infected cases per 10,000. The M-file can be found in appendix B.2.2

Using the core/non-core model, (2.11)-(2.22), it is also possible to explore the dynamics of the population divided by sexual activity. As described in §2.1.3 and §2.2, the core group represents 10% of the population N and has on average $4.8 \times$ 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 composition of the core/non-core divide over the 3 year timespan, which is most pronounced in the infectious classes. This divide can be seen in figure 3.5.

Figure 3.5 shows that initially the infectious core group experiences rapid growth, before plateauing and moving towards equilibria. This surge can be attributed to the increased sexual activity of the group, allowing infection to quickly propagate through core group individuals; whilst the infectious non-core group experiences a slow decline, as the lower sexual partner rate cannot support infection against the additional re-screening. Furthermore, examining population levels after 3 years shows the core group to be responsible for approximately 32% of infection, despite only representing 10% of population. Figure 3.5 shows the infectious class $I = I_1 + I_2$ in terms of a core/non-core divide, however the composition of infection can also be looked at in terms of the separate I_1, I_2 classes.

3.1. Deterministic SITS Model with National Screening and Targeted Re-screening

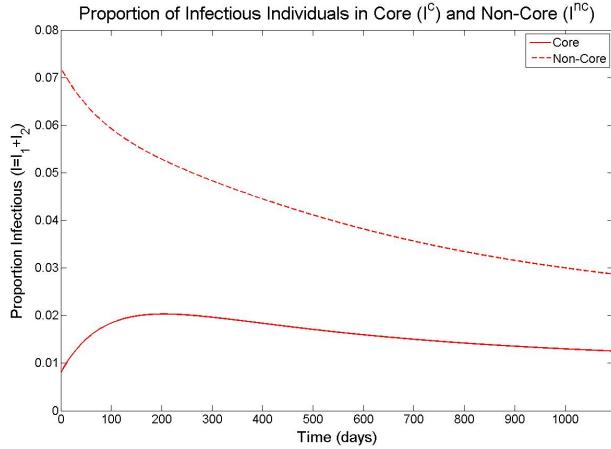


Figure 3.5: Core/Non-core divide in infectious class I_1 , with national screening at 16% and targeted re-screening at 50%. The M-file can be found in appendix B.1.3

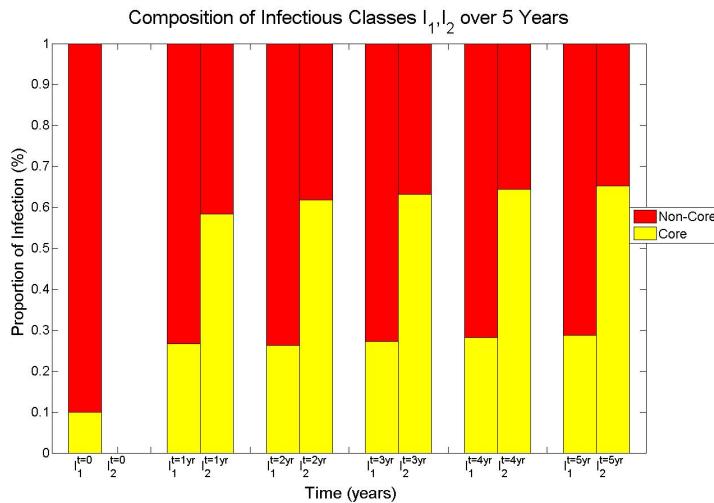


Figure 3.6: Composition of (I_1, I_2) over time with regard to core/non-core groups (national screening at 16%, targeted re-screening at 50%). The M-file can be found in appendix B.1.3

Figure 3.6 shows the distribution of infection between core and non-core groups in both the standard infection class I_1 and the observed infection class I_2 . After the initial rise of cases into the previously empty I_2 class, figure 3.6 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 3.6. A full

figure of each core/non-core infection class can be seen in additional appendix graph A.7.

Despite figures 3.1-3.6 demonstrating changes in population levels over time for differing screening and re-screening rates, population levels are not the best measure of control methods.

3.1.3 Prevalence, Incidence, and Positivity

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.

Prevalence

As defined in definition 2.1, prevalence is the proportion of individuals infected and is calculated as $\frac{I+T}{N}(t)$. It is often used as an estimate of how common a disease is within a population over a period of time. Although T has been previously defined as a separate class from I , individuals within T are currently undergoing treatment and still carry the infection, though they do not spread it as are told to abstain from sex. They are therefore included when calculating prevalence, as it is a measure of how much infection is present. By comparing levels of screening it is possible to predict the impact of different screening techniques on overall infection within the population.

With the only active control method being national screening fixed at 16% coverage, prevalence will reduce to its equilibrium value over time, as seen in additional appendix figure A.8. This is not unexpected as it is simply following the dynamics already shown in figures 3.1. By now introducing targeted re-screening, not only can the reduction in prevalence as a result of the additional control measure be seen, but also the speed of the reduction.

Figure 3.7 shows that by including targeted re-screening on a population with a fixed 16% national screening coverage, larger reductions in prevalence occur at a significantly faster rate, particularly between 0% and 50% re-screening. As figure 3.7a depicts, to achieve a reduction to 7.25% would take approximately 3 years when using 16% national screening coverage with no re-screening, however when half of those screened return for a second screening after 4 months (attendance of re-screening at 50%) the same reduction is achieved after only 530 days, under half the time required beforehand. By increasing attendance of re-screening to 100% this time continues to drop (though at a slower rate) to approximately 460 days. In addition, previously unattainable rates

3.1. Deterministic SITS Model with National Screening and Targeted Re-screening

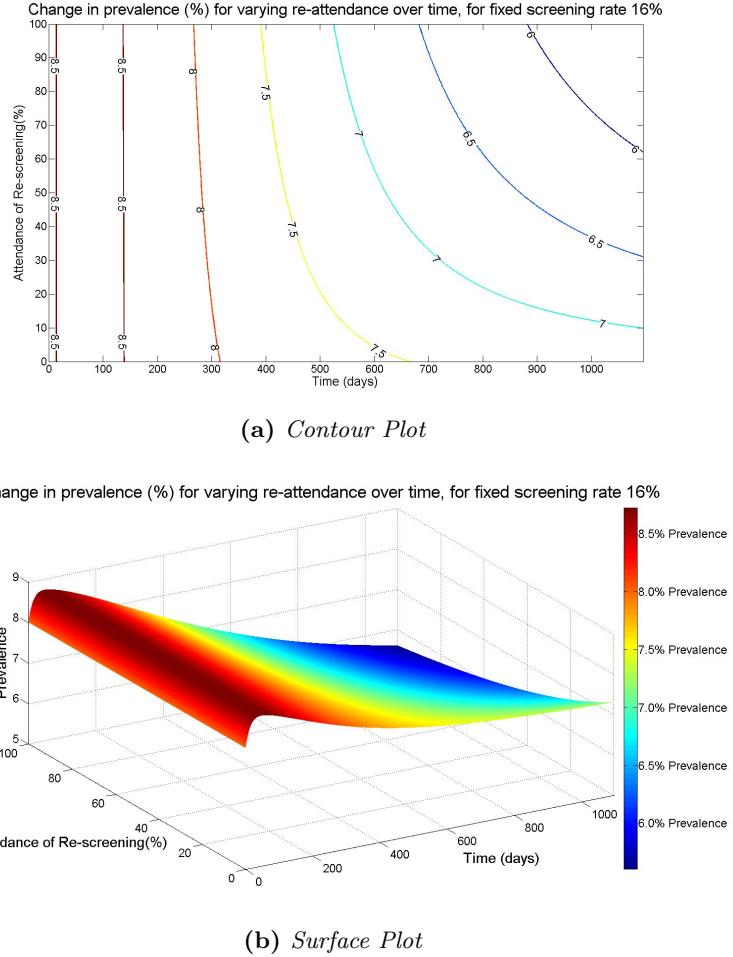


Figure 3.7: Change in prevalence over 3 years with national screening at 16% and re-screening at 0-100%. The M-file can be found in appendix B.2.3

of prevalence, such as a reduction to 6%, can now be reached with higher rates of re-screening attendance. Greater rates of reduction can also be seen by combining increased national screening coverage with varying rates of re-screening attendance over time, as can be seen in additional appendix figure A.9.

Examining changes in prevalence based on varying screening and re-screening rates is perhaps best compared via a contour plot with values taken after 3 years. Choosing to vary national screening coverage between 10% (below the current average of 16%) and 43% (the target suggested by Turner and Adams [37]), and re-screening attendance between 0% (re-screening is not used) and 100% (re-screening is mandatory) results in the reductions seen in figure 3.8.

Unsurprisingly, figure 3.8 shows that lowest rates of prevalence are achieved at the high-

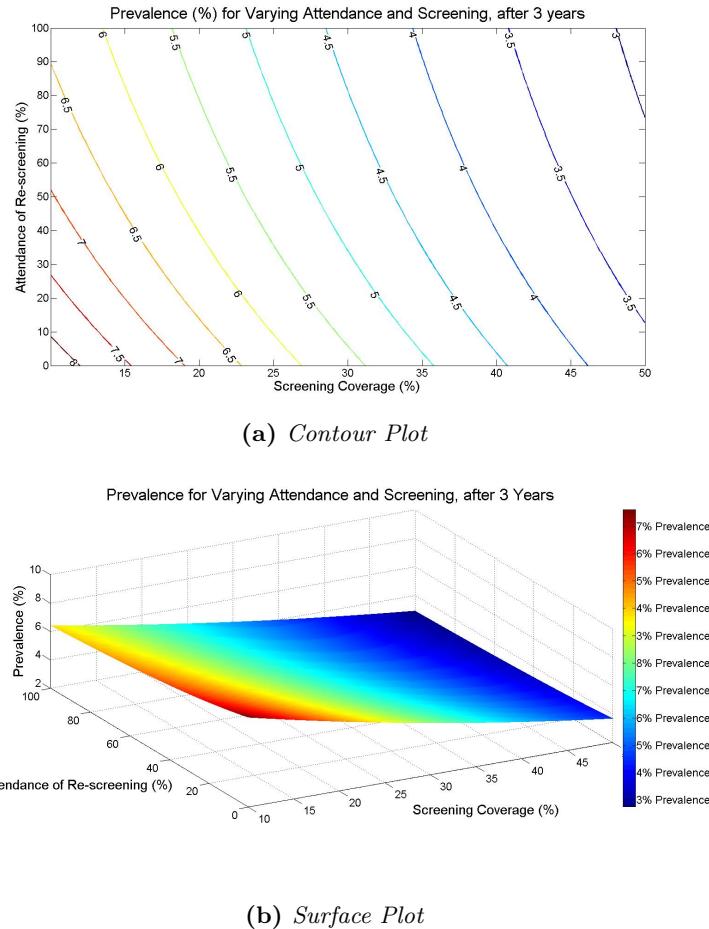


Figure 3.8: Reductions in prevalence for variable screening and re-screening after 3 years. The M-file can be found in appendix B.2.5

est levels of screening coverage (50%) and re-screening attendance (100%), allowing an unprecedented reduction to 3% prevalence. However, considering that currently the NCSF 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 3.8a 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 3.8a 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.

Take 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%, na-

3.1. Deterministic SITS Model with National Screening and Targeted Re-screening

tional 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 $2.25 \times$ 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. In terms of numerics, assuming the population $N = 10000$, an increase from 16%-36% coverage would require an additional 2000 individuals screened per year, of whom may not initially be interested in chlamydia screening, whilst an increase from 16%-24% with 100% re-screening attendance would require an additional 800 individuals taking two screens per year resulting in an extra 1600 screens, of whom will have already experienced screening once and hence understand the necessities of it.

An extension of this is to consider prevalence for the core/non-core model (2.11)-(2.22), where, due to the increased infection levels of core individuals seen in figures 3.5 and 3.6, the additional assertion that re-screening attendance for core members is always greater than re-screening attendance for non-core members, though it averages to the same attendance used in figure 3.8. This can be achieved using equation (3.1).

$$\hat{g} = 0.1\hat{g}_c + 0.9\hat{g}_{nc} \quad \text{where } \hat{g}_c > \hat{g}_{nc} \quad \forall \hat{g}, \hat{g}_c, \hat{g}_{nc} \in [0, 1] \quad (3.1)$$

As was done for prevalence in figure 3.8, screening coverage and re-screening attendance are varied across values of 10%-50% coverage and 0%-100% attendance. This is then overlaid on top of the prevalence contour plot seen in figure 3.8a to compare differences in prevalence levels. The resulting plot can be seen in figure 3.9.

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 (3.1) they cannot be fixed to any value. Therefore, \hat{g}_c and \hat{g}_{nc} are calculated by a pseudo shooting method. For each level of attendance $\hat{g} \in [0, 1]$, \hat{g}_c is looped through all possible values between [0,1]. For each of these \hat{g}_c values, the inbuilt function `fzero` is

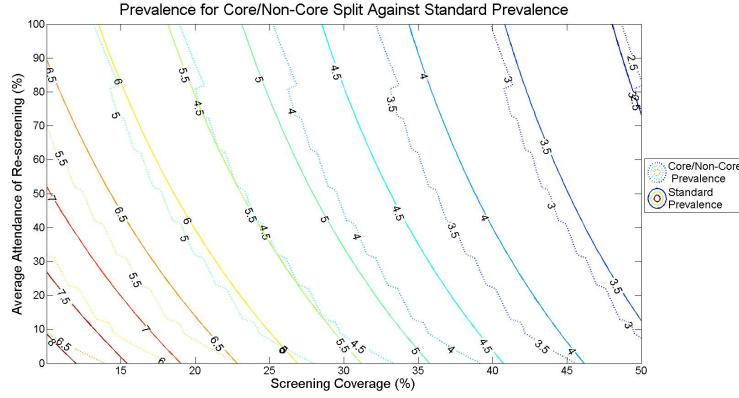


Figure 3.9: Prevalence when $\hat{g}_c > \hat{g}_{nc}$ against standard prevalence. Dashed lines denote when $\hat{g}_c > \hat{g}_{nc}$, solid lines represent standard prevalence shown in figure 3.8. The M-file can be found in appendix B.2.6

used to solve equation 3.1 for \hat{g}_{nc} by altering \hat{g}_{nc} values between [0,1]. If this \hat{g}_{nc} is less than the current \hat{g}_c then it is stored and used to calculate prevalence for the current attendance \hat{g} , however if not then it moves to the next $\hat{g}_c \in [0, 1]$. This can be seen in the M-file located in appendix B.2.6.

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.

Incidence

Unlike prevalence, which measures the total proportion of infection in a population, incidence measures the rate of occurrence of new cases of infection. It is defined as:

Definition 3.1 (Incidence):

The number of new cases within a population in a given year:

$$\int_{t_i}^{t_{i+1}} \sum_{j=1,2} \beta_j k_j S_j^{c+nc} \frac{I^{c+nc}}{N}$$

Whilst prevalence indicates how widespread the infection is within the population, incidence conveys information about the potential risk of contracting the infection. Incidence gives an indication of disease turnover, which can impact the efficacy of control

3.1. Deterministic SITS Model with National Screening and Targeted Re-screening

methods [48] [45]. Therefore it is important to ensure a good match between model and real incidence. For this reason is it often important to analyse both prevalence and incidence when examining potential chlamydial control methods.

