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Full Length Research Paper

Simplifying mathematical modelling to test intervention strategies for *Chlamydia*

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In recent years, there has been a rise in applications of mathematical modelling in sexually transmitted infections. This paper outlines a new approach to mathematical modelling that tests intervention efforts on *Chlamydia*. The aim was to produce a simple model that can be used when new data comes to hand without the need to re-run the simulation. A simple model was developed to study the effects of interventions in lowering rates of *Chlamydia* in a high-risk population of 16 to 24 year olds. Parameters are informed by the best available data. The model was verified by running it backwards in time to see if it correctly 'retrodicts' rates of *Chlamydia* in the past. The model predicted that *Chlamydia* would disappear long-term if there were 45% condom use, annual check-ups and 23.5% successful contact tracing among the high-risk 16 – 24 year old age group. The model's expressions can be applied readily to different populations of interest and to address specific questions, indicating that the model is a quick and easy tool to apply in public health policy making.

Key words: Mathematical modelling, *Chlamydia*, public health interventions, partner notification, annual check-up, condom use.

INTRODUCTION

In recent years there has been a rise in the applications of mathematical modelling in infectious disease epidemiology (Garnett, 2002; Fone et al., 2003; Grundmann and Hellreigel, 2006). Mathematical models have been utilised to forecast the course of epidemics, the cost-effectiveness of different interventions (Duncan and Hart, 1999; Jolly et al., 2001) and to inform estimates of biological and epidemiological parameters that are difficult to measure (Garnett, 2002; Turner et al., 2006). Population modelling techniques from mathematical bio-logy have been combined with sexual network analysis from sociology to investigate the impact of sexual behaviours on the transmission of Sexually Transmitted Infections (STIs) (Jolly et al., 2001; Riolo et al., 2001; Potterat et al., 2002; Cabral et al., 2003; Pinkerton et al., 2003; Turner et al., 2006). However, these models are often complex and difficult to understand (Garnett, 2002).

Furthermore, the models are informed by estimates of parameters from singular geographically specific studies and so do not generally provide exact analytical solutions. This results in the models having to be re-run every time new data comes to hand.

The purpose of this paper is to replace the mathematical modelling process of the natural sciences with those of the physical sciences to develop a model that can explore the impact of intervention options on the transmission of *Chlamydia trachomatis* (*Chlamydia*). This has the advantage of simplifying the modelling process. Chlamydia is the most commonly diagnosed STI in the United Kingdom (Adams et al., 2004a, b; Heath Protection Agency, 2005; Hawker et al., 2005). The main interventions used to lower prevalence of *Chlamydia* are partner notification (contact tracing), screening and the primary prevention method of condom usage during sexual intercourse. We aim to derive simple algebraic expressions for the prevalence of *Chlamydia* that can

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be used when new data come to hand without the need to re-run the simulation. These expressions could also be applied immediately to different populations of interest.

METHODS

Mathematical modelling is a powerful field of procedures in the natural and physical sciences. In brief, a mathematical model is an abstract model that uses mathematical language to describe the behaviour of a system. It typically uses a set of variables and a set of equations that establish relationships between the variables. Mathematical models enable one to understand the nature of complex systems that cannot be solved exactly. Also known as computer simulation modelling, mathematical modelling is different to the modelling techniques in statistics, where a single equation is used such as ordinary least squares linear regression or logistic regression. The mathematical model has the potential for producing simulations suited to making predictions and exploring the limits of predictability. Using only those factors that are considered relevant to disease transmission, different scenarios can be explored under varying conditions and can be used to address specific questions. For instance, they can test the effects of different preventative strategies on the transmission of *Chlamydia*. A model is validated by comparing its results with qualitative observations or quantitative data from the real world (Garnett, 2002).

Our model focuses on the effects of interventions on lowering exposure to *Chlamydia* in a high-risk population of sexually active 16 – 24 year olds. It tests the impact of three preventative strategies: condoms, screening and partner notification. Mathematical models' parameters are informed by data taken from the literature (Jolly et al., 2001; Pinkerton et al., 2003; Cabral et al., 2003; Doyle et al., 2006). Our model uses estimates from systematic reviews, the British National Survey of Sexual Attitudes and Lifestyles (2000) (Johnson et al., 2001; Fenton et al., 2001; Turner et al., 2006) and routine surveillance on the target population by Health Protection Agency. While the risk of acquiring STIs involves the infectiousness of an individual and susceptibility of the partner to a new infection, (Doherty et al., 2005), the main behavioural determinants of STI transmission are condom usage, two plus sexual partners in the previous 12 months and frequency of sexual acts.

