Development of a chlamydia infection model for evaluating costs and outcomes of health interventions

Entwicklung eines Chlamydien-Infektionsmodells zur Evaluierung von Kosten und Nutzen von Gesundheitsinterventionen

Abstract

Introduction: Chlamydia is a very common bacterial sexual transmitted infection (STI) among young adults. High numbers of asymptomatic cases hamper a timely treatment start, whereas the treatment itself is efficient and cheap. Proactive screening can decrease this mismatch. There are many models which are able to evaluate and simulate different screening options.
Most of them though are based on old or insufficient data, are not accessible for everybody, or are not designed in a user-friendly way.
Aim: We want to determine the feasibility of developing an easy-to-use chlamydia infection model, which can be easily updated to reflect changes in medical knowledge.
Methods: Starting with a literature review, we have set up a chlamydia infection model. This model was refined with the help of STI experts. The model was implemented by using the programming language Java (version 1.6). We validated the model using internal and external validation methods.
Results: The implementation of the model allows users to edit all parameters. The model consists of two separate sub-models. One sub-model simulates health effects of chlamydia for individuals, including the different outcomes in males and females. The other sub-model tracks the spreading of chlamydia within the computed cohort and regards heterosexual as well as homosexual partnerships. Both sub-models are independent of each other and therefore easily exchangeable. The overall model can be kept up to date by either updating single parameters of the model or exchanging a sub-model.
The model can be operated by graphical user interfaces to enable non-health economists and non-modelling experts to work with this disease model.
Discussion: We showed the feasibility of implementing an easy-to-use chlamydia model. This study can be regarded as a step towards developing more user-friendly decision support tools in health economics to assist decision makers in medicine.

Keywords: Chlamydia trachomatis, decision support techniques, models, theoretical, models, economical, nonlinear dynamics

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Zusammenfassung

Einleitung: Chlamydien sind unter jungen Erwachsenen eine verbreitete bakterielle sexuell übertragbare Krankheit (STI). Aufgrund einer hohen Anzahl an asymptomatischen Fällen ist es schwer die Behandlung zeitnah zu beginnen, obwohl diese an sich effizient und günstig ist. Proaktives Screening kann diese Diskrepanz verringern. Es gibt bereits viele Krankheitsmodelle, die in der Lage sind, verschiedene Screeningoptionen gegeneinander abzuwägen.
Ein Großteil davon beruht jedoch auf veralteten Daten, ist nicht frei verfügbar oder nicht leicht zu bedienen.

Ziele: Wir wollen herausfinden, ob es möglich ist ein Chlamydien-Infektionsmodell zu entwickeln, welches einfach zu bedienen ist und auf leichte Art und Weise aktualisiert werden kann um auf Änderungen des zugrunde liegenden medizinischen Wissens reagieren zu können.

Methodik: Wir haben, beginnend mit einer Durchsicht der bereits existierenden Literatur, eine neues Chlamydien-Infektionsmodell entworfen. Zusammen mit klinischen STI Experten wurde dieser Entwurf verfeinert. Das Modell wurde dann in der Programmiersprache Java (Version 1.6) realisiert. Anschließend validierten wir das Modell mit Hilfe interner und externer Validierungsmethoden.

Ergebnisse: Die finale Version des Models erlaubt es Benutzern, alle Parameter anzupassen. Das Modell besteht aus zwei Submodellen. Eines davon simuliert die Effekte, die eine Chlamydien-infektion auf eine einzelne Person hat und berücksichtigt dabei unterschiedliche Krankheitsverläufe für Männer und Frauen. Das andere Submodell modelliert die Verbreitung von Chlamydien in der simulierten Kohorte unter Berücksichtigung von hetero- und homosexuellen Partnerschaften. Beide Submodelle sind weitestgehend unabhängig voneinander und daher leicht auszutauschen. Dadurch kann das gesamte Modell aktuell gehalten werden, indem entweder einzelne Parameter aktualisiert werden oder ein Submodell ausgetauscht wird.

Das Modell wird mittels grafischen Benutzeroberflächen bedient. Diese ermöglichen Nutzern, welche keine Gesundheitsökonomen oder Gesundheitsmodellierer sind, mit dem Modell zu arbeiten.