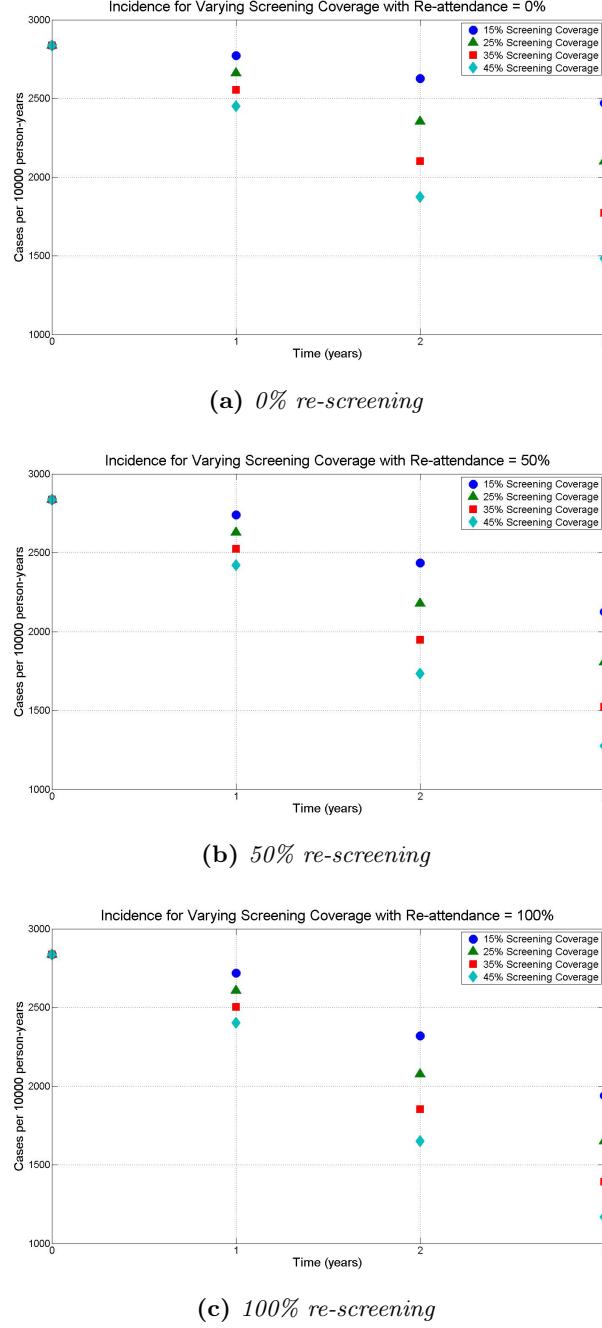


Figure 3.10: Incidence levels over 3 years for varying screening coverage with 0%, 50%, 100% re-screening. The M-file can be found in appendix B.2.4

The values shown in figure 3.10a act as baseline values before the introduction of targeted re-screening. It is possible to compare these values to both similar studies and

real world data in order to assess the quality and accuracy of the model. When comparing three different individual based models, Kretzschmar *et al.* found that incidence fell between 500 and 4000 cases per 10000 person-years for the 16-24 age cohort, whilst Batteiger *et al.* found real world incidence to be approximately 3400 cases per 10000 person-years [48] [53]. The initial baseline value of 2825 cases here falls somewhere between the HPA and ClaSS models, with average values slightly higher than those of the HPA model, yet lower than those of the ClaSS model [48]. Furthermore, attention is drawn to a recently published study into repeat chlamydia testing in young adults, the first investigation of its kind [54]. With 60% re-screening attendance 3 months after initial screening (at 16% screening coverage), the authors found incidence of new cases to be 1840 per 10000 person-years [54]. 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, (2.11)-(2.22), and both published individual based models and real world data, suggesting the compartmental model accurately represents chlamydial dynamics and potential risk of contracting the infection.

Comparing figures A.9 and 3.10 shows that incidence follows a similar pattern to prevalence, with the largest reductions in incidence occurring at high levels of national screening combined with high re-attendance rates. Previously, when examining prevalence, it was shown that a reduction to 5% could be achieved by either increasing screening to 36% with 0% re-screening, or by increasing screening to 24% with 100% re-screening. A similar relationship can be seen in figures 3.10a and 3.10c. In figure 3.10a, after 3 years of screening coverage at 35% with 0% re-screening, the number of cases per 10000 person-years drops from 2825 to approximately 1800. Whilst in figure 3.10c, after 3 years of screening coverage at 25% with 100% re-screening, the number of cases per 10000 person-years drops from 2825 to approximately 1650, mirroring the relationship seen with prevalence.

Positivity

In recent years positivity has become a deciding factor in the analysis of potential chlamydia control schemes. Positivity is a measure of the proportion of positive results (i.e. screens of infected individuals) seen per screen per year, and has become one of the most important quoted statistic for screening programmes.

When calculating positivity, the treatment class T is not included since individuals undergoing treatment will not be screened. In terms of the model presented here, positivity for screening can be separated into positivity of national screening, and positivity of re-screening, as it is likely to see differing values for the two.

3.1. Deterministic SITS Model with National Screening and Targeted Re-screening

Definition 3.2 (Positivity of National Screening):

$$Pos_{NS} = \frac{1}{365} \int_{t_i}^{t_{i+1}} \frac{I_1^{c+nc} + I_2^{c+nc}}{S_1^{c+nc} + S_2^{c+nc} + I_1^{c+nc} + I_2^{c+nc}} dt$$

Definition 3.3 (Positivity of Targeted Re-screening):

$$Pos_{TR} = \frac{1}{365} \int_{t_i}^{t_{i+1}} \frac{I_2^{c+nc}}{S_2^{c+nc} + I_2^{c+nc}} dt$$

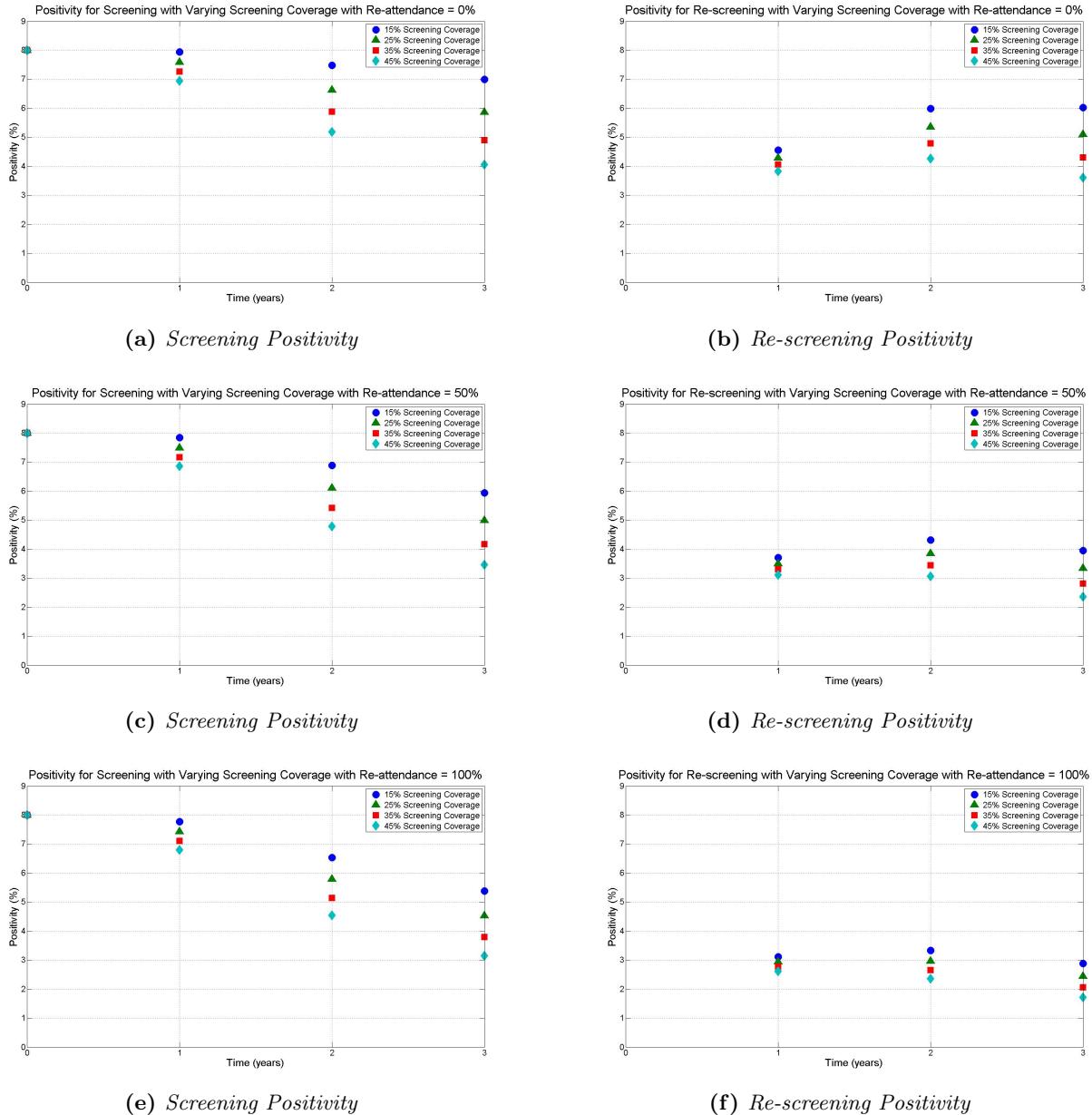


Figure 3.11: Positivity for national screening and targeted re-screening

Positivity is able to provide a clear indication of where screening and re-screening are most effective. Figures 3.11a, 3.11c, 3.11e show positivity values for national screening closely following a similar pattern as prevalence, figure A.9, with lower positivity values corresponding to lower prevalence values. As figures 3.11a, 3.11c, 3.11e show, these lower values are achieved at higher levels of both screening and re-screening, where there is less infection present in the population, hence seeing a reduced number of positive screens. Figures 3.11b, 3.11d, 3.11f suggest a significantly different story for re-screening positivity. For low levels of screening coverage and re-screening attendance, figure 3.11b, positivity initially sees a rise, due to the observed classes S_2, I_2 gaining individuals from their initial state of $(S_{20}, I_{20}) = (0, 0)$ as the system moves to equilibrium. After this, depending on levels of screening and re-screening, positivity may plateau (figure 3.11b) or decrease to lower levels (figure 3.11f), corresponding with reduced prevalence due to lack of infection.

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 3.11 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 effected, 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.

Comparing positivity levels of baseline national screening before re-screening, figure 3.11a, against real world data can also assist in analysing the accuracy of the model. In an annual report by the NCSP, which assessed data collected from participating clinics between 2008/09 (4 years after its launch), they found positivity among individuals aged 15-24 years to be 7.2%, for an average 16% screening coverage across the UK, with lower and upper positivity limits of [2.5%,8.5%] depending on age and sex [28]. This compares favourably to figure 3.11a, where after 3 years with screening coverage at 15%, positivity is approximately 7%, but reaches as high as 8% in earlier years, suggesting an adequate representation of the real world scenario.

3.2 Cost Analysis

Although analysing control strategies in terms of prevalence, incidence and positivity provide many ways in which to compare the effectiveness of potential control strategies;

due to the public health aspect of this project, it is necessary to consider monetary costs associated with different control schemes. Using the model, (2.11)-(2.22), and making use of a published costings tool [55], it is possible to allocate costs to differing levels of screening, performing a cost-effective analysis of the model to explore the economic impact of changes to national screening and targeted re-screening. Since financial resources are assumed to be limited, the cost analysis aims to advise PCT's on distribution of wealth over the two schemes.

3.2.1 Costs

The cost analysis here aims to analyse the potential costs of running either chlamydia schemes to a governing body, such as a local PCT. Therefore, despite costs being associated with both the running of the service and treatment of infection, cost of treating infection or developing conditions will not be included here, as the model concerns itself with the cost of increased screening, not treatment.

The cost of a single screen incorporates the use of screening facilities, analysis of samples, and notification of result, and has been estimated at approximately £43.65 per individual per screen, though recent studies have suggested this could be as low as £32.01 [55]. This costing applies to both a standard screen, and re-screening as it is assumed that screening conditions, such as time taken, are uniform across all screens.

In order to consider the additional costs of re-screening it is necessary to understand how re-screening would be implemented in a clinical setting, if it were to become common policy. Targeted re-screening only picks out individuals in the observed classes S_2, I_2 , those individuals who have recently been treated for chlamydia infection. Since all suspected infected individuals can only move into the treatment class T once they have received a positive chlamydia screen, it is assumed that these individuals will at one point find themselves in their local clinic, either for testing or results. Although there has been recent promotion for ‘test at home’ chlamydia kits, the model does not differ screening between the widely used in clinic NAAT chlamydia screen, and take home kits. Therefore it can be assumed every individual who is tested will visit a clinic. Furthermore, those who test positive for infection are generally required to return to the clinic for advice and treatment [56]. For ease of appointment booking it would make most sense for positivity tested individuals to book a re-screen for 4 months later whilst visiting the clinic, saving on additional expenses of phone calls and making use of current administration and booking services already in effect. Despite this, a small additional cost of £2.76 per re-screen shall be added to account for the initial contact and extra administration costs required, mirroring the initial contact cost for partner notification used by Turner *et al.* [55]. On top of this, in recent years

there has been a rapid increase in the use of automated text messaging services to remind individuals of appointments ahead of time. The NHS has been one to take advantage of this and since 2004 has made use of a 10p per text outpatient reminder service [57]. To maximise attendance of re-screens it is recommended that all individuals receive a single text reminder ahead of screening, as well as an extra reminder to those who miss appointments asking to rebook. These costs are summarised by the table of costs, 3.2. This enables costs to be expressed as a linear equation dependent on screening coverage $365g$ and re-screening attendance \hat{g} , as seen in equation (3.2).

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 3.2: Costs of control strategy

$$\begin{aligned} Cost(g, \hat{g}) = & 43.65(S_1(t) + S_2(t) + I_1(t) + I_2(t))g \times 365 \\ & + (2.76 + 0.10 + 43.65\hat{g} + 0.1(1 - \hat{g}))(S_2(t) + I_2(t)) \end{aligned} \quad (3.2)$$

3.2.2 Cost and Cost-Effectiveness of Model

In order to compare with both prevalence and numerical results of similar studies, costs are taken at the end of year 3, as the system approaches equilibrium, and are considered for ranges of screening coverage from 10%-50% and ranges of re-screening attendance from 0%-100%. This leads to the cost figure 3.12.

Since cost is simply a linear equation with increased monetary value assigned to re-screening, the relationship seen in figure 3.12 is not unexpected, with the largest costs assigned to higher levels of combined screening and re-screening. Examining screening coverage at 16% with re-screening attendance at 0% yields a figure of £68706.53 per day, as can be seen in figure 3.12. Setting identical parameters and making use of the costings tool published by Turner *et al.* results in a similar figure of £69840.00 per day, demonstrating a close likeness between the model costs, and published costing tools.

