TITLE: Static Versus Dynamic: Does it matter what modelling approach is used in the Economic Evaluation of Chlamydia Trachomatis Screening

AUTHOR: Tracy Roberts,

Health Economics Unit, University of Birmingham

ABSTRACT

Background

Economic evaluations of interventions to control for infectious diseases have been relatively uncommon in the mainstream literature. Whilst it is widely acknowledged that model based economic evaluations must reflect the needs of the decision problem and be representative of the natural history of the disease, in practice these requirements are often overlooked when applied to economic evaluations of infectious disease interventions as evidenced in recent systematic reviews. In this paper the theoretical foundations of infectious diseases are considered and the extent to which the static modelling approaches of decision trees or Markov models typically favoured by health economists are appropriate or adequate in an evaluation of an infectious disease intervention.

Methods

Alternative modelling approaches using decision analysis to represent the static model and discrete event simulation to represent dynamic model are both used in the economic evaluation of a Chlamydia screening programme and the results are compared.

Results

The results of the static models were associated with systematically more favourable results than the dynamic counterpart, but the direction of the bias is not necessarily predictable

Conclusion

The paper presents the argument that the appropriate model to use in an economic evaluation of a screening programme for an infectious disease such as Chlamydia trachomatis is a transmission dynamic model. Whilst there is increasing acknowledgment of this fact, the published evidence suggests that it is not supported in practice. Health economist and modellers must refrain from the thoughtless application of their standard toolkit to disease areas in which more sophisticated methods are required.

Pages = 20

WORD COUNT (excl abstract, appendix and reference list) = 7,219

Appendix Figure 2 available on HESG Website

Introduction

Chlamydia trachomatis is the commonest reported sexually transmitted infection in developed countries (WHO, 2001). The asymptomatic nature of the disease means that treatment is often delayed, leading to an increased risk of complications and transmission to partners. Complications in women include pelvic inflammatory disease, ectopic pregnancy and infertility, along with neonatal complications in their children. The majority of economic evaluations in the published literature have concluded that Chlamydia screening is cost-effective (Roberts et al, 2006). This was also the conclusion of a review of economic evaluations carried out by other authors (Honey et al, 2002).
An analysis of the underlying modelling approach showed that the majority (i.e. 55%) of the Chlamydia screening evaluations were based on a decision tree or Markov model. In the infectious disease literature these models are defined as 'static' because they assume a constant force of infection. 35% of the studies used a model that assumed a non-constant force of infection. The remaining 10% used no model.

Brennan et al (2006) suggested that static models, such as decision trees or Markov models are the main approaches adopted by health economists. Under the definitions used by Barton et al (2004) and Brennan et al (2006), 'static' models are models where 'interactions between individuals', necessary to transmit an infectious disease, *cannot* be accommodated. However since interactions between *individuals* is not always required for the transmission of an infectious disease, although essential for a sexually transmitted disease, such a definition can cause confusion.

History of Models Used To Evaluate Chlamydia Screening

A systematic review of economic evaluations found that models which assumed a 'non-constant force of infection' were identified in the earliest years of the review in the studies by Buhaug et al (1989) and Buhaug et al (1990) who used difference equations (Roberts et al, 2006). But these studies were both preceded by the evaluations such as those of Phillips et al (1987) and Trachtenberg et al (1988) and then followed with evaluations by authors such as Genc et al (1996) and Paavonen et al (1998). These latter four studies represent just a few of those that had used simple decision trees, assumed independence of individuals and assumed a constant force of infection. In 2000, a re-emergence of economic evaluations based on models that assumed a non constant force of infection was again apparent: Welte et al (2000) carried out an economic evaluation based on the underlying clinical transmission dynamic model developed by Kretzschmar et al (2001). Simultaneously, a system dynamic model was develop to accommodate the transmission of Chlamydia and the cost-effectiveness of opportunistic screening in the UK was developed by Townshend and Turner (2000). However, nine economic evaluations of Chlamydia screening published since 2000 all used decision trees, or similar, which again overlooked issues associated with the 'interactions', or 'non constant force of infection' and assumed individuals were independent (Hu et al, 2004; Mrus et al, 2003; Blake et al, 2004; Ginocchio et al, 2003; Mehta et al, 2002; Wang et al, 2002; Postma et al, 2001; Van

Valkengoed et al, 2001; Goeree et al, 2001). Following these studies, and almost as if representing a game of 'ping pong', the six latest empirical economic evaluations have used models which do take into account the so called interactions between individuals that are associated with an infectious disease (de Vries et al, 2006; Anderson et al, 2006; Adams et al, 2007, Evenden et al, 2005; Welte et al, (2005) Roberts et al, 2008). All of these last 6 papers, cited either Roberts at 2004 (de Vries et al, 2006; Anderson et al, 2006; Adams et al, 2007) Welte et al, (2005)) or Barton et al 2004 (Evenden et al, 2005) when explaining choice of model.

The use of extreme choices of the available modelling approaches, apparent within the economics of Chlamydia screening literature is perplexing. On the one hand it is possible that analysts were unaware that taking into account the wider effects associated with the 'interactions' between individuals when evaluating an infectious disease was required. They simply applied the most commonly used and straight forward modelling approach for economic evaluations, namely the decision tree, without questioning the appropriateness. After all, the techniques summarised by the two modelling Taxonomy papers of Barton et al (2004) and Brennan et al (2006) have been defined only very recently. Yet, the issue of non independence of individuals associated with an infectious disease was recognised and considered relevant by authors such as Buhaug et al (1989 & 1990), Welte et al (2000) and Townshend and Turner (2000), before Barton et al (2004) and Brennan et al (2006) articulated their recommended approaches. It is possible that analysts were aware of the wider effects associated with 'interactions' but deliberately ignored them because they considered that disregarding them would not significantly bias the results of the analysis.