Diskussion: Wir haben gezeigt, dass es möglich ist, ein Chlamydien-Infektionsmodell zu entwickeln, welches einfach zu bedienen ist. Diese Arbeit kann als erster Schritt in Richtung weiterer nutzerfreundlicher Modellierungssoftware angesehen werden, um Entscheidungsträger in der Medizin und Gesundheitsökonomie zu unterstützen.

Schlüsselwörter: Chlamydia trachomatis, Entscheidungsunterstützung, theoretische Modelle, ökonomische Modelle, nicht-lineare Dynamiken, Markov-Modellierung

Introduction

Chlamydia

Chlamydia trachomatis causes chlamydia infections (CT), the most common bacterial sexually transmitted infection (STI) in the United Kingdom (UK). Young adults account for more than 65% of all cases, but the infection can affect sexually active people of any age. The majority of cases (>50% in men, >70% in women) are asymptomatic, which is why the National Chlamydia Screening Programme in the UK recommends proactive screening for young adults. Different testing methods are in use, including point of care testing which gives results right away. Furthermore, there are also various highly effective treatment alternatives available with Doxycyline and Azithromycin being the most common ones [1].

If chlamydia is left untreated sequelae can emerge, affecting the patients' quality of life even years after the chlamydia infection is cured. Symptoms and sequelae differ between sexes as they primarily affect the genito-urinary organs. Reactive arthritis and infertility can be a consequence of a chlamydia infection. Furthermore females might develop chronic pelvic pain and ectopic pregnancy, whereas male sequelae could be epididymitis or prostatitis, both of which could become chronic [2], [3].

Health economics

Chlamydia does not only decrease the health of an individual, it also costs money to diagnose and treat patients. As resources in the health sector are finite, it is advisable to determine how to get the best value for money. Health economic evaluations deal with exactly this kind of question, comparing the health benefit of interventions with the arising costs of these interventions.

To compare health effects between different people an objective measure for the health of a patient is needed. Quality Adjusted Life Years (QALY) are such a kind of measure. They describe the Quality of Life (QoL) of a patient over time. For example, a person who lives 4 years with a QoL of 50% has a QALY of 2 (equals 0.5 multiplied by 4 years). QALYs are just one example for utilities which can be used in health economics, other measurements are also established [4]. Details about QoL assessment are beyond the scope of this paper and can be found elsewhere [5].

The second component of health economic evaluations are costs, which can take various forms, for example direct and indirect costs. If we combine both QALYs and costs we can calculate the cost-effectiveness of an intervention. The equation for an Incremental Cost-Effectiveness Ratio (ICER) to compare two alternative interventions is shown in Equation 1 [6].

$$ICER = \frac{Costs_{new} - Costs_{standard}}{QALY_{new} - QALY_{standard}}$$

Equation 1: Calculation of Incremental cost-effectiveness ratio, where Costs$_{new}$ = Costs of new intervention; Costs$_{standard}$ = Costs of treatment as usual (TAU)/ control; QALY$_{new}$ = Total QALYs of new intervention; QALY$_{standard}$ = Total QALYs TAU/control

The ICER on its own is difficult to interpret. A negative ICER, for example, can indicate either a decrease in costs with an increase in QALYs or a decrease in QALYs and an increase in costs. On the other hand, a positive ICER can result from an increase in both costs and QALYs or a decrease in both, costs and QALYs. These examples show that the ICER cannot be interpreted on its own but should always be examined in the context of the direction of change in costs and QALY.

Disease modelling

There are various possible screening and treatment methods for chlamydia. Furthermore, the part of the population which should be covered by treatment can vary. As screening methods and uptake, as well as the treatment method can be combined in various different ways, a multitude of combinations emerges. Disease modelling can be a useful tool to compare these in terms of costs and QALYs.

There are many different ways to model diseases, one of which is Markov modelling. Markov models consist of health states, which are connected by transitions. Health States are used to describe the progress of the disease. These health states have to cover all aspects of the disease and their definitions must not overlap with each other. As Markov models are deterministic models, transitions describe pre-defined proportions of the cohort which transit from their current health state to another health state. Transitions only depend on the current state and not on the history of states. This feature is called Markov property, or memorylessness of a Markov model [7].

Another way to use the structure of a Markov model is to look at patients individually. Then the transitions are no longer interpreted as proportions of the population of this state which makes a transition, but as transition probability for an individual. The transition probability is only affected by the attributes of a person and the state they are currently in. As this modelling approach looks at individual patients it is also called microsimulation [8].