Further information can be gained by assessing the changing cost effectiveness of the model over varying coverage and attendance. Cost effectiveness is a measure of cost per health benefit, in this case positive screening and treatment of infection, and has become widely used in public health settings. It allows for multiple health campaigns

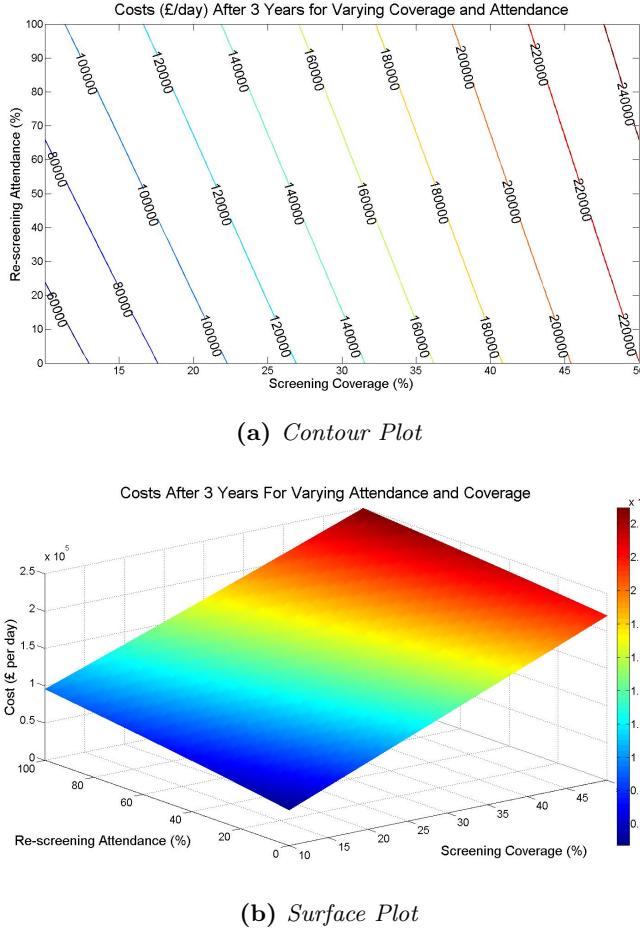


Figure 3.12: Costs per day for varying levels of screening coverage and re-screening attendance. The M-file can be found in appendix B.2.5

to be compared on a price per benefit scale, and can be calculated by equation 3.3.

$$CostEff(g, \hat{g}) = \frac{Cost(g, \hat{g})}{Pos_{NS} \times (N - T(t))g365 + Pos_{TR}(S_2(t) + I_2(t))\hat{g}} \quad (3.3)$$

Using positivity values shown in figure 3.11 it is possible to plot cost effectiveness for varying coverage and attendance values with ranges of 10%-50% and 0%-100% respectively. This can be seen in figure 3.13, where increased combined coverage and attendance results in sufficiently higher costs per positive screen. This is due to higher levels of screening and re-screening reducing overall prevalence, as seen in figure 3.8. Therefore, cost per positive screen increases as infection becomes rare, and more resources are wasted on negative screens in attempts to detect remaining infection. Baseline values of the model at 16% screening with 0% re-screening shows a cost efficiency of £626.00 per positive screen. As before, comparing this with Turner's costings tool by setting identical parameters gives a result of £623.57 per positive screen, showing a

close similarity between the two models [55].

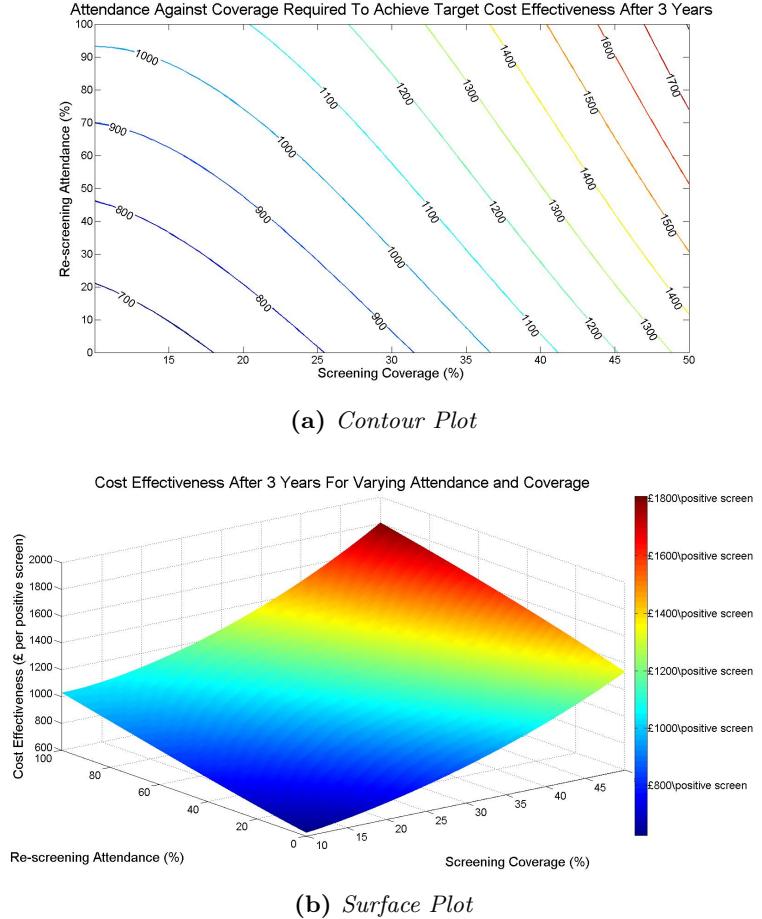


Figure 3.13: Cost effectiveness (£ per positive screen) for varying levels of screening coverage and re-screening attendance. The M-file can be found in appendix B.2.5

It is important to not only assess the cost effectiveness of a control scheme in terms of cost per screen, but also in comparison to reductions in prevalence achieved by said scheme. A control scheme that greatly reduces prevalence is unlikely to be taken on in a public health setting if the cost effectiveness is too high. Overlaying the prevalence figure 3.8a onto the cost effectiveness contour 3.13a gives an accurate representation of the prevalence:cost effectiveness ratio as can be seen in figure 3.14.

Figure 3.14 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 approx-

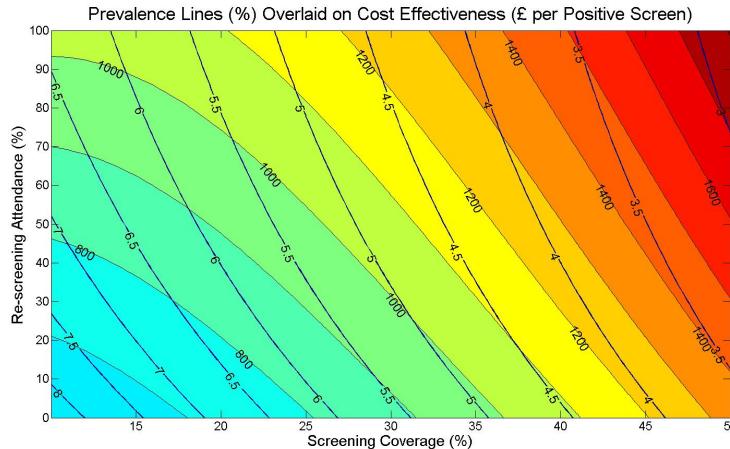


Figure 3.14: Prevalence (%) (lines) overlaid onto cost effectiveness (£ per positive screen) (filled blocks) for varying screening coverage 10%-50% and re-screening attendance 0%-100%. The M-file can be found in appendix B.2.5

imately £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, considering the ideas discussed in §3.1.3; 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.

Chapter 4

Discussion

In this project a deterministic compartmental model was constructed to assess the spread of the chlamydia infection through a population of 16-25 year old sexually active individuals. The model was used to explore and investigate the impact of two control strategies, the currently used National Chlamydia Screening Programme and a potential new strategy, targeted re-screening on previously infected individuals. By comparing levels of infection, prevalence, incidence, positivity, cost and cost effectiveness, caused by differing efficacy, the model considered how the potential scheme of targeted re-screening could benefit a public health setting.

4.1 Mathematical and Biological Conclusions

As with all mathematical models, any results gained can only be interpreted in light of the core assumptions made. Despite this, the analysis of the model shown in §3 allows for a number of conclusions to be discussed, and the development of further work based on the ideas and concepts presented here.

Analysis of the model demonstrated that for any combination of screening coverage and re-screening attendance over 16% coverage and 0% attendance (representative of the current levels seen in UK clinics), health authorities would see a reduction of infection within the 16-25 year old sexually active community. The highest levels of prevalence (8.25%) were shown to exist at the lowest levels of screening coverage (10%) with no attempt at re-screening, representing areas of the country where coverage falls below the national average. While the lowest levels of prevalence (3%) were seen at the highest levels of combined coverage (50%) and attendance (100%). While higher levels are clearly the most effective in reducing long term prevalence, these targets may be unrealistic, especially when compared to the current levels of screening. This was highlighted as a benefit of using targeted re-screening in conjunction with national screening. Large increases in national screening could be offset by smaller increases in

targeted re-screening to obtain similar reductions in prevalence.

Prevalence is one of many analytical tools used by health authorities to assess the potential application of chlamydial control schemes, and should not be solely relied on to explore the impact of suggested strategies. Therefore incidence, the number of new cases per year, was also used to ascertain the effect of targeted re-screening on new cases per 10,000 person-years. It was shown that targeted re-screening would greatly reduce incidence, regardless of national screening coverage. Lowest incidence levels appeared after 3 years of constant national screening coverage at 45% and re-screening attendance at 100%, however significant reductions could be seen with as little as 50% attendance. Baseline incidence values from the model were also compared to both published studies and clinical data, and were found to show a close synergy between published values and those outputted by the model. Incidence values at 16% screening coverage and 60% re-screening attendance were also compared to a recent study on repeat chlamydia screening of young adults in england, and were found to differ by only 10.1%.

Along with prevalence and incidence, positivity has become a deciding factor in assessing the effectiveness of potential chlamydia control schemes. This was explored in terms of both national screening and targeted re-screening and it was shown that, whilst screening positivity was greatly reduced by both increased screening coverage and re-screening attendance, increased screening coverage had little effect on re-screening positivity. Baseline positivity values from the model were compared against published data, finding a close similarity between model values and those published by the National Chlamydia Screening Programme. Together with the likeness shown in incidence between published and model data, this supports the model as an accurate and robust representation of real world chlamydia dynamics in a sexually active young adult population.

As well as considering the implications of running targeted re-screening as a new control strategy on prevalence, incidence and positivity; the effect of introducing this new scheme into an already established population undergoing national screening was explored. The model showed that for all levels of re-screening attendance, clinics would initially see an influx of new patients due to the increased number of screens, however after 129-150 days of the new strategy, this level would drop below the baseline of 0% attendance due to reductions in prevalence, taking a total time of approximately 400 days since implementation to compensate for the initial increase in recognised cases.

A core/non-core divide by sexual activity was also explored in terms of population and

infection levels. It was shown that despite the core group representing only 10% of population, after 3 years it was responsible for approximately 32% of infection. Infection within the observed infection class I_2 was also shown to become heavily saturated with those core infectious individuals over time, due to high likelihood of re-infection during the observation period as a result of increased sexual activity levels. Further reductions in prevalence were shown to be obtainable when ensuring attendance for core individuals was greater than attendance for non-core individuals, as this diverted some re-screening efforts from non-core individuals to the more frequently infectious core individuals, further reducing prevalence.

As with all infection control strategies, along with effectiveness in reducing infection of current and new cases, a crucial deciding factor as to whether a potential strategy should be implemented into clinical practice is the cost of said strategy to the public health services. A scheme that is too expensive or cost inefficient is unlikely to be considered as a viable control strategy for the spread of chlamydia, despite how effective it may be at reducing infection. This was considered for the model at hand by linking to a previously published costings tool currently used by health care providers [55]. Cost effectiveness was then compared to prevalence values to analyse the different prevalence levels associated with varying cost effectiveness, dependent on screening coverage and re-screening attendance. It was shown that although cost (£) per positive screen was higher when implementing targeted re-screening, the additional cost was marginal, and could be less than the additional resources required to increase national screening. Baseline costs from the model were also compared to the published costings tool, and demonstrated a close resemblance between simulated and published data.

4.1.1 Limitations

Although many of the results discussed here show promise, the model has been limited by a number of factors. As with the assumptions outlined in §2.1.1, limitations must be considered in order to understand how the model could apply to a real world scenario.

As mentioned in §1, chlamydia is most frequently asymptomatic in females. However the model here does not distinguish between genders and assumes an even mixing of male and female individuals. As such many parameter values, have been averaged over both male and female values. Dividing the model by gender would allow for a more accurate representation of parameter values, and due to higher asymptomatic rates, is likely to show higher levels of infection becoming present in the female infection classes than those in the male group.

The population is assumed to have some heterogeneous mixing, but with each indi-

vidual forming sexual partnerships without preference. In model (2.5)-(2.10) this is defined as each individual having $k = 2.07$ partners at any time, though this is later refined for the core/non-core model (2.11)-(2.22) to having $k_1 = 5.76$ for core individuals, and $k_2 = 1.66$ for non-core individuals. Assuming individuals interact in the same way is unrealistic. Though some heterogeneity is allowed for by the core/non-core sexual activity divide, a truly heterogeneous system allows differing values for each individual. Any individuals within a monogamous relationship with another uninfected partner will become isolated from the infection and the rest of the population, a concept explored by Chen *et al.* [36]. Similarly, it should also be considered that if on average each individual has 2.07 sexual partners, one partner may be more regularly seen, having more contact and greater chance of transmission if infected; whilst the second partner may only be seen at certain times. A more accurate scenario would be to further divide into more sexual activity classes or to allow for a more heterogeneous population.

Parameter estimation was paramount to this project. Values were fitted based on the best published data available at the time however there is still some uncertainty around certain quantities. This applies in particular to the costs of re-screening, since as a potential strategy not currently in clinical use, there is no costings data to base estimations on. Instead, estimations were based on the next closest thing, screening costs and with aspects taken from partner notification.

Despite these limitations, the model presented here has demonstrated targeted re-screening as a potentially viable new control strategy for the spread of chlamydia. Showing that with increased re-screening of previously infected individuals, it is able to greatly impact and reduce infection prevalence, incidence and positivity in a cost effective manner when combined with the already present National Chlamydia Screening Programme.

4.2 Future Work

Although this project has reached many conclusions regarding the impact of targeted re-screening on chlamydia infections, there is still some scope for future work. Future work should aim to solve the limitations mentioned, with perhaps the greatest addition being an extended clinic trial of targeted re-screening, in a similar vein as the recently published study by Woodhall *et al.* [54]. However a wider range of re-screening attendance values should be chosen, of which to compare the model against.

The model could also be further refined to more accurately represent chlaymdial dynamics and improve parameter estimation. As mentioned in §4.1.1, a large limitation

with the model was the assumption of random mixing within the population. The next logical step in the future models should be to adapt the system equations (2.11)-(2.22) into a pairwise approximation model. Ideally this would have been incorporated here, however due to the size of the model, computational power, and time available, this was not possible. Although a pairwise adaption of the model would allow for network elements to be included, these have been shown to be most beneficial when assessing strategies involving contact tracing along partnership connections, of which this model does not do [40]. Therefore despite pairwise models often being preferred over compartmental models, the lack of one is not greatly detrimental to the results shown in this project.

4.2.1 Extensions and Applications to Other Areas

Ignoring the unavoidable increase in complexity caused by extensions to the model, there are many possible avenues of development available for future expansions to the model. It would be possible to alter the model to include differences between genders. This would require subdividing the population by gender, resulting in twice as many equations as shown in (2.11)-(2.22), but would allow for a more detailed parameter estimation and exploration into infection differences as outlined in §1.1. This would enable the control strategy to be assessed in terms of not only core and non-core members (figure 3.9), but of gender and gender-core combinations, in a similar vein as Hethcote and Yorke [30].

Similarly, the infection classes $I_1^c, I_1^{nc}, I_2^c, I_2^{nc}$ could be subdivided into either symptomatic or asymptomatic states, since chlamydia is frequently asymptomatic. This would allow for prevalence to be explored in terms of the rate at which individuals become symptomatic or asymptomatic. It is likely that this would result in greater reductions in prevalence seen for higher rates of symptomatic infection, since asymptomatic individuals do not actively seek treatment. This would also allow for additional concepts not considered in this model, such as any immunity gained for individuals who clear infection naturally, to be explored explicitly.