Thus, a fundamental question is raised: What is the difference in the results, and to the policy recommendations, when the economic evaluation of Chlamydia screening are based on a different modelling approach? The fact that most of the evaluations led to the same conclusion, that screening is cost–effective, despite the fact that the full range of alternative modelling approaches are represented in the published evaluations, could lead to the supposition that the modelling approach chosen does not really matter. However, such a supposition takes no account of the differences in empirical results which support the conclusions of cost-effectiveness. The conclusions of the studies might diverge if any pre-determined acceptable willingness to pay thresholds existed. Furthermore, if the modelling approach was considered not to matter, one would question the effort and distinction regarding the appropriate model types asserted by authors such as Brennan et al (2006) and Barton et al (2004).

The objective of this paper is to compare two fundamentally different modelling approaches in the economic evaluation of screening programmes for Chlamydia trachomatis. One of the two modelling approaches is based on decision analysis, namely the simple decision tree. The alternative approach being compared uses discrete event simulation, and is often referred to as a 'transmission dynamic' approach.

Models Used For Other Infectious Diseases: Externalities And Vaccination Programmes

Edmunds et al (1999) also noted that models used to calculate the health benefits (and thus cost-effectiveness) of vaccination programmes could be divided into the two main categories of static and transmission dynamic models. The authors suggested (Edmunds et al, 1999; Beutels et al, 2002) that guidelines that attempt to ensure quality and standardisation of economic evaluations such as those produced by Drummond et al (1996) need additional specific guidelines for the economic evaluation of vaccination programmes. The key argument in the vaccination scenario is that mass vaccination not only reduces the incidence of disease in those immunised but also indirectly protects non-vaccinated susceptibles against infection. The concept of indirect protection of susceptibles is termed 'herd immunity'. In economic terminology, when the actions of one intervention affect the environment for others, it is referred to as an 'externality'. Since mass vaccination results in fewer 'infectious' individuals in the population and the number declines as more individuals are vaccinated, only a dynamic framework can take account of the declining rate at which susceptibles become infected. In a static model framework this rate would remain unaltered, thus ignoring the fact there will be fewer and fewer susceptibles to who risk infection.

Infectious diseases such as Chlamydia present specific challenges for economic evaluation in addition to those apparent in the vaccination scenarios. Individuals who have a sexually transmitted infection can transmit the disease and the risk of infection to any one individual will depend on the population prevalence of the disease and the likelihood of sexual interaction with the infected individual. Screened and treated individuals will not transmit infection, but are susceptible to re-infection, and sexual partners that remain untreated can also continue to transmit infection. For the purpose of evaluating screening programmes, it is, therefore, questionable for individuals to be treated as independent or for the force of infection to be considered constant.

The difference between vaccination programmes and Chlamydia screening programmes is obvious. A vaccination program can offer some lasting immunity while an individual who is screened and treated for Chlamydia is not immune but is returned to the susceptible state. Because the individual is susceptible again, they risk becoming re-infected with the disease. Therefore, the condition for herd immunity does not exist or, if it does, it is transient at best. When an individual is screened and treated for Chlamydia there is a point in time at which they no longer have the disease. Thus, at that point there is a positive externality that they can no longer transmit the disease to anyone else. If this positive externality existed in isolation (or if the individual was immune) it could be argued that any static models of Chlamydia screening risks under-estimating the true effectiveness of the screening programme and that screening would in fact be more cost-effective than the Incremental Cost-Effectiveness Ratio would suggest. The argument being akin to the one of Herd immunity. Thus, if the positive externality existed in isolation and the ICER estimated by a static model suggested screening would be cost-effective, then because of the direction of the bias, the conclusion of cost-effectiveness is likely to be correct.

However, there also exists a counter-acting force which does not exist in the vaccination scenario. Once screened and treated for chlamydia, the individuals become susceptible again, and thus, they risk being re-infected, especially if they return to partners who have not been treated or do not reduce promiscuous sexual activity. These two forces for Chlamydia act in opposing directions and the overall balance of these forces will depend on the composition of the population screened, in terms of capturing highly promiscuous or non promiscuous sections of the population. It also depends on whether the sexual mixing is random across sexual activity groups or assortive (highly promiscuous with highly promiscuous). In the same way that Brisson and Edmunds (2003) argue that static (constant force of infection) models fail to capture the positive externality of herd immunity in the case of vaccination, in the case of Chlamydia screening, static models cannot capture the overall balance on the number of cases of infection caused by these two opposing forces.

Infectious Diseases and the Transmission dynamic model

The common feature of infectious diseases is that they transmit to cause the infection of another (human) individual and, under certain conditions, an epidemic can occur. The most important quantity governing whether or not an epidemic will develop is how many other people one person infects.

According to the theory as described by Anderson and May (1991) and Nokes and Anderson (1988), models of infectious disease transmission need to represent the population level effect of processes which occur at the individual level. An uninfected individual's risk of becoming infected (referred to as the force of infection) depends on the prevalence of infectious individuals, which is a population level characteristic. It also depends on the *rate* of contact between individuals and the infectiousness of infected individuals. Thus the transmission of infection in a population is a dynamic process and the individual risk of infection can change over time. The model used to represent an infectious disease needs to be able to incorporate this change in the ***force of infection*** (often represented by the symbol **λ).** Therefore, the population rate of infection depends upon the number of susceptibles and the number of infecteds. It is non-linear and it is this non-linearity that is considered key to the requirement of a model that can accommodate and represent a *change* in the force of infection.

One of the most basic and widely used approaches to modelling infectious diseases is the use of differential equations (Anderson and May, 1991). The approach is equivalent to the system dynamics approach to modelling. First the population is divided into compartments according to the biological properties of the different stages of the infection. The models are constructed on two key pieces of information. The first is the population size and characteristics - for example, the number of susceptible, infectious or immune individuals in the population. Second, the rate of movements between population groups is necessary and thus rules by which the rates are calculated are required e.g. birth rate, incidence of infection, recovery rate etc. The rules are then applied repeatedly and the system develops. An illustration of compartmental model representing an infectious disease is presented in the appendix.

Compartmental models versus discrete event simulation approach

For sexually transmitted diseases, National surveys of sexual attitudes and lifestyles suggest that most people have few different sexual partners and few have many (Anderson and May, 1991). Thus, it follows that those with high rates of sexual partner change, often referred to as the 'core group', play a disproportionate role in the spread of infection relative to their proportional representation in the community. Thus, characteristics such as heterogeneity would have to be incorporated as well as the randomness associated with the spread of the disease.