For the purposes of the model, discriminate use of condoms in casual partnerships versus long-term monogamous partnerships are not essential, what is important is the effectiveness of condoms in preventing *Chlamydia*. Systematic reviews on condom usage have shown that condoms are 90% effective on a per-act basis for both HIV and STIs (Pinkerton et al., 2003, 2007). Unfortunately, there is little evidence of how regularly 16 to 24 year olds use condoms for sexual encounters. In addition, studies on condom usage in the reduction of STI transmission tend to focus on the impact of a consistent use of condoms (Warner et al., 2004; Holmes et al., 2004), yet the percentage of those who use condoms 100% of the time is small. In the National Survey of Sexual Attitudes and Lifestyles conducted in 2000, 33% of men and 24.1% of women in the UK reported using a condom on all occasions in the previous four weeks (Johnson et al., 2001). In our model, we will explore the effects of varying condom use in sexual acts to uncover the effects of inconsistent use of condoms.

Sexually transmitted infections are spread through sexual interactions between individuals so the greater the number of people with whom an individual has sexual relationships the greater the likelihood of coming in contact with sexually transmitted infections. Irrespective of whether condoms are used or not, having two or more sexual partners in the previous 12 months increases the risk of exposure to an STI (Fenton et al., 2000; Johnson et al., 2001; Heffernan, 2004; Hawker et al., 2005). Firstly, it is likely that the relationships are non-monogamous and they tend to be casual, short term or one night stands. Secondly, people with multiple partners over a twelve month period are more likely to have concurrent or overlapping relationships, which facilitate rapid transmission of an STI. One relationship may be ending whilst another is commencing, allowing infection to be spread before the symptoms can appear. However, an individual risk of acquiring an STI is a function only of the total number of partners. It does not depend upon whether they are concurrent or sequential. In relation to *Chlamydia*, it has been demonstrated that the number of secondary cases produced by the initial case is highest for those who had two plus partners compared to those with just one in the time period (Fenton et al., 2000; Jolly et al., 2001; Potterat et al., 2002).

Frequency of sex is the third behavioural factor in the transmission of chlamydia. In the UK, males aged 16 to 24 years have sex on average 6.9 times a month, whilst females reported an average of 7.7 times (Johnson et al., 2001). In addition, 54.8% of the male and 44.8% of the females report having sexual intercourse within 4 weeks of meeting a new sexual partner (Johnson et al., 2001).

In our model, the following parameters are fixed (that is, we are not free to change them):

1. Initial fractional prevalence of *Chlamydia* among 18 to 24 year olds, $I(0) = 0.01$ (Health Protection Agency, 2007).
2. Average number of new sexual partners per year, $y_p = 2$ (Fenton et al., 2001; Jolly et al., 2001; Johnson et al., 2001; Potterat et al., 2002; Heffernan, 2004; Hawker et al., 2005).
3. Average number of sexual encounters with each partner, $s = 44$. This is based on 16 to 24 year olds having sex an average of 88 times per year (Johnson et al., 2001) and an average of 2 new sexual partners per year.
4. Probability of transmission of *Chlamydia* from an infected to a susceptible per unprotected sexual act, $p = 0.0375$ (Turner et al., 2006).
5. Effectiveness of condoms in preventing the spread of *Chlamydia*, $e = 0.90$ (Pinkerton et al., 2003, 1997).

We treat the following as variables that we can adjust to find the best intervention strategy: T, the average time between check-ups; c, the fraction of condom use on a per act basis; and r, the number of contacts screened per diagnosed case.

Condom use

For simplicity, we use a population averaging model. While a more complete treatment might use a selective mixing model and also consider individual based simulations rather than population averages, the aim of the present treatment is to gain straightforward insights into the effectiveness of different intervention strategies. This should enable us to highlight features that could be studied further in more detailed models and test different strategies that ethics would not allow to be tested in real populations.

We denote the fractional prevalence of *Chlamydia* in the population under study at time t as $I(t)$. If each person has (an average) s sexual encounters with each new partner, then the prevalence at a slightly later time $t + dt$ can be written as,

$$I(t + dt) = I(t) + y_p [1 - (1 - p(1 - ce))^s] I(t)(1 - I(t))dt, \qquad (1)$$

where the probability of transmission per unprotected encounter is p, the average fraction of condom use is c, the average number of new partners per person per year is yp, and the effectiveness of condoms in preventing transmission is e. This can be rearranged to give a simple nonlinear differential equation,

$$\frac{dI}{dt} = y_p [1 - (1 - p(1 - ce))^s] I(1 - I), \qquad (2)$$

This equation can be solved numerically to find the prevalence of chlamydia at subsequent times.