A key limitation of the model is the limited amount of heterogeneity, as discussed in §4.1.1. The model could be extended to allow for further heterogeneity within the population by taking the metapopulation approach and forming several smaller homogeneous populations (similar to the core/non-core approach) with certain individuals forming connections between.

With all these extensions, the model would likely become more accurate and provide improved guidance to public health services at the cost of computational intensity.

Until this can be achieved, the model and approached detailed in this project can still provide adequate comparisons that will help to assess the potential of targeted re-screening as an opportunistic control strategy for chlamydia infections.

Although this model was built with chlamydia infection in mind, it can be easily adapted to represent gonorrhoea by a simple change in parameter estimations. It would not be able to be used for incurable infections such as HIV as the system requires individuals to return to a susceptible state, however is equally applicable to any re-occurring infection (both sexual and non-sexual) that requires direct contact for infection to spread, and with a little work could be altered for infections such as candidiasis (thrush).

4.3 Recommendations

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.

The model considered ranges of screening coverage from 10%-50% and re-screening attendance from 0%-100%. 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 3.8) and incidence (figure 3.10) 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 3.9). 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 3.14). 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.

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Appendix A

Additional graphs

Unfortunately due to the limitations of this thesis not all graphs could be included in the main body of text. Provided here are additional graphs that while may be useful, are not necessary for the understanding of the main content.

A.1 Sensitivity of β_2 , r_2 , d_2

Despite figure 2.4 displaying the impact of variations of β_2 , r_2 , d_2 to the baseline estimates on the endemic equilibrium, due to scale figure 2.4 may appear unclear. Provided here are some additional, more detailed graphs, for the sensitivity analysis of β_2 , r_2 , d_2 .

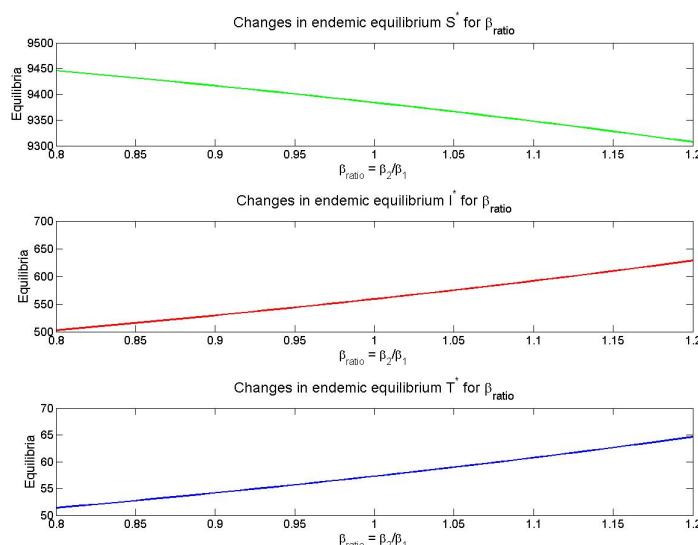


Figure A.1: Impact of varying β_2 on individual endemic steady state values (S^* , I^* , T^*), with r_2, d_2 fixed at baseline values. The M-file can be found in appendix B.2.1

Figure A.1 shows the same results as figure 2.4a at a larger scale and divided into each

infection class.

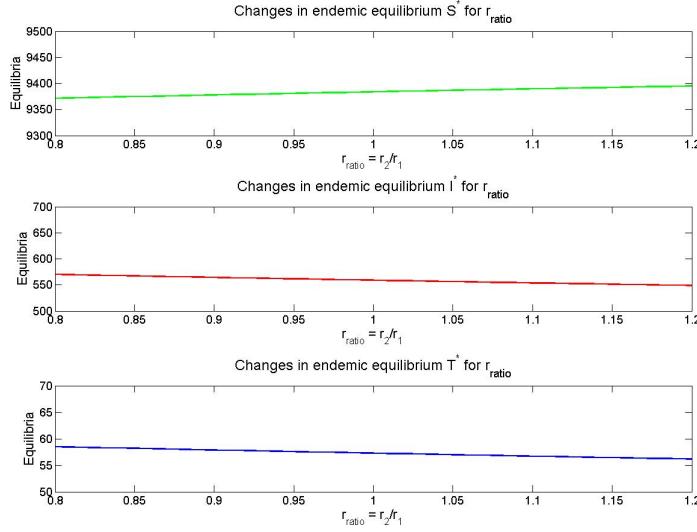


Figure A.2: Impact of varying r_2 on individual endemic steady state values (S^*, I^*, T^*), with β_2, d_2 fixed at baseline values. The M-file can be found in appendix B.2.1

Figure A.2 shows the same results as figure 2.4b at a larger scale and divided into each infection class.

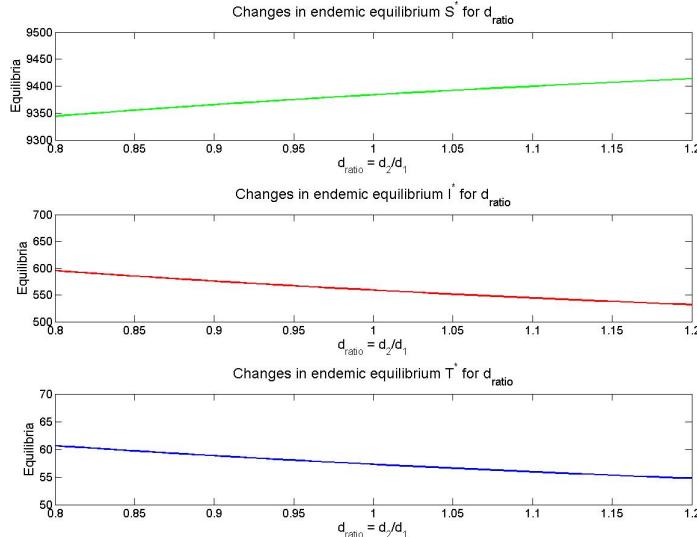


Figure A.3: Impact of varying d_2 on individual endemic steady state values (S^*, I^*, T^*), with β_2, r_2 fixed at baseline values. The M-file can be found in appendix B.2.1

Figure A.3 shows the same results as figure 2.4c at a larger scale and divided into each infection class.

A.2 Population Graphs

Since population level graphs provide little information when compared to graphs of prevalence, incidence and positivity, they are not required for the general understanding of the project. However, they may add a layer of clarity to the population dynamics at play and hence are provided here.

A.2.1 Base SITS System (2.1)-(2.4)

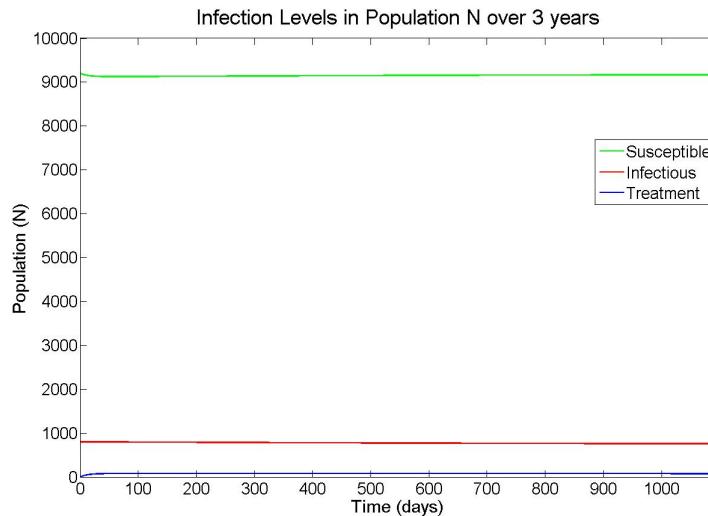


Figure A.4: Base deterministic SITS population model with national screening at 16%. The M-file can be found in appendix B.1.1

Figure A.4 shows the same results as figure 3.1 however with infection classes plotted on the same scale.

A.2.2 Extended SITS System (2.5)-(2.10)

Figure A.5 shows the same results as figure 3.2 however with infection classes S and I split into S_1, S_2 and I_1, I_2 .

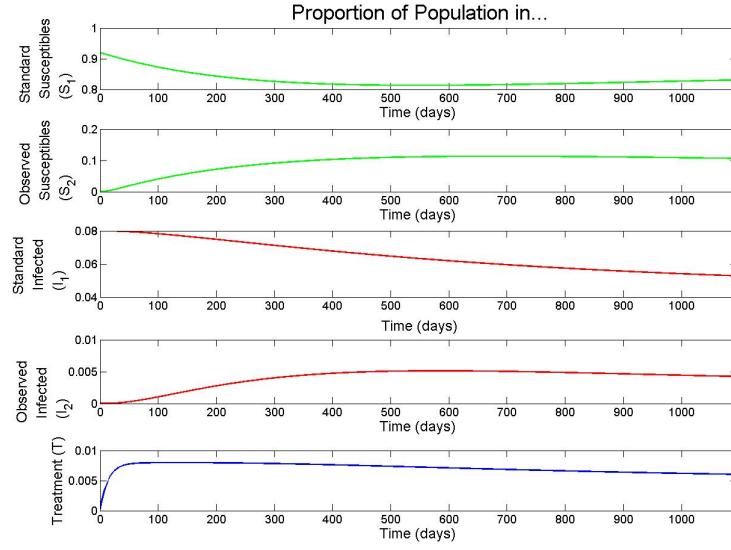


Figure A.5: Proportion of population in (S_1, S_2, I_1, I_2, T) classes with national screening at 16% and targeted re-screening at 50%. The M-file can be found in appendix B.1.2

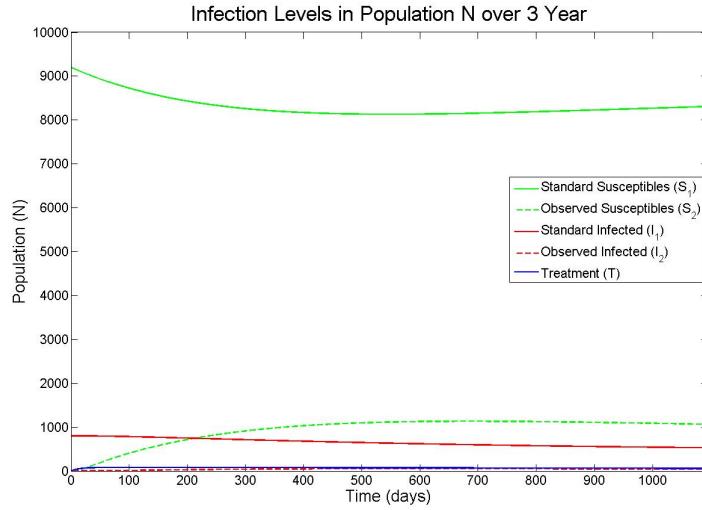


Figure A.6: Extended deterministic SITS population model with national screening at 16% and targeted re-screening at 50%. The M-file can be found in appendix B.1.2

Figure A.6 shows the same results as figure A.5 however with infection classes plotted on the same scale.

A.2.3 Core/Non-Core SITS System (2.5)-(2.10)

Figure A.7 shows all infection classes S_1, S_2, I_1, I_2, T divided into core/non-core groups, plotted on the same scale.

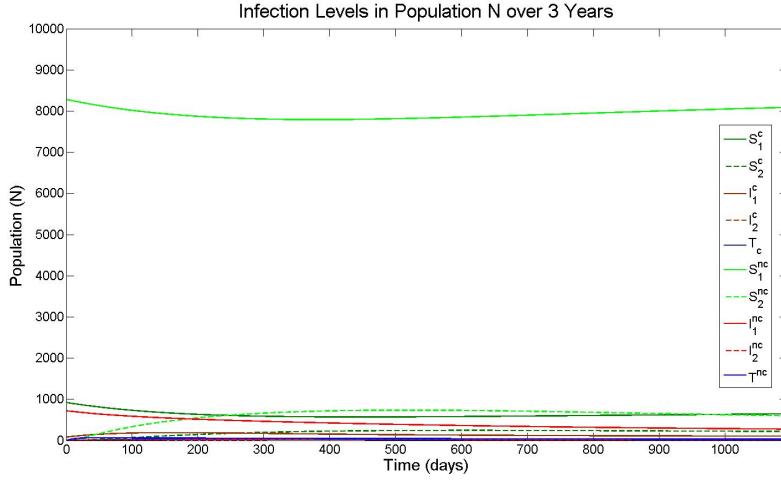


Figure A.7: Core/non-core deterministic SITS population model with national screening at 16% and re-screening at 50%. The M-file can be found in appendix B.1.3

A.3 Prevalence Graphs

Whilst the prevalence graphs seen in §3.1.3 show prevalence levels for varying screening coverage and re-screening attendance, the plots can be hard to read. The prevalence figures here show additional plots that may clarify any misinterpretation.

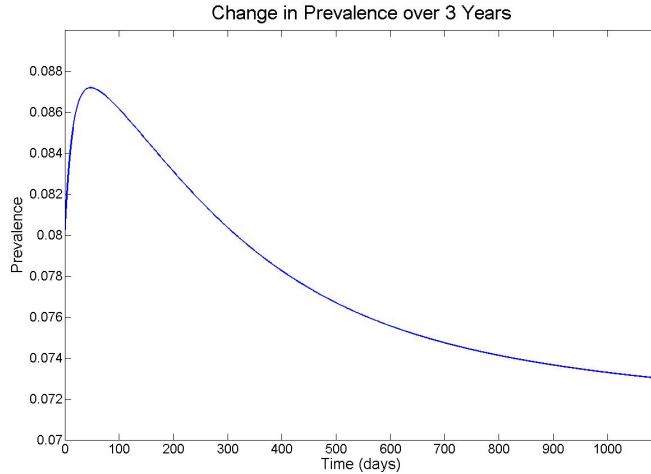
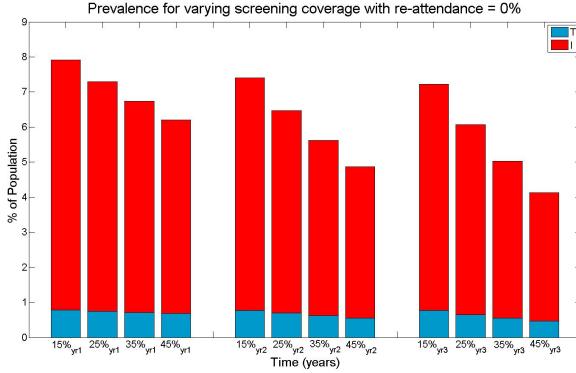
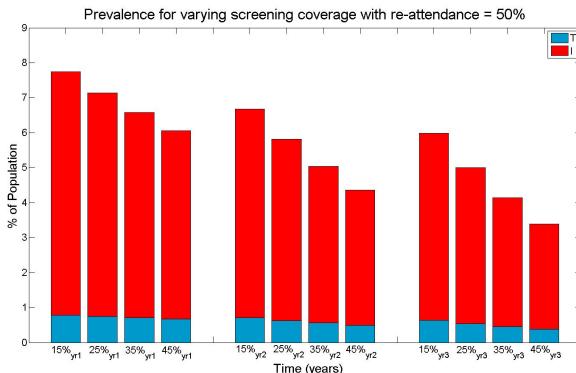


Figure A.8: Change in prevalence over 3 years with national screening at 16% and re-screening at 0%. The M-file can be found in appendix B.2.3

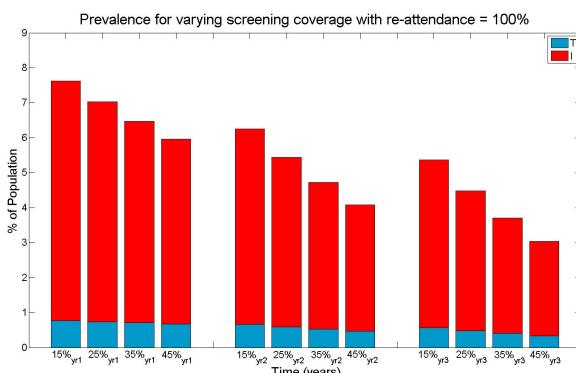
Figure A.8 shows baseline prevalence of national screening at 16% coverage, prior to the implementation of targeted re-screening, over 3 years.