We can refer to these individuals in the microsimulation also as agents. Agents are entities, either living or static, of the real world, which can interact with each other. If they are used to simulate scenarios we also call this agent-based modelling [9]. In agent-based modelling each agent is described by a set of attributes, these attributes can change due to events, which either involve one or multiple agents.

Whereas many chlamydia models exist, most of them are set up in a way so that they can answer one specific research question. This is only one out of many example where research software cannot be reused due to a narrow field of application. Typically, these disease models are complicated to use and therefore, only accessible to modelling experts. There might be a need for disease models which non-experts users can operate to gain initial understanding of a modelling problem before these users consult disease modellers. Especially in the vivid market of chlamydia screening and treatment a generic model could make a difference.

Aims

This study aims to examine the feasibility of developing an easy to use chlamydia model. Our scoping of the literature has shown that there is no such model currently available. To develop such a model it is necessary to develop a new and highly detailed chlamydia model. As complex models might hamper non-expert users from using the model it will be examined whether it is possible to hide the complexity of disease modelling behind graphical user interfaces (GUIs). Nevertheless, the user should be able to edit every parameter of the model, as we know that medical knowledge changes fast. A different input can also be used to fit the model into another setting. We therefore aim to find the balance between editability and user-friendliness.

Methods

The model development was broken down into two main questions:

- What is the natural progress of chlamydia infection and how can this be altered by treatment?
- How does CT spread within a population?

The first question is answered using Markov microsimulations. It is necessary to look at each sex separately due to the different disease process and consequences of chlamydia for males and females.

The second question deals with the transmission of chlamydia within a population. This is influenced by the existing partnerships in a population as well as screening and treatment interventions. We use agent-based modelling to simulate these processes which we call from here on "social model".

The entire model has been implemented using the programming language Java (version 1.6) in the integrated development environment (IDE) of Oracle Eclipse Mars [10]. This guarantees full flexibility in setting up the

models and no restrictions on model type. Furthermore, Java enables the implementation of GUIs.

Both sub-models are set up in such a manner that no direct communication between those sub-models is necessary. Instead, the sub-models communicate using a connector module with well-defined interfaces. This architecture enables future researchers to replace one sub-model by another completely different sub-model if it implements the same interface.

Although both sub-models are mostly independent there is some need for information exchange. A connector module is used to forward important events from one sub-model to another, using their interfaces.

Disease model development

A scoping of the literature was used to gain an overview over the current state of CT modelling. The search strategy consisted of two main parts, one part to find articles related to chlamydia and another part to find disease modelling papers. Each part consisted of various search terms, which were combined using the "OR" operator. Both parts were then combined using the "AND" operator. We searched Medline, using the PubMed interface for articles related to chlamydia modelling, published after 2000, to focus on the most recent models as we did not plan to do a full systematic review. To be included in the overview, the modelling study had to be freely accessible and report different health states to describe the progress of a chlamydia infection. We considered every article type as long a sufficient level of detail was provided to understand the functionality of the model.

The search retrieved approximately 1,500 articles, out of which 71 were eligible for full text screening. From those we identified 15 papers for inclusion in the overview. Using these articles, we extracted a duplicate free set of all health states which were used in these articles to describe the progression of [11], [12], [13], [14], [15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25]. We added "reactive arthritis" to these health states as it was never used by any model, but mentioned by basic literature on chlamydia. Using these extracted states, we developed two chlamydia disease sub-models one for each sex, as the disease symptoms differ between the sexes. Further sex-specific sequelae models have been introduced. The planned model structure was validated with STI experts and their feedback was used to amend the models.

The default time horizon was set to 10 years with a warm up period of 1 year. The model uses a default cycle length of one day. Default discount factors for effects and costs were set to 3.0%. These parameters can be changed by users to fit their purposes.

Discounted costs are summed up for each day over all persons and all models. The costs for each health state are added to the persons' sum once the person entered this health state. Utilities are accessed by using QoL. The QoL over all sub-models of one person is combined by using the main chlamydia value as a base value. If a

sequela is present this value will be decreased by a decrement assigned for each sequela.