Screening ('check-ups')

So far, the model does not include the effect of people seeking treatment. For planning and auditing purposes of a screening programme, a useful measure is patient attendance at a clinic or site within a one year period (Salisbury et al., 2006), that is, annual check-ups. This model explores the effect of an annual (or other frequency) visit at a clinic. The effect of check-ups and treatment can be incorporated into the model by adding the term –I/T to the right hand side of (2), where T is the average number of years between check-ups. This gives:

$$\frac{dI}{dt} = y_p [1 - (1 - p(1 - ce))^s] I(1 - I) - I/T. \quad (3)$$

We should also account for the fact that people are in the high-risk category, of interest in this model, only between the ages of 16 and 24. After the age of 24, it has been shown that the prevalence of *Chlamydia* reduces dramatically due to changes in sexual behaviours (Boekeloo et al., 2002: Adams et al., 2004a, b). This means that one ninth of the population 'drops out' each year and a new uninfected ninth enters the population. This can be accounted for with another term, –1/9. The prevalence is then given by:

$$\frac{dI}{dt} = y_p \Gamma I(1- I) - \left(\frac{T+9}{9T}\right) I, \quad (4)$$

where we have made the definition, $\Gamma = 1 - (1 - p(1 - ce))^s$. Γ can be interpreted as the total probability of transfer of infection between an average couple over the course of their relationship.

The model presented so far enables us to study how the prevalence of Chlamydia depends on the rate of condom use and on the average time between check-ups. The first term on the right hand side of Equation (4) represents the rate of increase of the prevalence and the second term represents the rate of decrease. This means that, to decrease the prevalence of Chlamydia, we could reduce the first term (e.g. by decreasing Γ by increasing the rate of condom use) or increase the size of the second term by reducing T, that is, the time between check-ups.

Partner notification

Partner notification or contact tracing is a well established intervention in the control of STIs (Cowan et al., 1996; Cabral et al., 2003; Tomnay et al., 2005; Low et al., 2007). This is the process whereby the sexual partners of people with *Chlamydia* diagnoses are informed of their exposure to the infection. They are then offered diagnosis, treatment and advice about preventing future infection. The idea behind this intervention strategy is that it identifies people who have had contact with the infection and are therefore more likely to have acquired it than a person selected at random from the population. We now outline how this can be incorporated in our model.

At time t, the prevalence of the infection is I(t). This means Idt/T is the fraction of the population that is treated between t and t + dt. The fraction of the population that presents itself for screening based on contact tracing is then rIdt/T, where r is the number of contacts that are screened for each chlamydia case diagnosed. To incorporate the effect of contact tracing in our model, we need to know the fraction of the informed partners that are infected. A first approach might be to assume they have the same rate of infection as the general population, that is, I(t). However, such an approach would be to deny the great advantage of contact tracing which identifies people that are more likely to be infected than the average. Instead, we calculate the probability that the notified partners are infected based on the fact that they have had sexual contact with at least one infected person. This gives the probability of infection as, $I + \Gamma (1 - I)$, that is, the probability they were already infected plus the probability they acquired an infection from their contact. The term that now needs to be added to (4) is $-rI(I + \Gamma (1 - I))/T$.

The new differential equation, including contact tracing, is:

$$\frac{dI}{dt} = y_p \Gamma I(1 - I) - \left(\frac{T + 9}{9T}\right) I - \frac{r}{T} I(I + \Gamma (1- I)). \quad (5)$$

This equation is the basis of our model.

RESULTS

Figure 1 illustrates the results for different average periods between check-ups keeping all other parameters fixed at their current values. There is a dramatic decrease in the prevalence of Chlamydia between check-ups every 15 months and every 12 months. There is a further dramatic decrease when check-ups are every 9 months on average.

Figure 2 shows the effect of condom use when all other parameters are fixed at their current values. It is clear that condom use enables substantial decreases in the infection rates. There is a significant reduction in the prevalence of the infection for a 25% increase in the per-act rate of condom use.

Figure 3 illustrates the effect of contact tracing with all other parameters fixed at their current values. We see that there is an increase in the prevalence of the infection when the rate of contact tracing is decreased by 25% and a decrease when the rate is increased by 25%. While contact tracing achieves a notable reduction in the prevalence of the infection, the effects are not as powerful as for either condom use or the frequency of check-ups. Contact tracing may not be a successful strategy in reducing the incidence of *Chlamydia* in the absence of other strategies. It seems likely that a combination approach will be the best strategy.