(a) 0% re-screening



(b) 50% re-screening



(c) 100% re-screening

Figure A.9: Prevalence for varying screening and re-screening coverage over 3 years. The M-file can be found in appendix B.2.4

Figure A.9 shows prevalence at the end of each year for varying national screening coverage and re-screening attendance. This shows the same result as figure 3.8 however with addition times rather than only after 3 years. The highest reductions in prevalence are seen with both increased national screening, and high rates of re-screening attendance.

Appendix B

MATLAB codes

B.1 Functions to Model Different SITS Systems

B.1.1 Base SITS System (2.1)-(2.4)

```
%%%%%%
% Author: Joel Lutman
% MSc Mathematical Biology
% University of Bath
% Title: Function to simulate populations S,I,T for base SITS model
% Date: 09/09/2012
%
% Note: While this file is the authors own work, the code originates from
%       the MATLAB codes provided in Keeling & Rohani's "Modeling
%       Infectious Disease in Humans and Animals", however has been largely
%       changed to represent the model in hand.
%%%%%
function [t,S,I,T] = model1(alpha, beta, k, r, g, d, a, S_0, I_0, T_0, time, N)

% Sets up default parameters if necessary.
if nargin == 0
    alpha = 2.74*10^(-4); % Maturity rate
    beta = 0.0051; % Transmission rate
    k = 2.07; % Number of sexual partners
    r = 0.0023; % Natural recovery rate
    g = 4.77*10^(-4); % National screening rate
    d = 0.0067; % Rate at which symptoms appear
    a = 0.0714; % Rate of treatment
    N = 10000; % Population size
    I_0 = 0.08*N; % Initial infectious (8% prevalence)
    S_0 = N-I_0; % Initial susceptibles
    T_0 = 0; % Initial in treatment
    time = 3*365; % Runtime
end

Check(alpha,0,'alpha'); % Checks parameters for negative values.
Check(beta(:,1),0,'beta');
Check(k,0,'k');
Check(r(:,1),0,'r');
Check(g(:,1),0,'g');
Check(d(:,1),0,'d');
Check(a,0,'a');
Check(time,0,'time');
Check(S_0,0,'S_0');
Check(I_0,0,'I_0');

S = S_0; % Initialises populations
I = I_0;
```

```

T = T_0;

options = odeset('RelTol', 1e-4); % Uses ode45 on differential equation solver DiffSolv
[t, pop]=ode45(@DiffSolv,[0 time],[S I T],options, alpha, beta, k, r, g, d, a, N);

S = pop(:,1)./N; % Calculate proportion of populations
I = pop(:,2)./N;
T = pop(:,3)./N;

figure; % Plots S,I,T graphs with scaled colours
subplot(3,1,1) % against time
h=plot(t,S,'-g');
xlabel 'Time (days)';
ylabel 'Susceptible';
title 'Proportion of Individuals in...';
axis([0 time 0.91 0.92]);
subplot(3,1,2)
h=plot(t,I,'-r');
xlabel 'Time (days)';
ylabel 'Infected';
axis([0 time 0.075 0.085]);
subplot(3,1,3)
h=plot(t,T,'-b');
xlabel 'Time (days)';
ylabel 'Treatment';
axis([0 time 0 0.01]);

S = S.*N; % Back into population levels
I = I.*N;
T = T.*N;

figure; % Plots population levels against time
plot(t,S,'-g',t,I,'-r',t,T,'-b');
xlabel 'Time (days)';
ylabel 'Population (N)';
legend('S','I','T');
axis([0 time 0 10000]);
title 'Infection Levels in Population N over 3 years';

function dPop=DiffSolv(t, pop, alpha, beta, k, r, g, d, a, N)
    % Calculates the differential rates used in ode45
S = pop(1);
I = pop(2);
T = pop(3);

dPop=zeros(3,1); % Differential equations
dPop(1) = alpha*N + r*I + a*T - (alpha + k*beta*(I/N))*S;
dPop(2) = k*beta*S*(I/N) - (alpha + r + g + d)*I;
dPop(3) = (g+d)*I - (alpha + a)*T;

function []=Check(Par, Value, Name) % Check's for negative parameter values
m=find(Par<Value);
if length(m)>0
    error('%s(%g) (%g) is less than %g',Name,m(1),Par(m(1)),Value);
end

```

B.1.2 Extended SITS System (2.5)-(2.10)

```

%%%%%
% Author: Joel Lutman
% MSc Mathematical Biology
% University of Bath
% Title: Function to simulate populations S,I,T for extended SITS model
% Date: 09/09/2012
%
% Note: While this file is the authors own work, the code originates from
%       the MATLAB codes provided in Keeling & Rohani's "Modeling"

```

B.1. Functions to Model Different SITS Systems

```

% Infectious Disease in Humans and Animals", however has been largely
% changed to represent the model in hand.
%%%%%%%%%%%%%%%
function [t,S1,I1,T,S2,I2] = model2(alpha,beta,k,r,g_1,attendance,d,a,Mu,S1_0,I1_0,S2_0,I2_0,T_0, ...
time,N)

if nargin == 0
    alpha = 2.74*10^(-4);
    beta = [0.0051; 0.0051];
    k = 2.07;
    r = [0.0023;0.0023*1.1];
    g_1 = 4.77*10^(-4);
    attendance = 0.5;
    d = [0.0067;0.0067*1.1];
    a = 0.0714;
    Mu = 0.0055;
    N = 10000;
    I1_0 = 0.08*N;
    S1_0 = N-I1_0;
    S2_0 = 0;
    I2_0 = 0;
    T_0 = 0;
    time = 3*365;
end
gamma = 0.0082;
epsilon = (attendance*gamma)/g_1;
g = [g_1; (epsilon+1)*g_1];

Check(alpha,0,'alpha');
Check(beta(:,1),0,'beta');
Check(k,0,'k');
Check(r(:,1),0,'r');
Check(g(:,1),0,'g');
Check(epsilon,0,'epsilon');
Check(d(:,1),0,'d');
Check(a,0,'a');
Check(Mu,0,'Mu');
Check(time,0,'time');
Check(S1_0,0,'S_0');
Check(I1_0,0,'I_0');

S1 = S1_0;
S2 = S2_0;
I1 = I1_0;
I2 = I2_0;
T = T_0;

% Initialises populations

options = odeset('RelTol', 1e-4); % Uses ode45 on differential equation solver DiffSolv
[t, pop]=ode45(@DiffSolv,[0:1:time],[S1 I1 T S2 I2],options,alpha, beta,k, r, g, d, a, Mu, N);

S1 = pop(:,1);
I1 = pop(:,2);
T = pop(:,3);
S2 = pop(:,4);
I2 = pop(:,5);

S = S1+S2;
I = I1+I2;

figure;
subplot(5,1,1) % Plots S1,S2,I1,I2,T proportions with scaled
h=plot(t,S1./N,'-g'); % colours against time
xlabel 'Time (days)';
ylabel 'Standard\nSusceptibles\nnewline (S_1)';
title 'Proportion of Population in...';
axis([0 time 0.8 1]);
subplot(5,1,2)

```

```

h=plot(t,S2./N,'-g');
xlabel 'Time (days)';
ylabel 'Observed\nline Susceptibles\nline (S_2)';
axis([0 time 0 0.2]);
subplot(5,1,3)
h=plot(t,I1./N,'-r');
xlabel 'Time (days)';
ylabel 'Standard\nline Infected\nline (I_1)';
axis([0 time 0.04 0.08]);
subplot(5,1,4)
h=plot(t,I2./N,'-r');
xlabel 'Time (days)';
ylabel 'Observed\nline Infected\nline (I_2)';
axis([0 time 0. 0.01]);
subplot(5,1,5)
h=plot(t,T./N,'-b');
xlabel 'Time (days)';
ylabel 'Treatment (T)';
axis([0 time 0. 0.01]);

figure; % Plots population levels against time
plot(t,S1,'-g',t,S2,'--g',t,I1,'-r',t,I2,'--r',t,T,'-b');
legend('Standard Susceptibles (S_1)', 'Observed Susceptibles (S_2)',...
       'Standard Infected (I_1)', 'Observed Infected (I_2)', 'Treatment (T)');
xlabel 'Time (days)';
ylabel 'Population (N)';
axis([0 time 0 N]);
title 'Infection Levels in Population N over 3 Year';

figure; % Plots S,I,T proportions with scaled
% colours against time
subplot(3,1,1)
h=plot(t,S./N,'-g');
xlabel 'Time (days)';
ylabel 'Susceptible';
title 'Proportion of Population in...';
axis([0 time 0.91 0.94]);
subplot(3,1,2)
h=plot(t,I./N,'-r');
xlabel 'Time (days)';
ylabel 'Infected';
axis([0 time 0.055 0.085]);
subplot(3,1,3)
h=plot(t,T./N,'-b');
xlabel 'Time (days)';
ylabel 'Treatment';
axis([0 time 0 0.01]);

function dPop=DiffSolv(t, pop, alpha, beta, k, r, g, d, a, Mu, N)
    % Calculates the differential rates used in ode45
S1 = pop(1);
I1 = pop(2);
T = pop(3);
S2 = pop(4);
I2 = pop(5);

dPop=zeros(5,1); % Differential equations
dPop(1) = alpha*N + r(1)*I1 + Mu*S2 - (alpha + k*(beta(1)*(I1/N) + beta(2)*(I2/N)))*S1;
dPop(2) = k*S1*(beta(1)*(I1/N) + beta(2)*(I2/N)) - (alpha + r(1) + g(1) + d(1))*I1;
dPop(3) = (g(1)+d(1))*I1 + (g(2)+d(2))*I2 - (alpha + a)*T;
dPop(4) = a*T + r(2)*I2 - (alpha + Mu + k*(beta(1)*(I1/N) + beta(2)*(I2/N)))*S2;
dPop(5) = k*S2*(beta(1)*(I1/N) + beta(2)*(I2/N)) - (alpha + r(2) + g(2) + d(2))*I2;

function []=Check(Par, Value, Name) % Check's for negative parameter values
m=find(Par<Value);
if length(m)>0
    error('%s(%g) (%g) is less than %g',Name,m(1),Par(m(1)),Value);
end

```

B.1.3 Core/Non-Core Extended SITS System (2.11)-(2.22)

```
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
% Author: Joel Lutman
% MSc Mathematical Biology
% University of Bath
% Title: Function to simulate populations S,I,T for core/non-core SITS model
% Date: 09/09/2012
%
% Note: While this file is the authors own work, the code originates from
% the MATLAB codes provided in Keeling & Rohani's "Modeling
% Infectious Disease in Humans and Animals", however has been largely
% changed to represent the model in hand.
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
function [t,Sc,Ic,Tc,Snc,Inc,Tnc] = model3(alpha,beta,k,r,g_1,attendance,d,a,Mu,Sic_0, ...
I1c_0,S2c_0,I2c_0,Tc_0,Nc,Sinc_0,Iinc_0,S2nc_0,I2nc_0,Tnc_0,Nnc,N,time)

if nargin == 0
    alpha = 2.74*10^(-4); % Sets up default parameters if necessary.
    beta = [0.0051; 0.0051]; % Maturity rate.
    k = [7.2;1.5]; % Transmission rate.
    r = [0.0023; 0.0023*1.1]; % Number of sexual partners.
    g_1 = 4.77*10^(-4); % Natural recovery rate.
    attendance = .5; % National screening rate.
    Mu = 0.0055; % Attendance at re-screening.
    d = [0.0067;0.0067*1.1]; % Rate of clearance from observation.
    a = 0.0714; % Rate at which symptoms appear.
    N = 10000; % Rate of treatment.
    Nc = 0.1*N; % Population size.
    Nnc = N-Nc; % Core population size.
    I1c_0 = 0.08*Nc; % Non-Core population size.
    Sic_0 = Nc-I1c_0; % Initial core infectious (8% prevalence).
    S2c_0 = 0; % Initial core susceptibles.
    I2c_0 = 0; % Initial core observed susceptibles.
    Tc_0 = 0; % Initial core infected.
    Iinc_0 = 0.08*Nnc; % Initial core in treatment.
    S1nc_0 = Nnc-Iinc_0; % Initial non-core infectious (8% prevalence).
    S2nc_0 = 0; % Initial non-core susceptibles.
    I2nc_0 = 0; % Initial non-core observed susceptibles.
    Tnc_0 = 0; % Initial non-core infected.
    time = 5*365; % Initial non-core in treatment.
    end % Runtime.

gamma = 0.0082; % Time spent in observation.
epsilon = (attendance*gamma)/g_1; % Calculate epsilon function.
g = [g_1; (epsilon+1)*g_1]; % Screening;Re-screening rates.

Check(alpha,0,'alpha'); % Checks parameters for negative values.
Check(beta(:,1),0,'beta');
Check(k(:,1),0,'k');
Check(r(:,1),0,'r');
Check(g(:,1),0,'g');
Check(gamma,0,'gamma');
Check(d(:,1),0,'d');
Check(a,0,'a');
Check(Mu,0,'Mu');
Check(time,0,'time');
Check(Sic_0,0,'Sic_0');
Check(I1c_0,0,'I1c_0');
Check(Sinc_0,0,'Sinc_0');
Check(Iinc_0,0,'Iinc_0');
Check(S2c_0,0,'S2c_0');
Check(I2c_0,0,'I2c_0');
Check(S2nc_0,0,'S2nc_0');
Check(I2nc_0,0,'I2nc_0');
Check(Tc_0,0,'Tc_0');
Check(Tnc_0,0,'Tnc_0');
```

```

S1c = S1c_0; % Initialises populations.
S2c = S2c_0;
I1c = I1c_0;
I2c = I2c_0;
Tc = Tc_0;
S1nc = S1nc_0;
S2nc = S2nc_0;
I1nc = I1nc_0;
I2nc = I2nc_0;
Tnc = Tnc_0;

options = odeset('RelTol', 1e-5); % Uses ode45 on differential equation solver DiffSolv.
[t, pop]=ode45(@DiffSolv,[0:1:time],[S1c I1c Tc S2c I2c S1nc I1nc Tnc S2nc I2nc],...
    options,alpha, beta, k, r, g, d, a, Mu, Nc, Nnc, N);

S1c = pop(:,1);
I1c = pop(:,2);
Tc = pop(:,3);
S2c = pop(:,4);
I2c = pop(:,5);
S1nc = pop(:,6);
I1nc = pop(:,7);
Tnc = pop(:,8);
S2nc = pop(:,9);
I2nc = pop(:,10);

Sc = S1c+S2c;
Ic = I1c+I2c;
Snc = S1nc+S2nc;
Inc = I1nc+I2nc;

figure; % Plots population levels.
plot(t,S1c,'-g',t,S2c,'-y',t,I1c,'-r',t,I2c,'-m',t,Tc,'-b',t,S1nc,'--g',t,S2nc,'--y',...
    t,I1nc,'--r',t,I2nc,'--m',t,Tnc,'--b');
legend('S1c', 'S2c', 'I1c', 'I2c', 'Tc', 'S1nc', 'S2nc', 'I1nc', 'I2nc', 'Tnc');
xlabel 'Time (days)';
ylabel 'Population (N)';
axis([0 time 0 N]);
title 'Infection Levels in Population N over 3 Years';

figure; % Plots Ic,Inc proportions levels against time.
plot(t,Ic./N,'-r',t,Inc./N,'--r');
legend('Core', 'Non-Core');
xlabel 'Time (days)';
ylabel 'Proportion Infectious (I=I_1+I_2)';
title 'Proportion of Infectious Individuals in Core (I^c) and Non-Core (I^{nc})';
axis([0 time 0 0.08]);

% Stores proportion of core/non-core within I1,I2 classes after each year.
Prop = zeros(17,2);
Prop(1,:) = [I1c(0*356 +1), I1nc(0*356 +1)]./(I1c(0*356 +1)+I1nc(0*356 +1));
Prop(2,:) = [I2c(0*356 +1), I2nc(0*356 +1)]./(I2c(0*356 +1)+I2nc(0*356 +1));
Prop(4,:) = [I1c(1*356 +1), I1nc(1*356 +1)]./(I1c(1*356 +1)+I1nc(1*356 +1));
Prop(5,:) = [I2c(1*356 +1), I2nc(1*356 +1)]./(I2c(1*356 +1)+I2nc(1*356 +1));
Prop(7,:) = [I1c(2*356 +1), I1nc(2*356 +1)]./(I1c(2*356 +1)+I1nc(2*356 +1));
Prop(8,:) = [I2c(2*356 +1), I2nc(2*356 +1)]./(I2c(2*356 +1)+I2nc(2*356 +1));
Prop(10,:) = [I1c(3*356 +1), I1nc(3*356 +1)]./(I1c(3*356 +1)+I1nc(3*356 +1));
Prop(11,:) = [I2c(3*356 +1), I2nc(3*356 +1)]./(I2c(3*356 +1)+I2nc(3*356 +1));
Prop(13,:) = [I1c(4*356 +1), I1nc(4*356 +1)]./(I1c(4*356 +1)+I1nc(4*356 +1));
Prop(14,:) = [I2c(4*356 +1), I2nc(4*356 +1)]./(I2c(4*356 +1)+I2nc(4*356 +1));
Prop(16,:) = [I1c(5*356 +1), I1nc(5*356 +1)]./(I1c(5*356 +1)+I1nc(5*356 +1));
Prop(17,:) = [I2c(5*356 +1), I2nc(5*356 +1)]./(I2c(5*356 +1)+I2nc(5*356 +1));

figure; % Stacked bar plot for I1,I2 showing
bar(Prop,'stacked'); % core/non-core composition after each year.
legend('Core', 'Non-Core');
xlabel 'Time (years)';