A compartmental models, such as that described and outlined in the appendix, would attempt to incorporate these basic characteristics. However, to incorporate all relevant characteristics adequately, especially heterogeneity aspects, the models that are required for a sexually transmitted infectious disease have recently been developed substantially and become much more complex than the compartmental models illustrated in the appendix (Kretzschmar et al, 2001, Roberts et al, 2008, Low et al, 2008). Additional sophistication is required in order to incorporate all known characteristics of the disease, which for sexually transmitted disease are more complex than for many other infectious diseases.

For instance, as the amount of heterogeneity increases, a realistic representation of the heterogeneity of sexual mixing would require a very large number of compartments to allow each compartment to be regarded as truly homogeneous. This means that the expected number of people in any compartment at any time might commonly be less than 1. For such modelling situations, it is increasingly considered much more efficient to use a different type of model, such as Discrete Event Simulation (DES) (Barton et al, 2004). Instead of modelling compartments and the system variables being counts in each compartment, it is possible to model the individuals and the system variables become the attributes of those individuals. For STDs, this type of modelling at the individual level has the further advantage that individuals can be matched to specific partners, so that contact tracing can also be modelled in a more intuitive manner.

The Chlamydia Screening Study

The Chlamydia screening studies project was funded by the UK Department of Health comprised clinical and cost-effectiveness analysis of non-selective population screening for asymptomatic Chlamydia trachomatis by means of home obtained urine specimens. It collected UK empirical data about coverage and uptake of screening, population Chlamydia prevalence, the effectiveness of partner notification, the performance characteristics of different laboratory tests, and the costs of screening. The full details of the Chlamydia screening study and the economic evaluation have been published. (Low et al 2008; Roberts et al 2008)

EMPIRICAL COMPARISON

In the following section, two different modelling approaches are compared. A static modelling approach represented by two different static models, based on examples from the published litertaure.

First a basic model which represents a decision tree but which does not include partner notification, re-infection or partner sequelae represented by the stage 1 static model; and second the stage 2 static model which does attempt to incorporate these features. Both static models are compared with a transmission dynamic model (TDM) which used Discrete Event Simulation (DES). All three models are compared against each other. All 3 models compared population screening for Chlamydia with a policy of no active screening. All models adopted the perspective of the health service and were based on an outcome of Major Outcome Averted (MOA) because there are no robust quality of life data available for this clinical condition. All models used the same data as far as possible: Cost data were collected prospectively in the study (Robinson et al, 2007). Data on screening prevalence and uptake and rates of partner notification were also collected prospectively in the ClaSS study (Low et al, 2007). Data on sequelae were estimated in a parallel cohort study in Sweden (Low et al 2006).

Economic evaluation alongside the Chlamydia screening programme: static model approach

Before constructing a static model to be used in the static model evaluation, the existing published static models were scrutinised and critiqued in order to build and develop on the best available decision tree structures and ensure that the model developed was the most appropriate to represent the Characteristics and features of the ClaSS project (Roberts, PhD Thesis 2008)

Stage 1 static Model

Many of the most basic structures of models reviewed were not suitable for use in the economic evaluation of the ClaSS project because they did not consider partner notification and the risk of re-infection to the index case, yet such basic structures comprised the majority of static evaluations. The model that was deemed to best represent the ClaSS project was the study by van Valkengoed et al (2001) which was a cost-effectiveness analysis of non-selective population screening for asymptomatic Chlamydia trachomatis by means of home obtained urine specimens – almost identical in its objective to the ClaSS project (Low et al, 2007). The diagram presented in Figure 1 shows the structure of the Stage 1 static model, in the form of a decision tree.

Stage 2 static model: Introducing partner notification and re-infection into the model

The stage 2 static model required data on partners' sequelae, re-infection and partner notification which the stage 1 structure was not designed to accommodate. The inclusion of all these structural adaptations into a static model was addressed in the literature by only one author but reported in two papers Postma et al (2000) and Postma et al (2001). By adapting the model structure to introduce complications experienced by partners, namely partner therapy and re-infection, the tree in Figure 1 is adapted to the much more complex structure presented in Figure 2 (appendix on HESG website).

The extent to which the two different static structures required different data is illustrated in Tables 1 and 2.

TRANSMISSION DYNAMIC MODEL USED FOR CLASS STUDY

The economic evaluation of Chlamydia trachomatis based on the transmission dynamic model has been published (Roberts et al, 2007).

The model

Although it is convention when models are reported to present them diagrammatically, the nature of the transmission dynamic model, which incorporates simultaneous interactions, makes it difficult to present a diagram either succinctly or correctly. In particular, the danger of attempting to present such models diagrammatically is that it will look like a decision tree and therefore be misleading in terms of what it represents, while the population effects which define it cannot be conveyed. The model is fully reported elsewhere (Low et al 2007, Roberts et al 2007).

The transmission dynamic simulation model was based on the framework of a model initially created by Kretzschmar (Kretzschmar et al, 2001) and used discrete event simulation. The model was parameterised wherever possible using empirical data collected in one of the four components of the ClaSS project (Low et al, 2007; Macleod et al, 2005; Low et al, 2006(b); Robinson et al, 2007). Nationally representative data from studies such as the second National Survey of Sexual Attitudes and Lifestyles (Fenton et al, 2001) were used to gauge the partner mixing that was assumed in the model.

As in the static modelling, the incidence rates of long-term complications associated with Chlamydia that required hospitalisation were based on data from the Uppsala Women's Cohort Study as no equivalent UK data were available (Low et al, 2006(a)). Additional data on the probabilities of long-term sequelae were identified in the review of economic evaluations were used in the sensitivity analyses.

In the TDM, the main inputs relating to Chlamydia transmission and progression were based on those in the original models used by Kretzschmar et al (2001) and Welte et al (2000) and are presented in Table 3. The probability estimates for pelvic inflammatory disease, ectopic pregnancy and infertility, estimated from the Swedish cohort study, were independently incorporated into the model. Empirical data from the ClaSS project (Low et al, 2007; Macleod et al, 2005) and from other sources (Laumann et al, 1999) were used to provide likely values for the number of partners, the frequency of partner change and changes in these parameters by age. The exact values used in the model were determined as part of the calibration process. This means that critical parameters such as population prevalence of Chlamydia by age were not directly entered but were adjusted until the model reproduced the observed Chlamydia prevalence pattern by age, and also had as close a fit as possible to the sexual behaviour parameters.