Development of a social model

Sexual contact networks describe how sexual partnerships build and dissolve within a population. As this process is likely to be the similar for most STIs (except human immunodeficiency virus), we did not limit our scoping searches to chlamydia, but also looked at studies about gonorrhoea and other STIs. Based on the sexual networks of these publications we developed a dynamic sexual contact network, which we then discussed and improved in further expert interviews. Overall, four experts were consulted in face-to-face interviews, which lasted approximately one hour each. These experts were two STI doctors, one policy makers in medicine and one academic with major experience in influencing policy decisions. This model parametrised using data from the UK National Survey of Sexual Attitudes and Lifestyles [26]. Besides sexual contacts, this part of the model focusses on the actual interventions, which are examined by the model. These were derived from National Chlamydia Screening Programme guidelines and parametrised using the target values of those guidelines [27].

Development of user interfaces

To match the user interface of the final tool with the requirements of a possible user of the tool, we used agile methods to develop the user interfaces. Firstly, we gathered information, which input parameters future user might want to edit most often and how they want to get the results presented. Based on this, a first set of mock-ups was developed. In further interviews, these mock-ups were refined until they matched with the expectations of the users. These user interfaces were connected with the connector module, which combined this information of the disease sub-model and the social sub-model.

Results

Disease models

We developed a main chlamydia disease model for each sex. The female sub-model is displayed in Figure 1; the male sub-model is displayed in Figure 2. Circles represent the different health states. Additionally, some features of the health states are described by the following coding:

- **Green:** A person being in this state is infective and can therefore transmit the disease
- **Red:** A person in this state knows about his/her chlamydia infection
- **Orange:** A person being screened should receive a positive chlamydia test result, if screened

Figure 1: The female main chlamydia model
Green states are infectious states, persons in red states know about their infection, orange states signalise, that screened persons will receive positive test results.
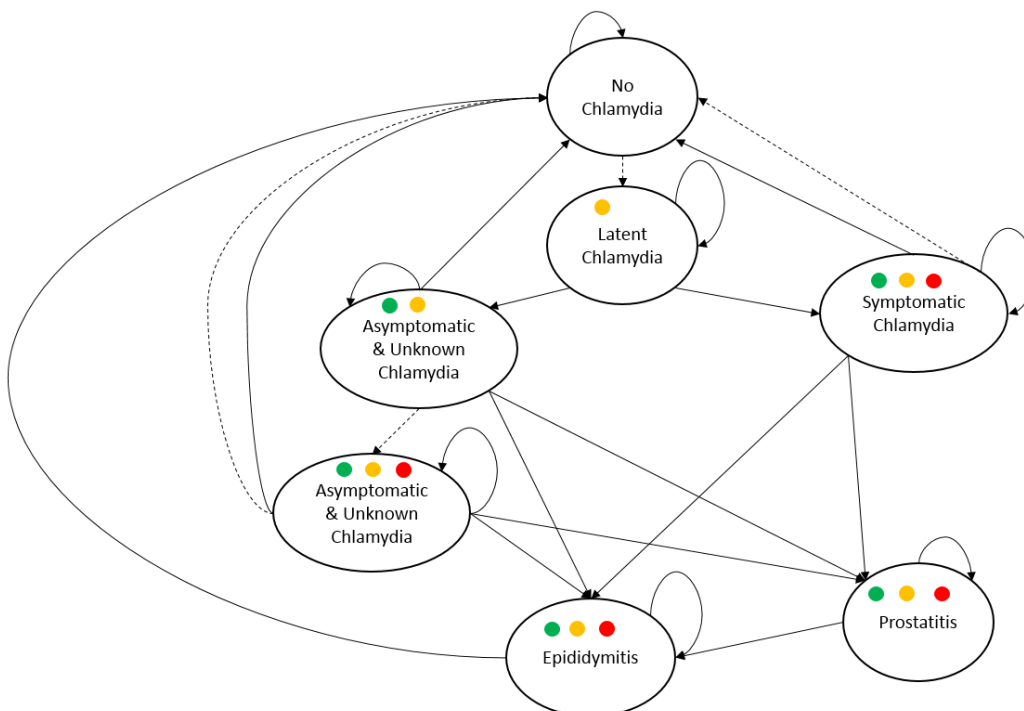

Figure 2: The male main chlamydia model
Green states are infectious states, persons in red states know about their infection, orange states signalise, that screened persons will receive positive test results.