```

```

ylabel 'Proportion of Infection (%)';
xtl={'I_1^{t=0}', 'I_2^{t=0}', 'I_1^{t=1yr}', 'I_2^{t=1yr}', 'I_1^{t=2yr}', 'I_2^{t=2yr}', ...
      'I_1^{t=3yr}', 'I_2^{t=3yr}', 'I_1^{t=4yr}', 'I_2^{t=4yr}', 'I_1^{t=5yr}', 'I_2^{t=5yr}'}; % Custom xtick labels
h=my_xticklabels(gca,[1:1:17],xtl);
title 'Composition of Infectious Classes I_1,I_2 over 5 Years';
axis([0 18 0 1]);

function dPop=DiffSolv(t,pop, alpha, beta, k, r, g, d, a, Mu, Nc, Nnc, N)
    % Calculates the differential rates used in ode45

S1c = pop(1);
I1c = pop(2);
Tc = pop(3);
S2c = pop(4);
I2c = pop(5);
S1nc = pop(6);
I1nc = pop(7);
Tnc = pop(8);
S2nc = pop(9);
I2nc = pop(10);

S1 = S1c+S1nc;
I1 = I1c+I1nc;
S2 = S2c+S2nc;
I2 = I2c+I2nc;

dPop=zeros(10,1); % Differential equations
% Core
dPop(1) = alpha*Nc + r(1)*I1c + Mu*S2c - (alpha + k(1)*(beta(1)*(I1/N) + beta(2)*(I2/N)))*S1c;
dPop(2) = S1c*k(1)*(beta(1)*(I1/N) + beta(2)*(I2/N)) - (alpha + r(1) + g(1) + d(1))*I1c;
dPop(3) = (g(1)+d(1))*I1c + (g(2)+d(2))*I2c - (alpha + a)*Tc;
dPop(4) = a*Tc + r(2)*I2c - (alpha + Mu + k(1)*(beta(1)*(I1/N) + beta(2)*(I2/N)))*S2c;
dPop(5) = S2c*k(1)*(beta(1)*(I1/N) + beta(2)*(I2/N)) - (alpha + r(2) + g(2) + d(2))*I2c;
% Non-Core
dPop(6) = alpha*Nnc + r(1)*I1nc + Mu*S2nc - (alpha + k(2)*(beta(1)*(I1/N) + beta(2)*(I2/N)))*S1nc;
dPop(7) = S1nc*k(2)*(beta(1)*(I1/N) + beta(2)*(I2/N)) - (alpha + r(1) + g(1) + d(1))*I1nc;
dPop(8) = (g(1)+d(1))*I1nc + (g(2)+d(2))*I2nc - (alpha + a)*Tnc;
dPop(9) = a*Tnc + r(2)*I2nc - (alpha + Mu + k(2)*(beta(1)*(I1/N) + beta(2)*(I2/N)))*S2nc;
dPop(10) = S2nc*k(2)*(beta(1)*(I1/N) + beta(2)*(I2/N)) - (alpha + r(2) + g(2) + d(2))*I2nc;

function []=Check(Par, Value, Name) % Check's for negative parameter values
m=find(Par<Value);
if length(m)>0
    error('%s(%g) (%g) is less than %g',Name,m(1),Par(m(1)),Value);
end

```

B.1.4 Core/Non-Core Extended SITS System (2.11)-(2.22) where $\hat{g}_c > \hat{g}_{nc}$

```

%%%%%
% Author: Joel Lutman
% MSc Mathematical Biology
% University of Bath
% Title: Function to simulate populations S,I,T for core/non-core SITS model
% where core attendance > non-core attendance
% Date: 09/09/2012
%
% Note: While this file is the authors own work, the code originates from
% the MATLab codes provided in Keeling & Rohani's "Modeling
% Infectious Disease in Humans and Animals", however has been largely
% changed to represent the model in hand.
%%%%%

function [t,Sc,Ic,Tc,Snc,Inc,Tnc] = model3_2(alpha,beta,k,r,g_1,attendance,d,a,Mu,S1c_0, ...
I1c_0,S2c_0,I2c_0,Tc_0,Nc,S1nc_0,I1nc_0,S2nc_0,I2nc_0,Tnc_0,Nnc,N,time)

% Sets up default parameters if necessary.
if nargin == 0 % Sets up default parameters if necessary.

```

```

alpha = 2.74*10^(-4); % Maturity rate.
beta = [0.0051; 0.0051]; % Transmission rate.
k = [7.2;1.5]; % Number of sexual partners.
r = [0.0023; 0.0023*1.1]; % Natural recovery rate.
g_1 = 4.77*10^(-4); % National screening rate.
attendance = .5; % Attendance at re-screening.
Mu = 0.0055; % Rate of clearance from observation.
d = [0.0067;0.0067*1.1]; % Rate at which symptoms appear.
a = 0.0714; % Rate of treatment.
N = 10000; % Population size.
Nc = 0.1*N; % Core population size.
Nnc = N-Nc; % Non-Core population size.
I1c_0 = 0.08*Nc; % Initial core infectious (8% prevalence).
S1c_0 = Nc-I1c_0; % Initial core susceptibles.
S2c_0 = 0; % Initial core observed susceptibles.
I2c_0 = 0; % Initial core observed infected.
Tc_0 = 0; % Initial core in treatment.
I1nc_0 = 0.08*Nnc; % Initial non-core infectious (8% prevalence).
S1nc_0 = Nnc-I1nc_0; % Initial non-core susceptibles.
S2nc_0 = 0; % Initial non-core observed susceptibles.
I2nc_0 = 0; % Initial non-core observed infected.
Tnc_0 = 0; % Initial non-core in treatment.
time = 5*365; % Runtime.

end

att1=[0:0.1:1];
att2=att1;
options = optimset('TolX',10^(-10000));
Flag=0;

for i=1:1:length(att1) % Loops through 0-1 for attendance core.
    attend1 = att1(i);
    if attendance<0.1 % If attendance is less than 10percent
        attendance1=3.5*attendance; % then default this approximation.
        attendance2=0.725*attendance;
    elseif attendance>0.9
        attendance1=attendance; % If attendance is greater than 90percent
        attendance2=attendance; % then default this approximation.
    else
        [attendy2,F]=fzero(@(attendy2) attend1*0.1 + attendy2*0.9...
            - attendance,[0 1],options); % Else use fzero to solve attendance equation.
        if (attend1>attendy2)&&(attendy2>=0)&&(Flag~=1)
            attendance1 = attend1; % If attendance(c)>attendance(nc)
            attendance2 = attendy2; % then store values.
            Flag = 1;
        else
        end
    end
end

gamma = 0.0082;
epsilon1 = (attendance1*gamma)/g_1;
epsilon2 = (attendance2*gamma)/g_1;
g = [g_1; (epsilon1+1)*g_1;(epsilon2+1)*g_1];

Check(alpha,0,'alpha'); % Checks parameters for negative values.
Check(beta(:,1),0,'beta');
Check(k(:,1),0,'k');
Check(r(:,1),0,'r');
Check(g(:,1),0,'g');
Check(gamma,0,'gamma');
Check(d(:,1),0,'d');
Check(a,0,'a');
Check(Mu,0,'Mu');
Check(time,0,'time');
Check(S1c_0,0,'S1c_0');
Check(I1c_0,0,'I1c_0');
Check(S1nc_0,0,'S1nc_0');

```

```

Check(I1nc_0,0,'I1nc_0');
Check(S2c_0,0,'S2c_0');
Check(I2c_0,0,'I2c_0');
Check(S2nc_0,0,'S2nc_0');
Check(I2nc_0,0,'I2nc_0');
Check(Tc_0,0,'Tc_0');
Check(Tnc_0,0,'Tnc_0');

S1c = S1c_0; % Initialises populations.
S2c = S2c_0;
I1c = I1c_0;
I2c = I2c_0;
Tc = Tc_0;
S1nc = S1nc_0;
S2nc = S2nc_0;
I1nc = I1nc_0;
I2nc = I2nc_0;
Tnc = Tnc_0;

options = odeset('RelTol', 1e-5); % Uses ode45 on differential equation solver DiffSolv.
[t, pop]=ode45(@DiffSolv,[0:1:time],[S1c I1c Tc S2c I2c S1nc I1nc Tnc S2nc I2nc],...
    options,alpha, beta, k, r, g, d, a, Mu, Nc, Nnc, N);

S1c = pop(:,1);
I1c = pop(:,2);
Tc = pop(:,3);
S2c = pop(:,4);
I2c = pop(:,5);
S1nc = pop(:,6);
I1nc = pop(:,7);
Tnc = pop(:,8);
S2nc = pop(:,9);
I2nc = pop(:,10);

Sc = S1c+S2c;
Ic = I1c+I2c;
Snc = S1nc+S2nc;
Inc = I1nc+I2nc;

% Calculates the differential rates used in the integration.
function dPop=DiffSolv(t,pop, alpha, beta, k, r, g, d, a, Mu, Nc, Nnc, N);

S1c = pop(1);
I1c = pop(2);
Tc = pop(3);
S2c = pop(4);
I2c = pop(5);
S1nc = pop(6);
I1nc = pop(7);
Tnc = pop(8);
S2nc = pop(9);
I2nc = pop(10);

S1 = S1c+S1nc;
I1 = I1c+I1nc;
S2 = S2c+S2nc;
I2 = I2c+I2nc;

dPop=zeros(10,1);
%core
dPop(1) = alpha*Nc + r(1)*I1c + Mu*S2c - (alpha + k(1)*(beta(1)*(I1/N) + beta(2)*(I2/N)))*S1c;
dPop(2) = S1c*k(1)*(beta(1)*(I1/N) + beta(2)*(I2/N)) - (alpha + r(1) + g(1) + d(1))*I1c;
dPop(3) = (g(1)+d(1))*I1c + (g(2)+d(2))*I2c - (alpha + a)*Tc;
dPop(4) = a*Tc + r(2)*I2c - (alpha + Mu + k(1)*(beta(1)*(I1/N) + beta(2)*(I2/N)))*S2c;
dPop(5) = S2c*k(1)*(beta(1)*(I1/N) + beta(2)*(I2/N)) - (alpha + r(2) + g(2) + d(2))*I2c;
%noncore
dPop(6) = alpha*Nnc + r(1)*I1nc + Mu*S2nc - (alpha + k(2)*(beta(1)*(I1/N) + beta(2)*(I2/N)))*S1nc;
dPop(7) = S1nc*k(2)*(beta(1)*(I1/N) + beta(2)*(I2/N)) - (alpha + r(1) + g(1) + d(1))*I1nc;

```

```

dPop(8) = (g(1)+d(1))*I1nc + (g(3)+d(2))*I2nc - (alpha + a)*Tnc;
dPop(9) = a*Tnc + r(2)*I2nc - (alpha + Mu + k(2)*(beta(1)*(I1/N) + beta(2)*(I2/N)))*S2nc;
dPop(10) = S2nc*k(2)*(beta(1)*(I1/N) + beta(2)*(I2/N)) - (alpha + r(2) + g(3) + d(2))*I2nc;

% Check's for negative parameter values
function []=Check(Par, Value, Name)
m=find(Par<Value);
if length(m)>0
    error('"%s(%g) (%=)g is less than %g',Name,m(1),Par(m(1)),Value);
end

```

B.2 Scripts to Analyse Screening/Re-Screening

B.2.1 Sensitivity of Steady States

```

%%%%%
% Author: Joel Lutman
% MSc Mathematical Biology
% University of Bath
% Title: Script to analyse sensitivity of steady states to changes in
% secondary values beta_2, r_2, d_2 by (+/-)20 percent
% Date: 09/09/2012
%%%%%

close all;                                         % Tidys command window.
clear all;

beta_1 = 0.0051;                                  % Baseline transmission rate.
betadiff = beta_1*0.2;                            % 20 percent difference.
beta_2 = linspace(beta_1-betadiff,beta_1+betadiff,50); % Creates beta_2 as a linear spacing either
beta_ratio = zeros(size(beta_2));                  % side of beta_1 by 20 percent.
S_eq = zeros(size(beta_2));                        % Allocates space for various vectors.
I_eq = zeros(size(beta_2));
T_eq = zeros(size(beta_2));

for m = 1:1:length(beta_2)                         % Loops through all the beta_2 values, calculating
    beta_ratio(m) = beta_2(m)/beta_1;              % the ratio of beta_2/beta_1.
    beta=[beta_1;beta_2(m)];
    [t,S,I,T,S2,I2] = model2(2.74*10^(-4),beta,2.07,[0.0023;0.0023],4.38*10^(-4),0.5,[0.0067;0.0067],...
        0.0714,0.0055,9171.17,754.05,0,0,74.78,10*365,10000); % Note the timestep of 10*365, makes sure values
                                                               % hit equilibrium.
    S_eq(m) = S1(end) + S2(end);                  % Stores S,I,T equilibrium points.
    I_eq(m) = I1(end) + I2(end);
    T_eq(m) = T(end);
end

figure;                                              % Plots S,I,T equilibria for
plot(beta_ratio,S_eq,'-g',beta_ratio,I_eq,'-r',beta_ratio,T_eq,'-b'); % beta_2=beta_1 (+/-) 20percent.
xlabel '\beta_{ratio} = \beta_2/\beta_1';             % Figure options.
ylabel 'Equilibria';
title 'Changes in endemic equilibrium (S^*,I^*,T^*) for \beta_{ratio}';
legend ('S^*','I^*','T^*');
axis([0.8 1.2 0 10000]);

figure;                                              % Plots individual S,I,T equilibria for
subplot(3,1,1);                                     % beta_2=beta_1 (+/-) 20percent.
h=plot(beta_ratio,S_eq,'-g');                       % S plot.
title 'Changes in endemic equilibrium S^* for \beta_{ratio}';
xlabel '\beta_{ratio} = \beta_2/\beta_1';
ylabel 'Equilibria';
axis([0.8 1.2 9300 9500]);
subplot(3,1,2);
h=plot(beta_ratio,I_eq,'-r');                      % I plot.
title 'Changes in endemic equilibrium I^* for \beta_{ratio}';
xlabel '\beta_{ratio} = \beta_2/\beta_1';
ylabel 'Equilibria';