Our model allows us to derive simple algebraic expressions for the likely long-term effects of any intervention strategy. The long-term prevalence of *Chlamydia*, I_{lt}, can be found by setting dI/dt to zero in Equation (5) and solving for I. This gives:

$$I_{lt} = \frac{9\Gamma (Ty_p - r) - (T + 9)}{9\Gamma (Ty_p - r) + 9r} \quad (6)$$

which could be useful for assessing the relative long-term benefits of different approaches.

In Figures 4 to 6, we have plotted respectively the long term prevalence of Chlamydia when we vary the period between check-ups, the rate of condom use and the rate of successful contact tracing. In each Figure, all other parameters are fixed at their current values. We see that, in each case, there is some critical value beyond which

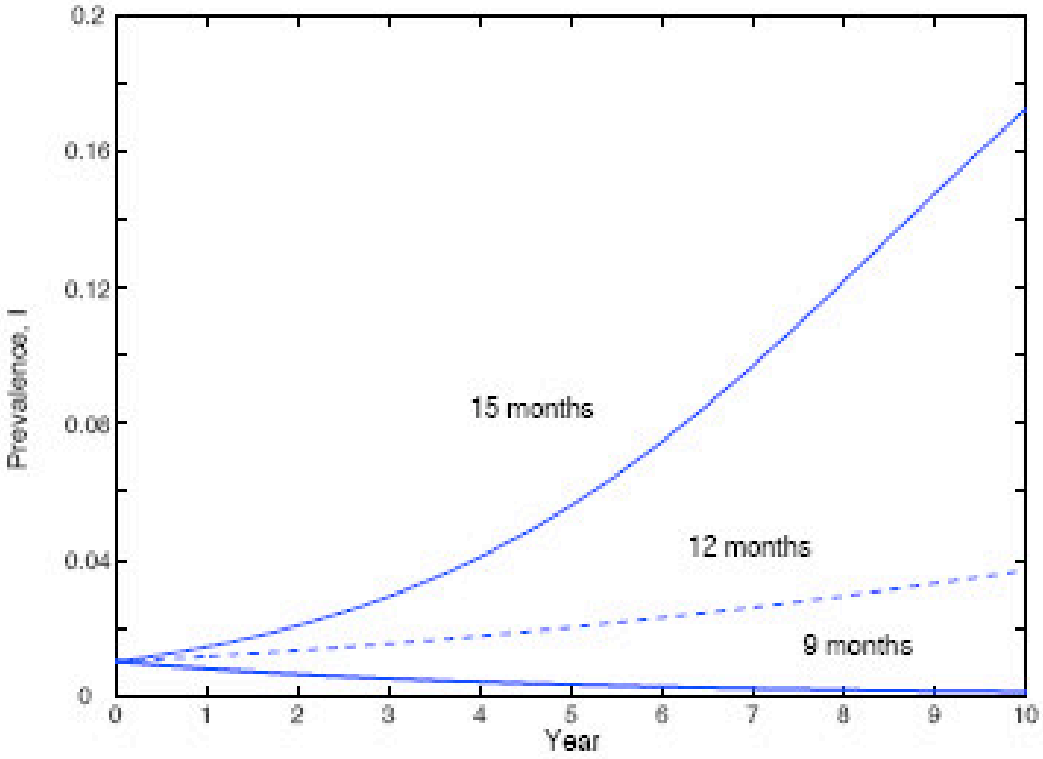

Figure 1. Effect of the time between check-ups with all other parameters remaining egual. The dashed line represents the current parameters and the two solid lines represent a 25% increase and a 25% decrease in the period between check-ups.