Results

The base case ICERs which compared non-selective proactive screening to no organised screening was estimated by the Stage 1 static model to be approximately £8,474 per MOA, by the Stage 2 static model to be approximately £13,344 per MOA and by the transmission dynamic model to be £19,300 per MOA. The full set of results including the sensitivity analysis are presented in Table 4.

The results of the three separate evaluations, based on the three different models, all suggest that proactively offered register-based Chlamydia screening, to females only, using home-collected specimens is an expensive intervention which is unlikely to be considered cost-effective by decision makers. For all three models, this conclusion was based on screening uptake levels reached in the ClaSS project, and an incidence of Chlamydia associated complications, estimated in a related Swedish study which is lower than previously assumed (Low et al, 2006(a)).

There are no pre-defined accepted thresholds for ICERs presented in 'major outcomes averted' for decision makers, but the base case results, produced by each of the three evaluations, are not likely to be considered cost-effective. This conclusion is drawn from the ICERs based on major outcomes averted where PID is the most commonly avoided outcome.

The base case results that are presented refer to the *best* base result each model would produce for decision makers, when each was utilising its own full structure. For instance, the base results for the Stage 2 static model include an attempt to capture re-infection and partner notification which the structure of the Stage 1 model does not accommodate. Therefore, in many ways the results are not directly comparable. In addition to their structural differences, the base case results for the Stage 1 and Stage 2 static models are not directly comparable with the base case results of the TDM model for a number of reasons. The primary reason is that the comparator is not 'exactly' the same. Both the static models compared non-selective population screening with no screening, where 'no screening' assumed that none at all took place. The TDM had the advantage that it could facilitate the assumption of background opportunistic screening that might exist in normal practice. Such an assumption better reflects the reality of current practice although no *active* screening programme is assumed. When the assumption of background opportunistic screening is removed from the TDM, the ICER falls from £19,300 to £17,900 which is slightly more favourable but only slightly closer to the Stage 2 static model result.

However, in the comparison it also must be noted that the main TDM result presented is that produced approximately 8 years after the introduction of the screening programme. Eight years was chosen arbitrarily to represent a snapshot of the ICER once the screening programme was in 'full swing' and represents the result that was presented to decision makers on the basis of the TDM.

One of the most notable features about the comparison of the results from all three models is that they follow a similar pattern in response to changes in parameters but appear to maintain a systematic difference. In all cases the Stage1 model produces the most favourable results and the TDM produces the least favourable. The ICERs for the TDM and the Stage 2 static model are closest, when both the Stage 2 static model and the TDM assume no background screening, and the estimated incidence of PID is approximately 25%. For this case the TDM estimates the ICER at approximately £7,000 per MOA, and the Stage 2 model presents an estimated ICER of £5,700 per MOA. (This is shown in Figure 3)

The key differences between static and dynamic models are primarily based on their different structures, but the Stage 1 and 2 static models differ from the TDM in that they both assume a constant force of infection whilst the TDM, by definition, does not. All three models have used identical data as far as possible. The key driver in the different amount of data used was that the Stage 1 model could not accommodate all the data inputted for the Stage 2 static model. In turn the Stage 2 static model could not accommodate all the data that was required for the TDM model. It was the variability in model structures that drove the variability in use of data.

Stage 1 static models

The evaluation based on the Stage 1 static model does not take the risk of re-infection into account, and given the infectious nature of the disease, presents only a partial effectiveness result, which might not be sustained over time if the screened and treated individuals become re-infected again. Under these circumstances it is not clear whether or not the result of the Stage 1 static model provides an under-estimate or a true estimate of the cost-effectiveness of Chlamydia screening. It will depend on how successful coverage is in terms of testing and treating the individuals who are most likely to be infected. In the case analysed, given the coverage was relatively low and that the evaluation focussed on females only, the likelihood for re-infection must be considered quite high, which would suggest that the Stage 1 static model results will make screening appear more cost-effective than it truly is. The force of infection that exists after the screening programme has not been considered in the analysis. It was not possible to include this in the structure. The extent of the risk for re-infection will depend on whether or not the coverage of the screening programme identified and successfully treated the 'core' group of individuals who have a high rate of sexual partnership formation. If the core group were captured by the screening programme, then the force of infection post-screening is likely to be low and the results may present an accurate estimate of the cost-effectiveness of the screening programme. On the other hand, if the core group were not captured by the screening programme, then the force of infection post-screening is likely to be high and the results of the evaluation based on the Stage 1 static model will make the screening programme look more cost-effective (i.e. more favourable) than it should.

There are very limited circumstances where such a model would provide accurate results and recommendations. These would be situations where the screening programme would not be intended to have any impact on the incidence of Chlamydia in the population, such as screening pregnant women for Chlamydia in order to prevent transmission to their babies. However, it will only be successful so long as the pregnant women do not return to their infected partners.

Stage 2 static model

The evaluation based on the Stage 2 static model attempts to include the risk of re-infection and the effects of partner notification but the true change in the force of infection as a result of screening and partner notification is difficult to estimate. The Stage 2 model clearly adds a one-off adjustment by

considering re-infection and partner notification. The overall balance of the opposing force of re-infection, against the change in the force of infection exerted by the screening programme, will still depend on the population included in the screening programme, and the likelihood of sexual partner mixing outside and beyond the screened population. The bias that will exist in these results is, therefore, more unpredictable in the Stage 2 model than for the Stage 1 static model. Thus, the Stage 2 static model could make screening look more or less favourable than it should but the balance of the opposing forces by such a static approach cannot be anticipated in advance. However, for the extreme example of screening pregnant women and providing partner notification to their infected partners, the model may prove appropriate because population effects are likely to be largely irrelevant.