```

```

axis([0.8 1.2 500 700]);
subplot(3,1,3)
h=plot(beta_ratio,T_eq,'-b'); % T plot.
title 'Changes in endemic equilibrium T^* for \beta_{ratio};';
xlabel '\beta_{ratio} = \beta_2/\beta_1';
ylabel 'Equilibria';
axis([0.8 1.2 50 70]);

%%
clear all; % Clears variables.
r_1 = 0.0023; % Baseline recovery rate.
rdiff = r_1*0.2; % 20 percent difference.
r_2 = linspace(r_1-rdiff,r_1+rdiff,50); % Creates r_2 as a linear spacing either
r_ratio = zeros(size(r_2)); % side of r_1 by 20 percent.
S_eq = zeros(size(r_2)); % Allocates space for various vectors.
I_eq = zeros(size(r_2));
T_eq = zeros(size(r_2));

for m = 1:1:length(r_2) % Loops through all the r_2 values, calculating
    r_ratio(m) = r_2(m)/r_1; % the ratio of r_2/r_1.
    r=[r_1;r_2(m)]; % Runs model2 with current r_1, r_2 values.
    [t,S1,I1,T,S2,I2] = case2(2.74*10^(-4),[0.0051;0.0051],2.07,r,4.38*10^(-4),0.5,[0.0067;0.0067],... % Note the timestep of 10*365, makes sure
        0.0714,0.0055,9171.17,754.05,0,0.74.78,10*365,10000); % values hit equilibrium.
    S_eq(m) = S1(end) + S2(end); % Stores S,I,T equilibrium points.
    I_eq(m) = I1(end) + I2(end);
    T_eq(m) = T(end);
end

figure; % Plots S,I,T equilibria for
plot(r_ratio,S_eq,'-g',r_ratio,I_eq,'-r',r_ratio,T_eq,'-b'); % r_2=r_1 (+/-) 20percent.
xlabel 'r_{ratio} = r_2/r_1'; % Figure options.
ylabel 'Equilibria';
title 'Changes in endemic equilibrium (S^*,I^*,T^*) for r_{ratio}';
legend ('S^*','I^*','T^*');
axis([0.8 1.2 0 10000]);

figure; % Plots individual S,I,T equilibria for
subplot(3,1,1) % r_2=r_1 (+/-) 20percent.
h=plot(r_ratio,S_eq,'-g'); % S plot.
title 'Changes in endemic equilibrium S^* for r_{ratio}';
xlabel 'r_{ratio} = r_2/r_1';
ylabel 'Equilibria';
axis([0.8 1.2 9300 9500]);
subplot(3,1,2) % I plot.
h=plot(r_ratio,I_eq,'-r'); % I plot.
title 'Changes in endemic equilibrium I^* for r_{ratio}';
xlabel 'r_{ratio} = r_2/r_1';
ylabel 'Equilibria';
axis([0.8 1.2 500 700]);
subplot(3,1,3) % T plot.
h=plot(r_ratio,T_eq,'-b'); % T plot.
title 'Changes in endemic equilibrium T^* for r_{ratio}';
xlabel 'r_{ratio} = r_2/r_1';
ylabel 'Equilibria';
axis([0.8 1.2 50 70]);

%%
clear all; % Clears variables.
d_1 = 0.0067; % Baseline symptomatic rate
ddiff = d_1*0.2; % 20 percent difference.
d_2 = linspace(d_1-ddiff,d_1+ddiff,50); % Creates d_2 as a linear spacing either
d_ratio = zeros(size(d_2)); % side of d_1 by 20 percent.
S_eq = zeros(size(d_2)); % Allocates space for various vectors.
I_eq = zeros(size(d_2));
T_eq = zeros(size(d_2));

for m = 1:1:length(d_2) % Loops through all the r_2 values, calculating
    d_ratio(m) = d_2(m)/d_1; % the ratio of d_2/d_1.

```

```

d=[d_1;d_2(m)]; % Runs model2 with current r_1, r_2 values.
[t,S1,I1,T,S2,I2] = case2(2.74*10^(-4),[0.0051;0.0051],2.07,[0.0023;0.0023],4.38*10^(-4),0.5,d,%
    0.0714,0.0055,9171.17,754.05,0,0,74.78,10*365,10000); % Note the timestep of 10*365, makes sure
S_eq(m) = S1(end) + S2(end); % values hit equilibrium.
I_eq(m) = I1(end) + I2(end); % Stores S,I,T equilibrium points.
T_eq(m) = T(end);
end

figure; % Plots S,I,T equilibria for
plot(d_ratio,S_eq,'-g',d_ratio,I_eq,'-r',d_ratio,T_eq,'-b'); % d_2=d_1 (+/-) 20percent.
xlabel 'd_{ratio} = d_2/d_1'; % Figure options.
ylabel 'Equilibria';
title 'Changes in endemic equilibrium (S^*,I^*,T^*) for d_{ratio}';
legend ('S^*','I^*','T^*');
axis([0.8 1.2 0 10000]);

figure; % Plots individual S,I,T equilibria for
subplot(3,1,1) % d_2=d_1 (+/-) 20percent.
h=plot(d_ratio,S_eq,'-g'); % S plot.
title 'Changes in endemic equilibrium S^* for d_{ratio}';
xlabel 'd_{ratio} = d_2/d_1';
ylabel 'Equilibria';
axis([0.8 1.2 9300 9500]);
subplot(3,1,2)
h=plot(d_ratio,I_eq,'-r'); % I plot.
title 'Changes in endemic equilibrium I^* for d_{ratio}';
xlabel 'd_{ratio} = d_2/d_1';
ylabel 'Equilibria';
axis([0.8 1.2 500 700]);
subplot(3,1,3)
h=plot(d_ratio,T_eq,'-b'); % T plot.
title 'Changes in endemic equilibrium T^* for d_{ratio}';
xlabel 'd_{ratio} = d_2/d_1';
ylabel 'Equilibria';
axis([0.8 1.2 50 70]);

```

B.2.2 Introducing Re-screening Mid-system

```

%%%%%%%%%%%%%%%
% Author: Joel Lutman
% MSc Mathematical Biology
% University of Bath
% Title: Script to introduce re-screening after 3 years of established
% national screening
% Date: 09/09/2012
%%%%%%%%%%%%%%%

clear all % Tidys command window
close all
clc

% Baseline run: Runs extended SITS model with default parameters and no re-screening
[t,S1,I1,T,S2,I2] = model2(2.74*10^(-4),[0.0051;0.0051],2.07,[0.0023;0.0023*1.2],4.77*10^(-4),...
    0,[0.0067;0.0067*1.2],0.0714,0.0055,9200,800,0,0,0,0,6*365,10000);

S_before = S1+S2; % Stores S,I,T values without
I_before = I1+I2; % re-screening in effect
T_before = T;

S1end=S1(3*365+1); % Stores S,I,T values with no
I1end=I1(3*365+1); % re-screening after 3 years
S2end=S2(3*365+1);
I2end=I2(3*365+1);
Tend=T(3*365+1);

area_matrix = zeros(5,3); % Allocates space

```

```

figure; % Plots either I or T (choose)
%plot(1:1:6*365+1,I_before,'-k'); %I % with no re-screening
plot(1:1:6*365+1,T_before,'-k'); %T
hold on;
i=1; % Initialises counter i
cmap = hsv(6); % Colormap for looping

for attendance = [0.2, 0.4, 0.6, 0.8, 1]; % Loops for re-screening attendance values
    % Runs extended SITS model with default parameters starting at S,I,T values from baseline run
    % after 3 years with re-screening value 'attendance'
    [t,S1,I1,T,S2,I2] = model2(2.74*10^(-4),[0.0051; 0.0051],2.07,[0.0023;0.0023*1.2],4.77*10^(-4),...
        attendance,[0.0067;0.0067*1.2],0.0714,0.0055,S1end,I1end,S2end,I2end,Tend,3*365,10000);

    S_after = S1+S2; % Stores S,I,T values
    I_after = I1+I2;
    T_after = T;

    for j=50:1:length(T); % Loops through T values and finds the time where
        if abs(T_before(j+3*365)-T(j))<.012 % T crosses the baseline value.
            location=j; % Stores this time
        else
            end
        end
    end % Calculates increased number cases
TreatmentIncrease= sum(T_after(1:location))-sum(T_before(3*365:3*365+location));

% Loops and sums from the baseline crossover point until the point when it has compensated
% for the previous increase in T
for s=location:1:length(T);
    if abs(TreatmentIncrease-abs(sum(T_before(3*365+location:3*365+s))...
        -sum(T_after(location:s))))<10
        TimeTaken=s; % Stores timetaken to compensate
    else
        end
    end
area_matrix(i,1) = TreatmentIncrease; % Outputs the number of increased
area_matrix(i,2) = location; % cases, time taken to cross baseline,
area_matrix(i,3) = TimeTaken+location; % time to compensate and T value at
area_matrix(i,4) = T_after(area_matrix(i,2)); % crossover for each attendance loop.

%plot(3*365+1:1:6*365+1,I_after,'Color',cmap(i,:)); % I % Plots either I or T (choose)
plot(3*365+1:1:6*365+1,T_after,'Color',cmap(i,:)); % T % with re-screening at 'attendance'

i=i+1; % Updates counter i
clear location % Clears placeholders location,TimeTaken
clear TimeTaken % and TreatmentIncrease
clear TreatmentIncrease
end

xlabel 'Time (years)'; % Figure options
ylabel 'Infected Cases per 10,000';
set(gca,'XLim',[0 6*365+1],'XTick',[0:365/2:6*365],'XTickLabel',[0:0.5:6]);
%axis([2*365 6*365 400 800]);
axis([2*365 6*365 45 75]);
legend('0% Reattendance', '20% Reattendance', '40% Reattendance', '60% Reattendance',...
    '80% Reattendance', '100% Reattendance');
title 'Introducing Re-screening at Varying Levels, after 3 Years of 0% Re-screening';

```

B.2.3 Measuring Changes in Prevalence over Time

```

%%%%%%%%%%%%%
% Author: Joel Lutman
% MSc Mathematical Biology
% University of Bath
% Title: Script compare prevalence for fixed national screening and
% variable targeted re-screening after 3 years

```

```
% Date: 09/09/2012
%%%%%%%%%%%%%%%
clear all % Tidys command window
close all
GTS=[0:0.01:1]; % GTS is a vector of all attendance
Prev=zeros((3*365)+1,length(GTS)); % rates between 0-1, step of 0.01
% Allocates space for prevalence vals

for i=1:1:101; % Loops through all attendance values
    attendance=GTS(i);
    [t,S,I,T] = model2(2.74*10^(-4),[0.0051; 0.0051],2.07,[0.0023;0.0023*1.1],4.77*10^(-4),... % running model2 for each attendance vals
        attendance,[0.0067;0.0067*1.1],0.0714,0.0035,9200,800,0,0,0,3*365,10000); % Calculates prevalences
    Prev(:,i) = (I(:,1)+T(:,1))./10000;
end

Prev=Prev.*100; % Prevalence as percent
figure;
plot(t,Prev(:,1)); % Plot baseline prev with no re-screening
ylabel ('Prevalence','fontsize',22); % and screening at 16 percent
xlabel ('Time (days)','fontsize',22); % Figure options
title ('Change in Prevalence over 3 Years','fontsize',26);
axis([0 3*365 7 9]);

figure;
[X,Y]=meshgrid(t,GTS.*100); % Create grid of time(x) against attendance(y)
[C,h]=contour(X,Y,Prev'); % Contour plot of prevalence on grid
text_handle = clabel(C,h); % Gets contour labels
set(text_handle,'fontsize',18); % Increase font on contour lines
xlabel ('Time (days)','fontsize',22); % Figure options
ylabel ('Attendance of Re-screening(%)', 'fontsize',22);
zlabel ('Prevalence','fontsize',22);
title ('Change in prevalence (%) for varying re-attendance over time, for fixed screening rate 16%',... % Labels colourbar ticks
    'fontsize',26);

figure;
surf(X,Y,Prev'); % 3D surface plot of prevalence on grid
shading interp; % Interpolated shading
colorbar('YTickLabel',{'6% Prevalence','6.5% Prevalence','7% Prevalence',...
    '7.5% Prevalence','8% Prevalence','8.5% Prevalence'}); % Figure options
axis([0 3*365 0 100 5 9]);
xlabel ('Time (days)','fontsize',22);
ylabel ('Attendance of Re-screening(%)', 'fontsize',22);
zlabel ('Prevalence','fontsize',22);
title ('Change in prevalence (%) for varying re-attendance over time, for fixed screening rate 16%',... % Labels colourbar ticks
    'fontsize',26);
```