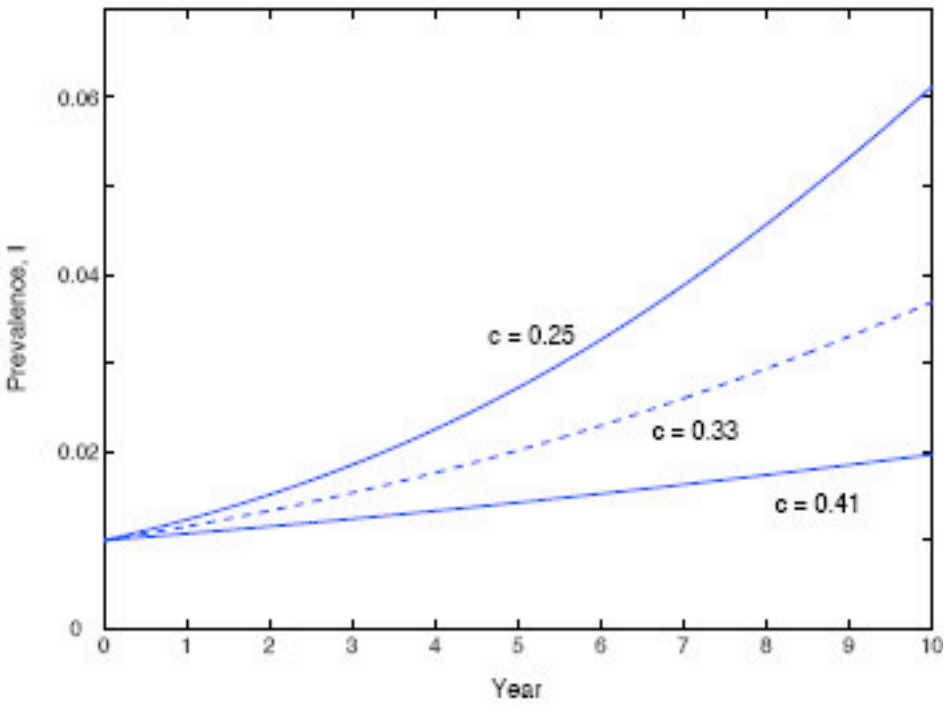

Figure 2. Effect of condom use with all other parameters remaining egual. The dashed line represents the current parameters and the two solid lines represent a 25% increase and a 25% decrease in the rate of condom use on a per act basis.

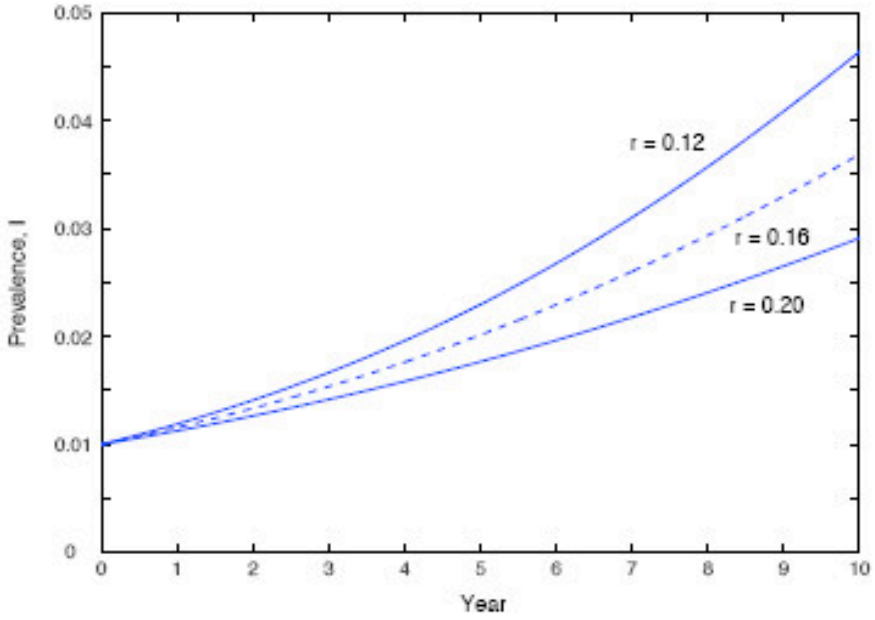

Figure 3. Effect of contact tracing with all other parameters remaining egual. The dashed line represents the current parameters and the two solid lines represent a 25% increase and a 25% decrease in the current rate of contacts who are successfully screened for each index case.