A modelled person that should receive a positive test result can get a negative result as the test sensitivity and specifity will be applied before delivering the result. Two different types of transitions are used in this model: Solid lines are used wherever a transition could happen due to the natural progress of the disease, or in other words whenever the transition is initiated by the disease sub-model. Dotted lines, on the other hand, are used whenever a transition is initiated by the social model.

The states "No Chlamydia", "Latent Chlamydia", "Symptomatic Chlamydia", "Asymptomatic and Unknown Chlamydia", and "Asymptomatic and Known Chlamydia" are used in the male and the female model and connected in the same way. An uninfected individual can only become infected through sexual contact with an infected individual per the social model. They then enter the stage "Latent Chlamydia" and afterwards will be either in the state "Asymptomatic Chlamydia" or "Symptomatic Chlamydia". In both cases, a natural curation of the disease is possible. We assume all symptomatic infected individuals will seek treatment. Treatment success then leads to curation. If asymptomatically infected individuals are screened, either by chance or by partner notification, they may become aware of the disease and subsequently start treatment.

Untreated female chlamydia, either asymptomatic or symptomatic, will develop into "pelvic inflammatory disease (PID)" if not cured spontaneously. PID has a probability of developing into an abscess if left untreated. If PID is treated, the female is "uninfected" and hence susceptible for a new episode of chlamydia again. Otherwise, the female might end up being in state "PID with complications" for one day before ending up in the uninfected state again. "PID with complications" is a marker state. The possibility of developing a sequela increases by the each of episodes of "PID with complications". Untreated male chlamydia might progress to either epididymitis or prostatitis, both of which could become chronic. The probability of having a sequela increases with each episode of chlamydia a male undergoes.

The sequelae are simulated in separate models (see Figure 3 for females and Figure 4 for males).
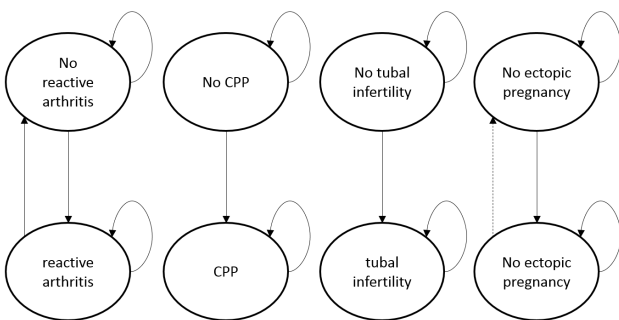

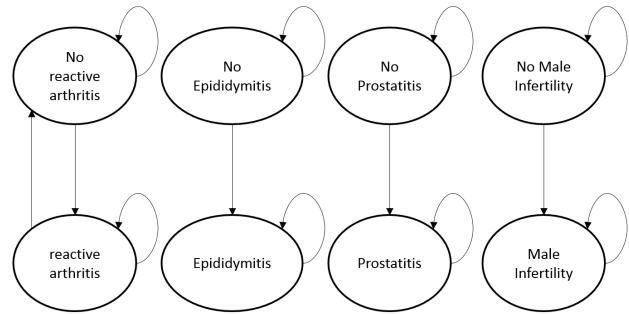**Figure 3: The female sequelae included in the model**

Figure 4: The male sequelae included in the model

In each cycle, a random number is drawn for each person and each of the sub-models. Based on this random number and the transition matrices (see Table 1 and Table 2) a transition into another state might or might not occur. All values are daily transition probabilities. If the referenced study used a different time interval, the probability was recalculated using Equation 2:

$$p_{new} = 1 - (1 - p_{old})^{\frac{t_{new}}{t_{old}}}$$

Equation 2: Equation to recalculate transition probabilities to a daily basis, where p_{new} = the newly calculated daily transition probability; p_{old} = the transition probability mentioned in the resource; t_{new} = 1 day; t_{old} = the time interval of the old transition probability (in days)

In some cases, only the average time in a health state was known. In this instance, the probability was chosen in such a manner that 50% of the population would have left this particular state by that day, as shown in Equation 3:

$$p_{new} = 1 - 0.5^{\frac{1}{t_{old}}}$$

Equation 3: Calculating a daily transition probability, if only a mean duration of stay in health stae is given, where p_{new} = the newly calculated daily transition probability; t_{old} = the referenced mean duration

All transition probabilities are to be regarded as suggestions based on sound references from the authors as users can alter each probability if needed.