B.2.4 Measuring Changes in Prevalence, Incidence, and Positivity in Discrete Time

```
%%%%%%%%%%%%%%
% Author: Joel Lutman
% MSc Mathematical Biology
% University of Bath
% Title: Script to analyse prevalence, incidence, positivity after each
% year for 15,25,35,45 percent screening coverage and 0,50,100
% percent re-screening attendance.
% Date: 09/09/2012
%%%%%%%%%%%%%

clear all % Tidys command window.
close all
clc

GTS=[0:0.5:1]; % Vector of attendance values 0,50,100 percent.
beta = [0.0051;0.0051]; % Some default parameters.
k=2.07;
```

```

N=10000;

for i=1:1:3; % Loops through attendance values.
    attendance=GTS(i);
    m=1; % Initialise counter m.
    Prev = zeros(15,2); % Allocates space for prevalence matrix.
    Incid = zeros(4,4); % Allocates space for incidence matrix.
    Pos1 = zeros(4,4); % Allocates space for positivity(screen) matrix.
    Pos2 = zeros(4,4); % Allocates space for positivity(re-screen) matrix.

    for g_1 = [0.15/365, 0.25/365, 0.35/365, 0.45/365] % Loops through coverage values 15,25,35,45 percent.
        [t,S1,I1,T,S2,I2] = model2(2.74*10^(-4),beta,k,[0.0023;0.0023*1.1],g_1,attendance,... % Runs model2 with current attendance
        [0.0067;0.0067*1.1],0.0714,0.0055,9200,800,0,0,0,3*365,N); % and screening rates.
        Prev(m,:) = [T(356+1),I1(356+1)+I2(356+1)]; % Stores prev after 1 year.
        Prev(5+m,:) = [T(2*356+1),I1(2*356+1)+I2(2*356+1)]; % Stores prev after 2 years.
        Prev(10+m,:) = [T(3*356+1), I1(3*356+1)+I2(3*356+1)]; % Stores prev after 3 years.
        PrevNew = Prev.*((100/10000)); % Calculates proportions.
        S=S1+S2;
        I=I1+I2;

        Incid(m,1) = (365/N)*(beta(1)*k*S1(1)*I1(1) +... % Calculates initial incidence.
            beta(2)*k*S2(1)*I1(1)+ beta(1)*k*S1(1)*I2(1) + beta(2)*k*S2(1)*I2(1));
        Incid(m,2) = (1/N)*(beta(1)*k*sum(S1(2:365+1).*I1(2:365+1)) +...% Calculates incidence after 1 year.
            beta(2)*k*sum(S2(2:365+1).*I1(2:365+1)) + beta(1)*k*sum(S1(2:365+1).*I2(2:365+1))...
            + beta(2)*k*sum(S2(2:365+1).*I2(2:365+1)));
        Incid(m,3) = (1/N)*(beta(1)*k*sum(S1(365+2:2*365+1).*I1(365+2:2*365+1)) +...
            beta(2)*k*sum(S2(365+2:2*365+1).*I1(365+2:2*365+1)) +... % Calculates incidence after 2 years.
            beta(1)*k*sum(S1(365+2:2*365+1).*I2(365+2:2*365+1)) +...
            beta(2)*k*sum(S2(365+2:2*365+1).*I2(365+2:2*365+1)));
        Incid(m,4) = (1/N)*(beta(1)*k*sum(S1(2*365+2:3*365+1).*I1(2*365+2:3*365+1))...
            + beta(2)*k*sum(S2(2*365+2:3*365+1).*I1(2*365+2:3*365+1)) + ...
            beta(1)*k*sum(S1(2*365+2:3*365+1).*I2(2*365+2:3*365+1)) + ...
            beta(2)*k*sum(S2(2*365+2:3*365+1).*I2(2*365+2:3*365+1)); % Calculates incidence after 3 years.
            % Screening positivity.

        Pos1(m,1) = (I1(1)+I2(1))/(S1(1)+S2(1)+I1(1)+I2(1)); % Calculates initial positivity.
        Pos1(m,2) = (sum(I1(1:1*365+1)+I2(1:1*365+1)))/(sum(S1(1:1*365+1)+... % After 1 year.
            S2(1:1*365+1)+I1(1:1*365+1)+I2(1:1*365+1)));
        Pos1(m,3) = (sum(I1(1*365+2:2*365+1)+I2(1*365+2:2*365+1)))/(sum(S1(1*365+2:2*365+1)+... % After 2 years.
            S2(1*365+2:2*365+1)+I1(1*365+2:2*365+1)+I2(1*365+2:2*365+1));
        Pos1(m,4) = (sum(I1(2*365+2:3*365+1)+I2(2*365+2:3*365+1)))/(sum(S1(2*365+2:3*365+1)+... % After 3 years.
            S2(2*365+2:3*365+1)+I1(2*365+2:3*365+1)+I2(2*365+2:3*365+1));
            % Re-screening positivity.

        Pos2(m,1) = (I2(1))/(S2(1)+I2(1)); % Calculates initial positivity.
        Pos2(m,2) = (sum(I2(1:1*365+1)))/(sum(S2(1:1*365+1)+I2(1:1*365+1));% After 1 year.
        Pos2(m,3) = (sum(I2(1*365+2:2*365+1)))/(sum(S2(1*365+2:2*365+1)+... % After 2 years.
            I2(1*365+2:2*365+1));
        Pos2(m,4) = (sum(I2(2*365+2:3*365+1)))/(sum(S2(2*365+2:3*365+1)+... % After 3 years.
            I2(2*365+2:3*365+1));

        m=m+1; % Updates counter m.
    end

    Pos1 = Pos1.*100; % Positivity as percent.
    Pos2 = Pos2.*100; % Attendance as percent.

    figure; % Plot stacked bar chart of prevalence
    bar(PrevNew, 'stacked'); % at current coverage/attendance vals.
    PrevTitle = sprintf(... % Prevalence for varying screening coverage with re-attendance = %g%%...
        ,attendance);
    title (PrevTitle);
    set(gca,'XLim',[0 14],'XTick',[1:1:14],'XTickLabel',{'15%','25%','35%','45%','','... % Custom xaxis labels.
        '15%','25%','35%','45%','','15%','25%','35%','45%',''});
    axis([0 15 0 9]);
    ylabel '% of Population';
    xlabel 'Years';

```

```

legend ('T','I');

t=0:1:3;
figure; hold on; % Plot data points of incidence at
plot(t,Incid,'*'); % current coverage/attendance vals
IncidTitle = sprintf(... % Incidence for Varying Screening Coverage with Re-attendance = %g%%,attendance);
title (IncidTitle,'fontsize',26);
ylabel ('Cases per 10000 person-years','fontsize',22);
xlabel ('Time (years)','fontsize',22);
legend ('15% Screening Coverage','25% Screening Coverage',...
'35% Screenin Coverage','45% Screening Coverage');
axis([0 3 1000 3000]);

t=0:1:3; % Screening positivity.
figure; hold on; % Plot data points of positivity at
plot(t,Pos1,'*'); % current coverage/attendance vals.
IncidTitle = sprintf(... % Positivity for Screening with Varying Screening Coverage with Re-attendance = %g%%,... attendance);
title (IncidTitle,'fontsize',26);
ylabel ('Positivity (%)','fontsize',22);
xlabel ('Time (years)','fontsize',22);
legend ('15% Screening Coverage','25% Screening Coverage',...
'35% Screenin Coverage','45% Screening Coverage');
axis([0 3 0 9]);

t=0:1:3; % Re-screening positivity.
figure; hold on; % Plot data points of positivity at
plot(t,Pos2,'*'); % current coverage/attendance vals.
IncidTitle = sprintf(... % Positivity for Re-screening with Varying Screening Coverage with Re-attendance = %g%%,... attendance);
title (IncidTitle,'fontsize',26);
ylabel ('Positivity (%)','fontsize',22);
xlabel ('Time (years)','fontsize',22);
legend ('15% Screening Coverage','25% Screening Coverage',...
'35% Screenin Coverage','45% Screening Coverage');
axis([0 3 0 9]);
end

```

B.2.5 Comparing Changes in Prevalence, Positivity, and Cost for Variable Screening and Re-screening after 3 Years

```

%%%%%%%%%%%%%
% Author: Joel Lutman
% MSc Mathematical Biology
% University of Bath
% Title: Script to analyse prevalence, cost, cost effectiveness against
% variable screening coverage (10-50 percent) and re-screening
% attendance (0-100 percent) after 3 years
% Date: 09/09/2012
%%%%%%%%%%%%%

close all % Tidys command window
clear all
clc
format long

GTS=[0:0.01:1]; % Vector of attendance 0-1, step 0.01.
Screening=[0.1:0.01:0.5]./365; % Vector of screening rates 10-50percent
Prev=zeros(length(Screening),length(GTS)); % perday, step 0.01.
Cost=zeros(length(Screening),length(GTS)); % Allocates space for prevalence, cost,
CostEff=zeros(length(Screening),length(GTS)); % and cost effectiveness.
N=10000;
CostPerScreen = 43.65; % Cost parameters.
ObsCosts = 2.76 + 0.1;

```

```

for k=1:1:41;                                % Loops through all screening coverage.
    ScreeningRate=Screening(k);
    for i=1:1:101;                            % Loops through all re-screening attendance.
        attendance=GTS(i);                   % Runs model2 with current coverage/attendance.
        [t,S1,I1,T,S2,I2] = model2(2.74*10^(-4),[0.0051;0.0051],2.07,[0.0023;0.0023*1.1],...
            ScreeningRate,attendance,[0.0067;0.0067*1.1],0.0714,0.0055,9200,800,0,0,0,3*365,N);
        Prev(k,i) = (I1(end)+I2(end)+T(end)).*(100/N); % Caluclates prevalence.

        Cost(k,i) = CostPerScreen*(N-T(end))*ScreeningRate*365 +...
            (S2(end)+I2(end))*(ObsCosts + CostPerScreen*attendance +...
            0.1*(1-attendance));                  % Caluclates cost.

        Pos1_year3 = (I1(end)+I2(end))/(N-T(end));      % Calculates screening positivity
        Pos2_year3 = I2(end)/(S2(end)+I2(end));          % Calculates re-screening positivity

        CostEff(k,i) = Cost(k,i)/(Pos1_year3*(N-T(end))*ScreeningRate*365 ...
            + Pos2_year3*(S2(end)+I2(end))*attendance); % Calculates cost effectiveness.
    end
end

Screening=Screening.*(365*100);                % Screening coverage as percent.
GTS=GTS.*100;                                  % Re-screening attendance as percent.
[X,Y]=meshgrid(Screening,GTS);                 % Creates mesh of coverage(x) against attendance(y);

%%
figure;                                         % 3D surface plot of prevalence on mesh.
surf(X,Y,Prev');                               % Interpolated shading.
shading interp;
xlabel ('Screening Coverage (%)','fontsize',22);
ylabel ('Attendance of Re-screening (%)','fontsize',22);
zlabel ('Prevalence (%)','fontsize',22);
title ('Change in prevalence after 3 years for varying re-attendance and screening rates',...
    'fontsize',26);
colorbar('YTickLabel',{'3% Prevalence','4% Prevalence','5% Prevalence',...
    '6% Prevalence','7% Prevalence','8% Prevalence','9% Prevalence'});

figure;
[C1,h1]=contour(X,Y,Prev');                    % Contour plot of prevalence on mesh.
text_handle=clabel(C1,h1);
set(text_handle,'fontsize',18);                  % Increase contour label fontsize.
xlabel ('Screening Coverage (%)','fontsize',22);
ylabel ('Attendance of Re-screening (%)','fontsize',22);
title (...,'Re-attendance against Screening Rate required to achieve target prevalence, after 3 years',...
    'fontsize',26);
set(h1,'ShowText','on');
view([0,90]);

%%
figure;                                         % 3D surface plot of cost on mesh.
surf(X,Y,Cost');                               % Interpolated shading.
shading interp;
xlabel ('Screening Coverage (%)','fontsize',22);
ylabel ('Re-screening Attendance (%)','fontsize',22);
zlabel ('Cost (\$)','fontsize',22);
title ('Change In Cost After 3 Years For Varying Attendance and Coverage','fontsize',26);

figure;
[C,h]=contour(X,Y,Cost');                      % Contour plot of cost on mesh.
text_handle=clabel(C,h);
set(text_handle,'fontsize',22);                  % Increase contour label fontsize.
xlabel ('Screening Coverage (%)','fontsize',22);
ylabel ('Re-screening Attendance (%)','fontsize',22);
title (...,'Attendance Against Coverage Required To Achieve Target Costs After 3 Years',...
    'fontsize',26);
set(h,'ShowText','on');

```

```

view([0,90]);

figure;                                     % Plots cost against variable coverage
plot(Screening, Cost(:,51));                 % for fixed attendance at 50percent.
xlabel ('Screening Coverage (%)','fontsize',22);
ylabel ('Cost (£ per day)');
title ('Change In Cost After 3 Years For Varying Coverage','fontsize',26);

figure;                                     % Plots cost against variable attendance
plot(GTS, Cost(6,:));                      % for fixed coverage at 16percent.
xlabel ('Re-screening Attendance (%)','fontsize',22);
ylabel ('Cost (£ per day)');
title ('Change In Cost After 3 Years For Varying Attendance','fontsize',26);
%%%
figure;                                     % 3D surface plot of cost effectiveness
surf(X,Y,CostEff);                         % on mesh.
shading interp;
xlabel ('Screening Coverage (%)','fontsize',22);
ylabel ('Re-screening Attendance (%)','fontsize',22);
zlabel ('Cost Effectiveness (£ per screen)','fontsize',22);
title ('Cost Effectiveness After 3 Years For Varying Attendance and Coverage',...
'fontsize',26);

figure;                                     % Contour plot of cost on mesh.
[C,h]=contour(X,Y,CostEff);
text_handle=clabel(C,h);
set(text_handle,'fontsize',18);              % Increase contour label fontsize.
xlabel ('Screening Coverage (%)','fontsize',22);
ylabel ('Re-screening Attendance (%)','fontsize',22);
title (... 'Attendance Against Coverage Required To Achieve Target Cost Effectiveness After 3 Years',...
'fontsize',26);
set(h,'ShowText','on');
view([0,90]);

figure;                                     % Filled contour plot of cost effectiveness
[C2,h2]=contourf(X,Y,CostEff,'TextStep',200); % on mesh, overlaid with contour plot of
text_handle1=clabel(C2,h2);                  % prevalence on mesh.
set(text_handle1,'fontsize',18);
hold on;
[C1,h1]=contour(X,Y,Prev,'LineWidth',1.5);
text_handle2=clabel(C1,h1);
set(text_handle2,'fontsize',18);
xlabel ('Screening Coverage (%)','fontsize',22);
ylabel ('Re-screening Attendance (%)','fontsize',22);
title ('Prevalence (Lines) Overlaid on Cost Effectiveness','fontsize',26);

```

B.2.6 Comparing Standard Prevalence to Core/Non-Core Prevalence

```

%%%%%%%%%%%%%
% Author: Joel Lutman
%           MSc Mathematical Biology
%           University of Bath
% Title: Script to analyse prevalence for core/non-core SITS model
%           where core attendance > non-core attendance
% Date: 09/09/2012
%%%%%%%%%%%%%

close all                                     % Tidys command window
clear all
clc
format long

GTS=[0:0.01:1];                             % Vector of attendance 0-1, step 0.01.
Screening=[0.1:0.01:0.5]/365;                % Vector of screening rates 10-50percent
Prev=zeros(length(Screening),length(GTS));    % perday, step 0.01.
N=10000;                                      % Allocates space for prevalence.

```

```

for k=1:1:length(Screening); % Loops through all screening coverage.
    ScreeningRate=Screening(k);
    for i=1:1:length(GTS); % Loops through all re-screening attendance.
        attendance=GTS(i); % Runs model3_2 with current coverage/attendance.
        [t,Sc,Ic,Tc,Snc,Inc,Tnc] = model3_2(2.74*10^(-4),[0.0051; 0.0051],[5.76;1.66],...
            [0.0023;0.0023*1.1],ScreeningRate,attendance,[0.0067;0.0067*1.1],...
            0.0714,0.0055,920,80,0,0,1000,8280,720,0,0,0,9000,10000,3*365);
        Prev(k,i) = (Ic(end)+Inc(end)+Tc(end)+Tnc(end)).*(100/N); % Caluclates prevalence.
    end
end

Screening=Screening.*(365*100); % Screening coverage as percent.
GTS=GTS.*100; % Re-screening attendance as percent.
[X,Y]=meshgrid(Screening,GTS); % Creates mesh of coverage(x) against attendance(y);
surf(X,Y,Prev'); % 3D surface plot of prevalence on mesh.
shading interp;
xlabel ('Screening Coverage (%)','fontsize',22);
ylabel ('Attendance of Re-screening (%)','fontsize',22);
zlabel ('Prevalence (%)','fontsize',22);
title (... % Contour plot of prevalence on mesh.
    'Change in prevalence after 3 years for varying re-attendance and screening rates',...
    , 'fontsize',26);

figure; % Contour plot of prevalence on mesh.
[C,h]=contour(X,Y,Prev','LineWidth',1.5);
text_handle=clabel(C,h);
set(text_handle,'fontsize',18);
xlabel ('Screening Coverage (%)','fontsize',22);
ylabel ('Attendance of Re-screening (%)','fontsize',22);
title (... % Re-attendance against Screening Rate required to achieve target prevalence, after 3 years'...
    , 'fontsize',26);
set(h,'ShowText','on');
view([0,90]);

```