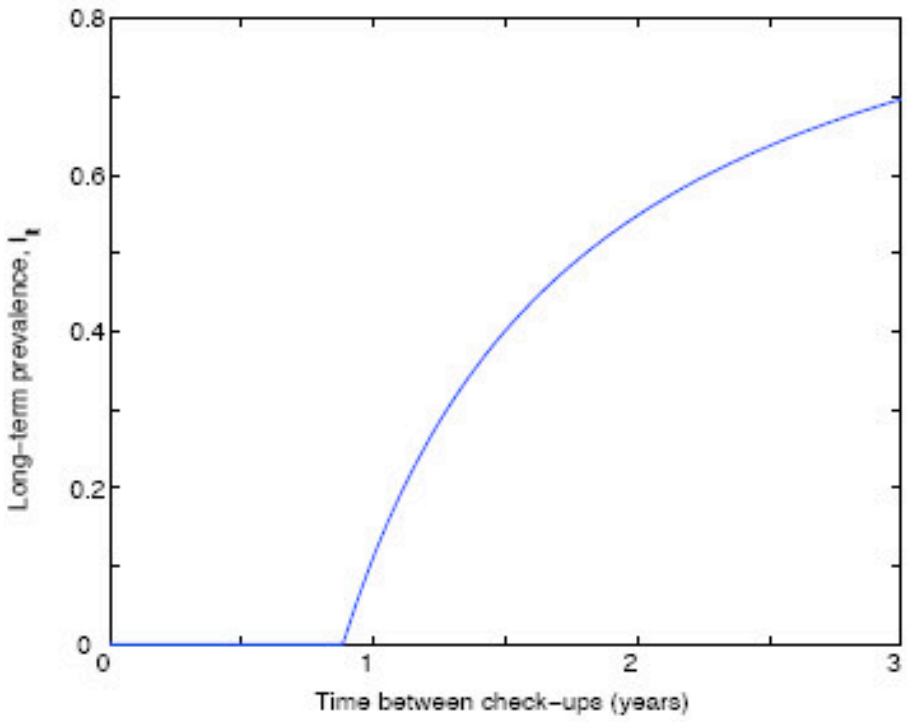

Figure 4. Long-term prevalence of Chlamydia as a function of time between check-ups.

the long term prevalence of the infection is zero. This critical value corresponds to the value that the parameter needs to have to effectively eradicate the infection in the long term. We can derive simple expressions for these

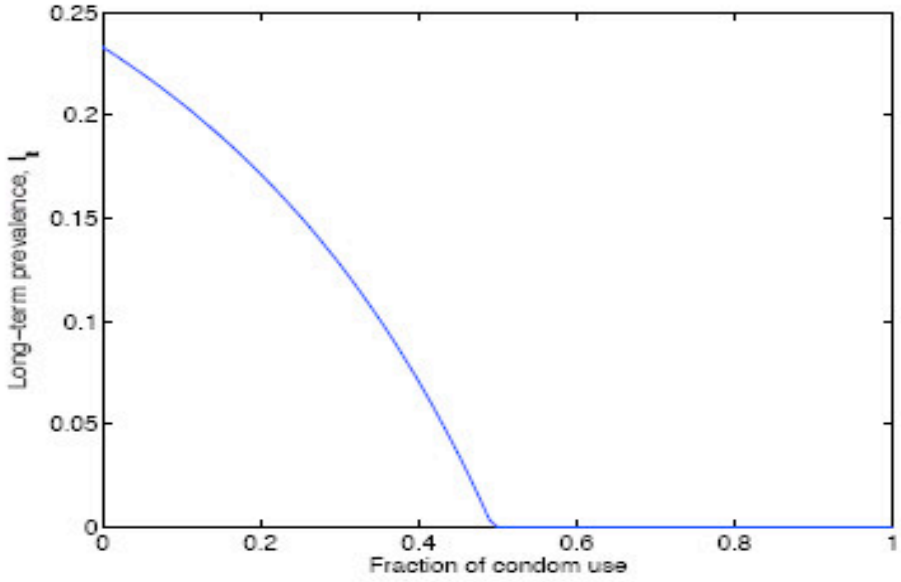

Figure 5. Long-term prevalence of Chlamydia as a function of condom use on a per-act basis.

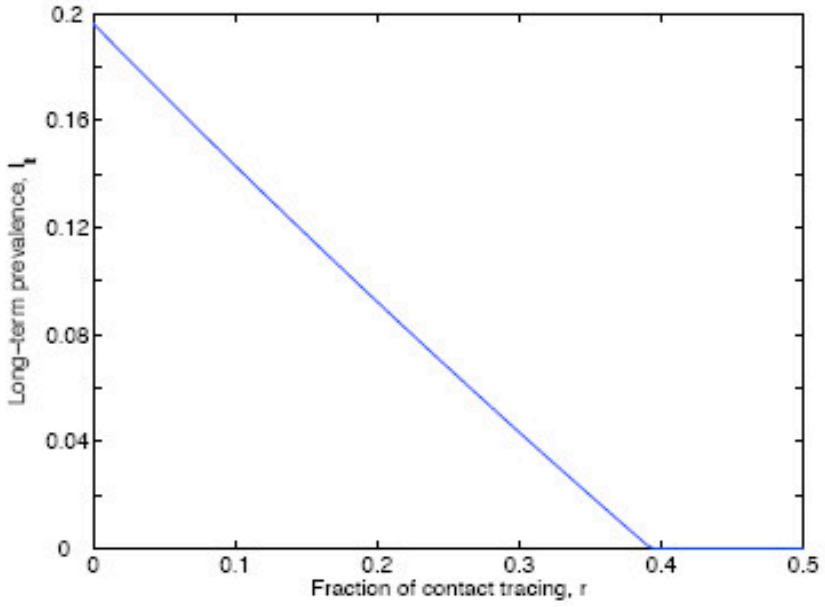

Figure 6. Long-term prevalence of Chlamydia as a function of fraction of successful contact tracing..