Transmission dynamic model

One of the main characteristics of the TDM is that it can adapt its estimations to the force of infection caused by the infectious disease and the counter variation in the force of infection that exists as the population is screened both in the first year and over subsequent years. In contrast, both static models estimated a one-off screening programme. A Markov model is typically adopted in health care evaluation to accommodate repeated clinical events but such models also assume a constant force of infection and, therefore, would not be able to take account of the change in the force of infection as a result of the introduction of the screening programme within the first year of screening or over subsequent years. Furthermore, the approximate adjustments that would be required to accommodate the opposing forces of screening and re-infection over time, via estimated transition probabilities in a Markov model, could risk producing results that are very biased.

It is clear from the sensitivity analyses that have been carried out that, given a different data set, a different assumption about the incidence of PID or a different decision making threshold, the static models could have led to results that fell within some pre-determined acceptable threshold, and thus led to results that would indicate screening was cost-effective. Yet at the same time the results of the TDM could have produced results that fell outside that acceptable threshold, leading to conclusions that non-selective Chlamydia screening was not cost-effective. So clearly all three models produce different results and are likely to lead to different recommendations to decision makers.

The attraction of the static models which have dominated the economic literature on Chlamydia screening is likely to be their simplicity both in setting up and executing. In contrast, a transmission dynamic model is complex, requiring specialist skills and a long running time. The simplicity and attraction of the static model is also based in part on the fact that it requires no explicit assumptions about transmission, progression, partner mixing and re-infection which characterise Chlamydia as an infectious disease but for which data are scarce and at best assumed. However, in omitting these issues, static models are ‘implicitly’ assuming that the values for these apparently un-required data are either zero or one. Such simplifying assumptions serve only to mask the greater uncertainty by omitting explicit reference to these factors.

Since the modelling approach clearly has an impact on the results, future researchers should not be indifferent to the choice of model. The appropriate modelling approach to use in the economic evaluation of screening for Chlamydia trachomatis must be one which takes into account the transmission dynamics unless the population effects associated with the programme are deemed irrelevant or insignificant for instance in the case of pregnant women. Transmission dynamic models are supported by the epidemiological theory of infectious diseases and more importantly by the available evidence. Other modelling approaches cannot take into account the natural history of the disease and are unable to incorporate the externalities associated with the non-constant force of infection.

The main strength of this study is that it has presented empirical evidence to show that the use of static models, an approach upon which the majority of published economic evaluations of Chlamydia screening have been based, will produce results that would be very different from those produced by a transmission dynamic model using the same data. A further strength of the study is that these results are relevant to policy makers now. Sexually transmitted infections and particularly Chlamydia, are a priority policy area for the UK Department of Health and currently there is a substantial investment into the extension of the opportunistic screening programme across England (http://www.dh.gov.uk; gateway ref: 5135).

In terms of limitations, although the results highlighted almost certainly have implications which are generalisable to other infectious diseases, particularly sexually transmitted infectious diseases, the empirical evidence now exists for Chlamydia only. One limitation is that the evaluation of screening programmes for a sexually transmitted disease, which involves both sexes should include both sexes and not females only in the analysis. However, the purpose of this paper was a comparison of results from different modelling approaches and therefore focussing on women only for these purposes is entirely reasonable. It is notable that the majority of published evaluations have focussed their analysis on the screening of females only and although the wisdom of such a focus is highly debatable it is not relevant to the current paper. From a comparative point of view, a main weakness in the empirical work is the fact that a less extensive sensitivity analysis was possible using the transmission dynamic model. The assumptions of partner mixing and the proportion of individuals belonging to the core group are likely to be important factors driving the change in the force of infection. A very recent study has compared the results of three alternative transmission dynamic models which have been used to evaluate Chlamydia screening. They have used as far as possible the same data and have been shown to produce different results also. The work is in progress but initial explanations are looking to the assumed heterogeneity in the populations and the assumptions made about sexual partnerships (Kretzschmar et al, 2007). Welte et al (2005) carried out a comparison of static and transmission dynamic models which evaluated opportunistic screening for Chlamydia trachomatis. The static model used in their comparison was a decision analysis model based on the model used by Postma et al (2000 & 2001) and thus should be almost identical in

structure to the Stage 2 static model. In an attempt to ensure their static model was as close as possible to their dynamic model, data on partner notification and re-infection were derived from their later dynamic model and used as inputs into their static model. Typically, static models do not have the benefit of a parallel dynamic model to provide them with inputs from derivations for the partner notification and re-infection rate. Welte et al (2005) found the results of their TDM to be more favourable than their static counterpart (which was comparable to the stage 2 static model in the current paper). The fact their result conflicts with the results of the current paper, supports the conclusion here that it is not possible to predict whether or not the (Stage 2) static model results present a systematically predictably more favourable or less favourable ICER for the cost effectiveness of screening.

Policy implications

The results presented in this thesis are relevant to the National Chlamydia Screening programme which is currently rolling out *opportunistic* screening across England at a cost of approximately £80 million (http://www.dh.gov.uk; gateway ref: 5135). It must be assumed that the decision to roll out the programme in 2003 was, in part, based on the assumption that it would prove to be cost-effective, as so many of the published studies up to that date, had made that assertion. There are two important reasons why the earlier models produced results favourable to screening. The first is that until recently a high probability of sequelae resulting from Chlamydia infection was assumed and many studies assumed this probability to be in the region of 25 to 40%. In the ClaSS study results of a new empirical study showed that the probability of sequelae associated with Chlamydia was likely to as low as 3%. It was this lower estimate that lead the models presented here to have higher cost effectiveness ratios than previous studies. But the second reason is that the majority of the earlier static models were based on the Stage 1 static model, these models are not supported by infectious disease theory and are shown to produce results which are different from those models supported by theory and are typically favourable towards screening.

Implications for economic evaluations of other infectious diseases

The inappropriate and widespread use of a static modelling approach to evaluate Chlamydia screening is highly likely to have contributed to the production of misleading results about its cost-effectiveness. This in turn appears to have led current decision makers to invest resources in programmes that do not represent good value for money; resources could have been put to more effective use elsewhere.