critical parameters by setting $I_{lt} = 0$ in Equation 7, to give:

$$9\,\Gamma\,(Ty_p - r) - (T + 9) = 0. \quad (7)$$

Using this expression, the critical value for the period between check-ups, Tcrit, is:

$$T_{crit} = \frac{1 + \Gamma r}{\Gamma y_p - 1} \quad (8)$$

which for present parameters gives $T_{crit} \approx 0.87$ (that is about 10.5 months) and agrees well with the value shown in Figure 4. This is not a substantial change from current targets. The critical value for Γ is:

$$\Gamma_{crit} = \frac{T + 9}{9(y_pT - r)}, \quad (9)$$

Which for present parameters gives $\Gamma_{crit} \approx 0.604$. This

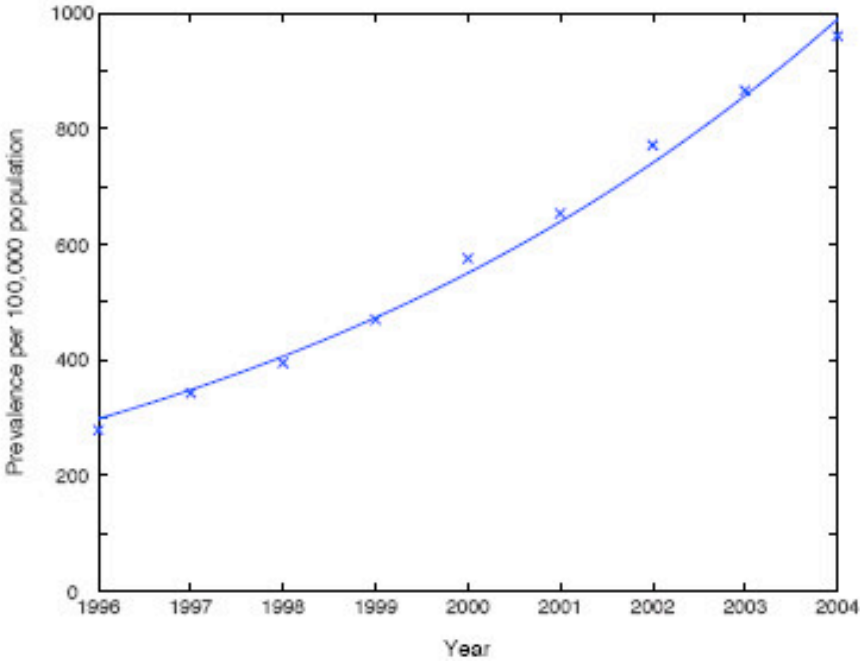

Figure 7. Model verification: The model is run backwards in time and compared with observed data.

corresponds to a rate of condom use of about 49% and agrees with the value in Figure 5.

Finally, the critical value for the rate of successful contact tracing, rcrit, is:

$$r_{crit} = Ty_p - \frac{T + 9}{9\,\Gamma}, \qquad (10)$$

which for present parameters gives $r_{crit} \approx 39\%$, in good agreement with the value in Figure 6.

Of course, these critical values are just approximate values. Among other things, they depend on there being no changes to the parameters in the intervening time. They should be treated more as relevant figures of merit for the different approaches. Overall, however, they are encouraging and show that relatively modest improvements can make a major difference to the prevalence of *Chlamydia*. This is likely to be particularly true when combination strategies are applied, e.g., our model predicts that *Chlamydia* would disappear long-term if we had 45% condom use, annual check-ups, and 23.5% successful contact tracing among the high-risk 16 – 24 year old age group. It would of course be preferable to do better than these targets since then the infection would be controlled more rapidly.

DISCUSSION

Model verification

All computer simulations should be validated. The accuracy of our model can be tested by using the current values of the parameters in our model and running the model backwards in time to see whether it correctly 'retrodicts' rates of *Chlamydia* in the past. To carry out this test, we need values for the parameters c, T, and r.

We take the rate of condom use on a per act basis among 16 - 24 year olds to be c = 0.33 (Wellings et al., 1994) and assume that check-ups are on average taken annually, that is, T = 1 (Boekeloo et al., 2005). This is a useful timeframe since the incubation period of *Chlamydia* is about three months and, in the UK, men consult their GP on average about 1.7 times per year, and women about 5 times (Salisbury et al., 2006). We will keep r as a fitting parameter, that is, r will be adjusted to find the best match between our model and the observed data.