Other infectious diseases would benefit from the same scrutiny that the current study has afforded the sexually transmitted disease, Chlamydia. Some very preliminary investigations suggest that there is cause for concern particularly with regard to economic evaluations of screening programmes for HIV. The authors of a relatively recent economic evaluation of HIV screening, which was published in the New England Journal of Medicine in 2005, used a Markov model in their evaluation which assumed a constant force of infection (Sanders et al, 2005). HIV does not comprise the same disease characteristics as Chlamydia, a key difference being that individuals infected with Chlamydia can be

treated and are therefore returned to their susceptible state, whilst in HIV they remain infected and infectious.

It is of particular concern that despite increasing acknowledgement of the requirement of a transmission dynamic model to evaluate an infectious disease, as opposed to a static model, the message appears to be very quickly and easily overlooked. In the recent text book by Briggs et al (2006), the authors explain the importance of using 'dynamic' as opposed to 'static' models for evaluating an infectious disease and present a very brief description of the issue of 'herd immunity' as explained in the studies of Edmunds et al (1999) and by Brisson and Edmunds (2003) (Briggs et al (2006) - see Section 3.3, page 65). However, earlier in the same text, the authors illustrate the details of a Markov model (which like decision trees assumes a constant force of infection) using a case study on the cost-effectiveness of therapy on patients with HIV (Briggs et al, 2006; page 30). This potentially misleading example is important, in part because HIV is probably the most serious infectious disease that currently exists in the world, and the resource investment applied to treat individuals and overcome the world wide problem it causes is immense.

The message from this paper is that the choice of model to use in an evaluation of an infectious disease such as Chlamydia trachomatis is likely to matter. Good quality economic evidence to decision makers is essential if the efficient and appropriate use of scarce resources is to be achieved. Health economists and modellers must refrain from the thoughtless application of their standard tool-kit to disease areas in which more sophisticated methods are required.

Table 1: Baseline probability estimates required from the ClaSS study to populate each static model

Variable (model name)	**Stage 1**	**Stage 2**
Prevalence (pInfected)	√	√
Response rate (pResponders)	√	√
Sensitivity	√	√
Specificity	√	√
Successfully treated# (pTreated)	√	√
All PID (pPid)	√	√
Infertility (pTI)	√	√
Ectopic Pregnancy(pEp)	√	√
Neonatal conjunctivitis and pneumonia (pNeoncomplications)	√	√
Probability that index case receives Partner therapy (pPartnertherapy)	n/a	√
Probability that partner receives treatment (pPartnertreated)	n/a	√
Probability of re-infection from untreated partner (pReinfection)	n/a	√
Probability of infected partner (pInfected)	n/a	√
Probability of Epididymitis in partner	n/a	√

Table 2: Complete set of parameters for population screening

Parameter	Value	95% CI	Source
Population prevalence of Chlamydia (age 16-24 years)	0.062	(0.049 – 0.078)	ClaSS
Compliance with screening (female)	0.39	(0.357 -0.423)	ClaSS
Sensitivity of screening test (female)	0.973	(0.906 – 0.997)	ClaSS
Specificity of screening test (female)	0.997	(0.992 -0.999)	ClaSS
Successfully treated	1	n/a	Assumption
PID	0.036	(0.03 – 0.04)	Swedish study (Low, 2006(a))
All PID	0.054	(0.027-0.10)	Appendix 2
Infertility	0.012	(0.006-0.024)	Appendix 2
Ectopic Pregnancy	0.012	(0.006-0.024)	Appendix 2
Neonatal conjunctivitis and pneumonia	0.013	(0.01-0.15)	Appendix 2
Probability that index case receives partner therapy	0.74	140/190 *	ClaSS
Probability that a partner will attend for treatment	0.45	92 / 206*	ClaSS
Probability of re-infection from untreated partner	0.68	n/a	Postma (2001) Schachter (1997)
Probability of infected partner	0.68	n/a	Postma (2001) Schachter (1997)
Epididymitis	0.011	(0.0027 -0.02)	Appendix 2

Table 3: Inputs relating to Chlamydia transmission and progression

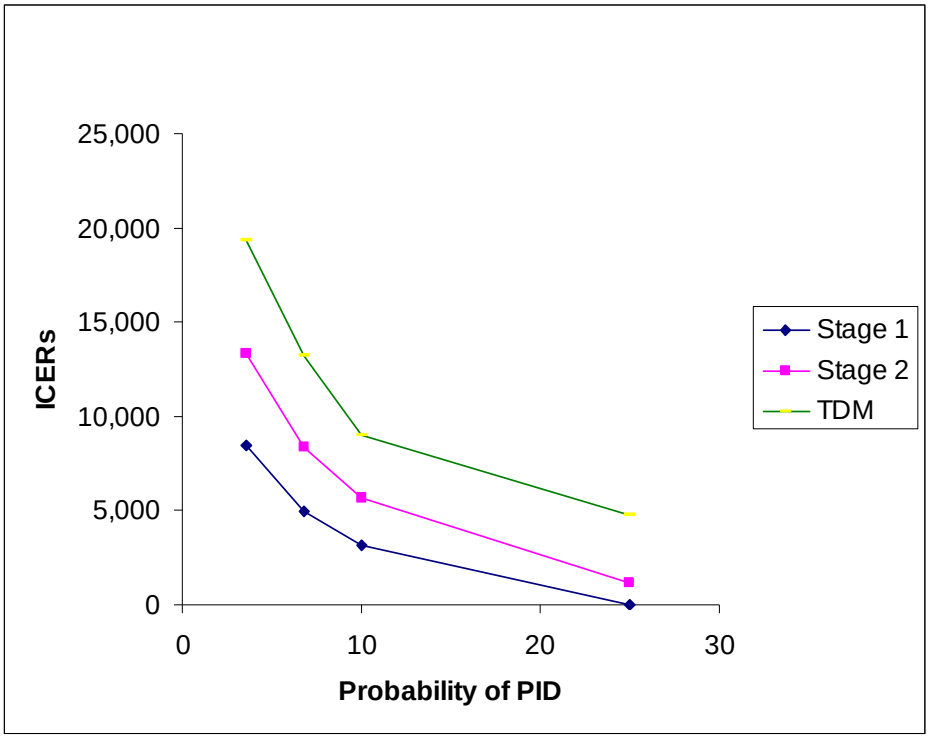
Parameter*		Value
Average probability of transmission male to female per day[#]		0.077
Average probability of transmission female to male per day[#]		0.061
Incubation period male (days)		10
Incubation period female (days)		12
Probability asymptomatic female		0.7
Probability asymptomatic male		0.25
Recovery rate per day, asymptomatic female		0.005
Recovery rate per day, symptomatic female		0.025
Recovery rate per day, asymptomatic male		0.005
Recovery rate per day, symptomatic male		0.03
Progression per day, Chlamydia to epididymitis		0.0001
	Estimate per episode	**Progression per day**
Progression of Chlamydia to severe PID[a]	0.036	0.00018
Infertility	n/a	0.0005
Ectopic Pregnancy	n/a	0.008
Neonatal complications	0.45	0.013

NOTES: *Parameters drawn from Kretzschmar et al (2001); [#]Transmission probabilities per day are based on a partnership specific rate of sexual contact multiplied by a transmission per contact. The latter based on Kretzschmar et al (2001). The transmission probabilities are not related to partnership duration. aThe model input is calibrated to the PID incidence estimated from the Uppsala Women's Cohort Study.(Low, 2006(a))

Table 4: Summary of ICERs estimated by Stage 1 and Stage 2 static models and compared with the results from the transmission dynamic model

	Static Models		TDM
Scenario	**Stage 1 static**	**Stage 2 static**	**ClaSS Transmission dynamic model**
Base case	8,474*	13,344*	19,300#
Response 60% female	5,488*	9,027*	15,700#
Incidence of PID = 0.068	4,973*	8,359*	13,200#
Incidence of PID in model = 0.1 equivalent to Welte et al (2000)	3,107*	5,702*	9,000#
Incidence of PID = 0.25 (unadjusted)	**Dominant***	1,147*	4,800#
PID in model 10%, Response rate 60%	1,516*	3,402*	5,400#
Base case with no background screening	8,474*	13,344*	17,900*
No background screening; and PID equivalent to 25% (by on the basis of 40% asymptomatic) thus 10% PID estimate actually in model	3,107*	5,702*	7,000*
Adjustment in unit costs applied to sequelae			
PID £30 [a]	9,945*	14,816*	20,500#
PID £30 [a], Infertility £3014	9,505*	14,375*	20,500#
PID and Infertility £3014 [b]	8,033*	12,903*	19,300#
Omit complication costs [b]	10,444*	14,727*	21,100#
All complications £3014 [b]	7,430*	12,598*	18,300#
All complications £6028 [b]	4,416*	9,973*	15,500#
Incidence equivalent to Welte, PID cost average £328 [c]	5,068*	7,663*	10,600#

Figure 3: Comparison of ICERs from the three models



Key References:

1. Anderson RM, May RM. Infectious diseases of humans: dynamics and control. Oxford Science publications. Oxford, UK. Oxford University Press. 1991; ISBN 0-19-854040-

2. Barton P, Bryan S, Robinson S. Modelling in the economic evaluation of health care: selecting the appropriate approach. Journal of Health Services Research & Policy 2004;9:110-8.

3. Brennan A, Chick SE, Davies R. A taxonomy of model structures for economic evaluation of health technologies. Health Economics 2006;15:1295-1310.

4. Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation. Oxford University Press. 2006 ISBN 0-19-852662-8

5. Brisson M, Edmunds WJ. Economic evaluation of vaccination programs: the impact of herd-immunity. Medical Decision Making 2003;23:76-82.

6. Kretzschmar M, Welte R, Van den Hoek A, Postma MJ. Comparative model-based analysis of a screening program for Chlamydia trachomatis infections. American Journal of Epidemiology. Am J Epidemiol 2001;153:90-101.

7. Kretzschmar M, Turner KME, Barton PM, Edmunds WJ, Low N. Evaluation of Chlamydia screening: Can individual based modelling provide answers? 17th International Society for Sexually Transmitted Diseases Research (ISSTDR) Seattle, USA. 31 July 2007

8. Low N, McCarthy A, MacLeod J, Salisbury C, Horner PJ, Roberts TE, et al. The Chlamydia screening studies: rationale and design. Sexually Transmitted Infections 2004;80:342-8.

9. Low N, McCarthy A, Roberts T, Huengsberg M, Sanford E, Sterne JA, et al. Partner notification of chlamydia infection in primary care: randomised controlled trial and analysis of resource use. BMJ 2006(b);332:14-19.

10. Low N, McCarthy A, Macleod J, Salisbury C, Campbell R, Roberts TE et al. Epidemiological, social, diagnostic, and economic evaluation of population screening for genital chlamydial infection: the Chlamydia Screening Studies Project. Health Technol Assess 2007; Vol. 11: No.8

11. Roberts T, Robinson S, Barton P, Bryan S, McCarthy A, MacLeod J, et al. The correct approach to modelling and evaluating Chlamydia screening.(letter) Sexually Transmitted Infections 2004;80:324-5.

12. Roberts T, Robinson S, Barton P, Bryan S, Low N, for the Chlamydia screening studies (ClaSS) project. Screening for chlamydia trachomatis: a systematic review of the economic evaluations and modelling. Sex Transm Infect 2006; 82:193-200.

13. Roberts T, Low N. Commentary: The cost effectiveness of opportunistic chlamydia screening in England (Adams EJ, Turner KME, Edmunds WJ). *Sexually Transmitted Infections.* 2007(a);83:275-276.

14. Roberts TE, Robinson S, Barton P, Bryan S, McCarthy A, Macleod J, Egger M, Low N, The cost-effectiveness of home based population screening for *Chlamydia trachomatis* in the UK: economic evaluation of the Chlamydia Screening Studies (ClaSS) Project. British Medical Journal. 2007(b);335:291-4

15. Robinson SM, Roberts TE, Barton PM, Bryan S, Macleod JA, McCarthy A *et al*. The health care and patient costs of an proactive chlamydia screening programme: the Chlamydia Screening Studies (ClaSS) project. *Sex Transm Infect* 2007;doi 10.1136/sti.2006.023374.