The results of this test are plotted in Figure 7. The solid line represents our model and it is compared to the reported rates of diagnosed *Chlamydia* infection from Health Protection Agency (crossed data points). These notifications are for 16 to 24 year olds of both sexes. The best agreement between the model and the observed data is shown for r = 0.16. Reported rates of contact tracing for *Chlamydia* have included 0.1 and 0.2 (*Chlamydia* Advisory Group, 2005; Turner et al., 2006) and a systematic review on the management of gonorrhoea and Chlamydia in GUM clinics in the UK found that contact tracing results in the treatment of about 0.61 partners per index case of *Chlamydia* (Low et al., 2004), that is, r = 0.61. The value of r derived from our model falls within the range of both these reported rates and shows our model is consistent

with the observed data. While this agreement does not guarantee that our model will accurately predict future prevalence, it does show that our model reflects past real trends of *Chlamydia* and we can be confident in using it to simulate the impact of different intervention strategies on *Chlamydia* transmission.

Use of model

Mathematical modelling processes utilised in physical sciences can be readily employed to examine the effectiveness of public health interventions on lowering rates of *Chlamydia*. Our model provides simple algebraic expressions for the long-term impact of different intervention strategies (equation 7) and for the critical values of parameters needed to effectively eradicate the infection (equations 8 to 10). These expressions are intended primarily as a guide to the likely impact of different approaches. They can be applied readily (without having to re-run any simulations) whenever new and improved data comes to hand. The expressions can also be run with local population data and so the model could be a quick and easy tool to apply in policy making.

Mathematical modelling is limited by parameter values being estimated with the best available data. When developing this model, we were forced to recognise the assumptions being made and cast a critical eye over the evidence used to estimate parameter values. Systematic reviews can help but systematic reviews are reliant on the quality of data already collected. Developing this model highlighted weaknesses in the existing literature. Firstly, there is a need for more rigour in surveying the numbers of partners notified and treated per individuals. The model assumed transmission probability for *Chlamydia* being 0.0375, though in truth, there is very little data on this parameter. Sexually transmitted infections are commonly underreported and estimates for parameters like condom usage and the number of partners notified per individual vary greatly from study to study (Weller et al., 2006; Mathews et al., 2006). The model also revealed that studies on condom usage and STIs focus on 100% use of condoms versus non-use (Warner et al., 2004; Holmes et al., 2004). More information is needed on the inconsistency of use, that is, the rate of condom usage on a per act basis. Thirdly, there was considerable variation with the estimates of parameters within and between men and women. In some instances, estimates were missing. However, with a model like the one presented here, the model can be elaborated to incorporate these parameters in the future.

Our model is simplistic but it can be further developed to include confounding factors, such as factors influencing condom use. Cost effectiveness is also omitted. The model could be adapted to find how much should be spent on each intervention strategy to maximise the reduction in the prevalence of *Chlamydia* for a given budget. In other words, for a given total budget, this model could be used to find how much should be spent on each intervention strategy to maximise the reduction in the prevalence of *Chlamydia*. Such an approach could be helpful in targeting key areas for a more detailed analysis and costing. This model could also be modified to include impact of other factors such as re-infection, self-cure and heterogeneous mixing of sexual partners.

However, the purpose of this paper was to step back from the trend of increasing complex mathematical models in the epidemiology of STIs to produce a simpler model that could be used to predict overall impact of public health interventions on *Chlamydia*. It is intended that public health practitioners could take equation (7) and by imputing their local data, they would be able to predict the long- term effects of intervention strategies in their populations. This (and the estimation of critical parameter values in equations 8 to 10) could aid cost-effective planning for reducing *Chlamydia* transmission. There is also the opportunity to change model assumptions and run a series of ‘what if’ scenarios, for example the effects of 50% versus 75% condom usage in sexual partnerships on the transmission of an STI.

Parameters can be changed easily to address specific questions or populations or to compare different strategies. This provides an interesting method to explore relationships between parameters and to predict outcomes without the constraints of getting appropriate sample sizes and significance testing. It also offers the advantage of incorporating existing evidence on social and behaviour determinants of STIs without having to commission a large survey to inform the estimates.

Conclusion

The trend in mathematical modelling may be towards more complex epidemiological models but simple models can still be produced which are user-friendly and practical in exploring the impact of intervention options on *Chlamydia*. Furthermore, it is possible to develop a model that is not dependent on estimates from a singular study and as a result, does not need to be discarded any time new data emerges. Once this type of model is developed, the parameters of the model can be changed or adapted to address specific questions or populations, for example, the effects of 50% versus 75% condom usage in sexual partnerships on the transmission of an STI in a defined age group. Future work should include further development for use in policies for restricting the transmission of STIs.

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