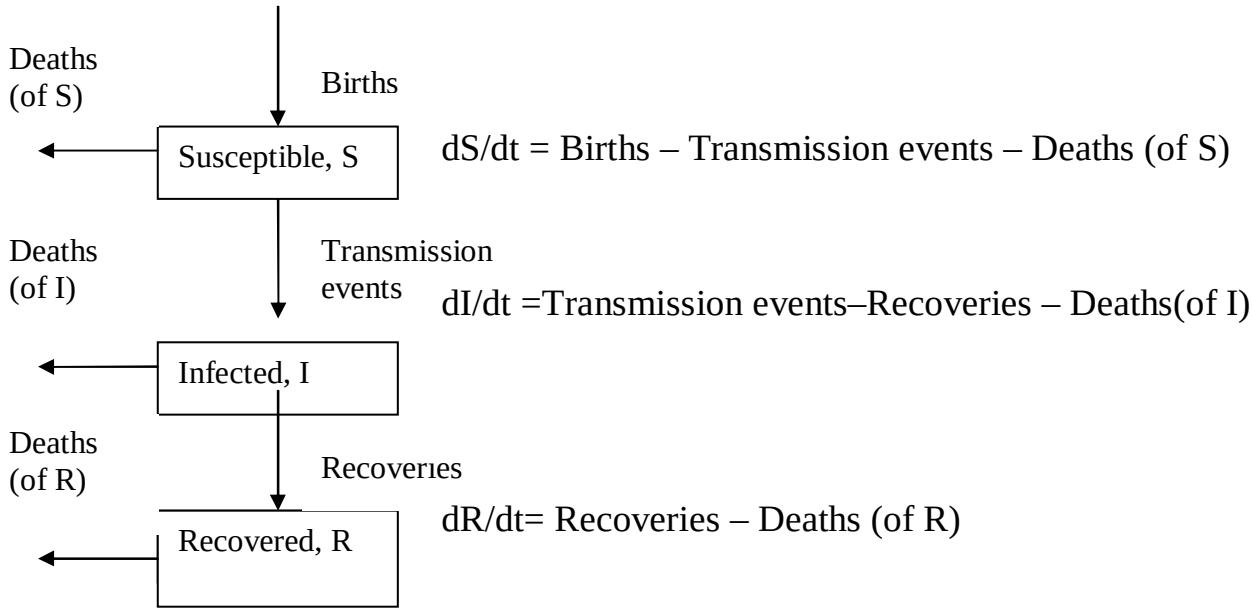
16. Sanders GD, Bayoumi AM, Sundaram V, Pinar Bilir S, Neuermans CP, Rydzak CE. et al. Cost-effectiveness of Screening for HIV in the era of Highly Active Antiretroviral Therapy. N Engl J Med 2005; 352:570-85

17. Welte R, Kretzschmar M, Leidl R, van den Hoek A, Jager JC, Postma MJ. Cost-effectiveness of screening programs for Chlamydia trachomatis: a population based dynamic approach. Sex Transm Dis 2000; 27:518-529.

18. Welte R, Postma M, Leidl R, Kretzschmar M. Costs and effects of Chlamydial screening: Dynamic versus static modelling. Sexually Transmitted Diseases 2005;32:474-83.

19. Van Valkengoed IGM, Postma MJ, Van den Brule AJC, Meijer CJLM, Bouter LM, Boeke AJP. Cost effectiveness analysis of a population based screening programme for asymptomatic Chlamydia trachomatis infections in women by means of home obtained urine specimens. Sexually Transmitted Infections 2001;77:276-82.

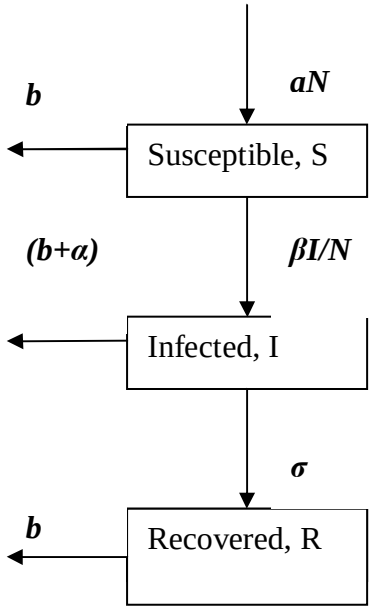
Appendix 1: Flow diagram for basic SIR (Susceptible - Infected –Recovered) model *An example would be childhood illness such as the measles.*



In the above model, susceptible individuals and recovered individuals can both die at a background 'non-diseased' rate. The infected individuals can die at both the background rate and at a disease-induced death rate.

Each term in these equations is a function of one or more of the state variables S, I and R meaning that the value of the terms changes as the state variable changes. In the equations which define each compartment of the model, presented below, any term relating to entry to a compartment has a positive sign whilst any term relating to leaving the compartment has a negative sign.

The set of equations for the basic SIR model



$$\frac{dS}{dt} = + aN - \beta SI/N - bS$$

$$\frac{dI}{dt} = + \beta SI/N - (b+\alpha)I - \sigma I$$

$$\frac{dR}{dt} = + \sigma I - bR$$

$$N = S + I + R$$

For the above set of simultaneous differential equations, N,S, I and R are variables and the following are all parameters:

a - the birth rate
b – the background death rate
α – the death rate due to the infection

β - the rate of transmission of infection
σ – the recovery rate

The transmission rate formula can be further analysed.
First, consider the situation of one susceptible individual
Let ***c*** represent the rate of contacting other individuals, which applies to all individuals irrespective of their infection status. Transmission requires contact with infected individuals.
Therefore, the rate of *contacting* infecteds is represented by
c**I/N**
where I/N is the proportion of the population infected. (I = number of infecteds; N = number in total population).
The rate of transmission from infecteds is represented by
pcI/N
Where **p** represents the probability of transmission when an infectious individual contacts a susceptible. The term represented by (7.8) is referred to as the ***force of infection*** and often represented by the symbol **λ.**

Appendix Figure 1: Stage 1 static model structure