If a female had at least one episode of PID, she is under risk for developing either of these sequelae: reactive arthritis, chronic pelvic pain (CPP), infertility or having an ectopic pregnancy. An ectopic pregnancy can only occur if the woman is pregnant, after the ectopic pregnancy she will be in the state "no ectopic pregnancy" again. Infertility and CPP are chronic conditions, which means that they are absorbing states and cannot be left. Reactive arthritis shows up in occasional episodes with a duration of 6 weeks [28], resulting in a transition probability of 1.63%. The probabilities for developing each of the sequela are shown in Table 3.

Table 1: Transition matrix of daily transition probabilities for the female chlamydia model
NC=No Chlamydia; LC=Latent Chlamydia; AUC=Asymptomatic and Unknown Chlamydia; AKC=Asymptomatic and Known Chlamydia; SC=Symptomatic Chlamydia; PID=Pelvic Inflammatory Disease; A=Abscess; PwC=PID with Complications

	NC	LC	AUC	AKC	SC	PID	A	PwC
NC	100%							
LC		91.67% [12, 31]	2.08% [12, 31]		6.25% [12, 31]			
AUC	0.78% [12, 31]		98.89% [13]			0.33% [12, 15, 32]		
AKC	0.78% [12, 31]			98.89% [13]		0.33% [12, 15, 32]		
SC	5.00% [31]				92.85% [13]	2.14% [12, 15, 32]		
PID						90.90% [18]	3.00% [33]	6.09% [13]
A							95.24% [33]	4.76% [33]
PwC								100%

Table 2: Transition matrix of daily transition probabilities for the male Chlamydia model
NC=No Chlamydia; LC=Latent Chlamydia; AUC=Asymptomatic and Unknown Chlamydia; AKC=Asymptomatic and Known Chlamydia; SC=Symptomatic Chlamydia; E=Epididymitis; P=Prostatitis

	NC	LC	AUC	AKC	SC	E	P
NC	100%						
LC		90.00% [12, 31]	2.50% [12, 31]		7.50% [12, 31]		
AUC	1.09% [31]		98.89% [13]			0.001% [12]	0.02% [13, 24]
AKC	1.09% [31]			98.89% [13]		0.001% [12]	0.02% [13, 24]
SC	6.99% [12, 31]				92.86% [13]	0.007% [12, 31]	0.14% [13]
E	2.39% [34]				97.61% [34]		
P	2.39% [35]						97.61% [35]

Table 3: Transition probabilities of developing a certain sequela
Each column contains the probability after the first/second/third episode of Chlamydia (for males) or PID with complication (for females). F=applicable for females; M=applicable for males; CPP=Chronic Pelvic Pain; TI=Tubal Infertility; EP=Ectopic Pregnancy; RA=Reactive Arthritis; CE=Chronic Epididymitis; CP=Chronic Prostatitis; MI=Male Infertility.

	Seq	1. Inc	2. Inc	3. Inc	References
F	CPP	12%	30%	45%	[19]
	TI	10%	20%	40%	[36]
	EP	4%	9%	10%	[19]
F/M	RA	4.10%	4.10%	4.10%	[37, 38]
M	CE	0%	0%	10%	[39]
	CP	10%	10%	10%	[40]
	MI	5%	5%	5%	[41, 42]

The male sub-model for reactive as well as the transition probabilities are the same as in equivalent female model. The three other sequela chronically manifest, which is realised by final states. The transition probabilities are shown in Table 3.

Default costs and utilities were assigned to each health state (see Table 4), which can be edited by users. Costs values were inflation-adjusted to represent the value of 2016. Costs in foreign currency were transformed into pounds using the exchange rate of the publication date.

Table 4: Costs and QoL values used in the model
Abbreviations see Tables 1, 2, and 3

	State	total Costs [Refs.]	QoL [Refs.]	QoL decrement [Refs.]
F	NC	£ 0	0.9 [43]	–
	LC	£ 0	0.9 [43]	–
	AUC	£ 0	0.9 [43]	–
	AKC	£ 0	0.87 [43]	–
	SC	£ 0	0.84 [43]	–
	PID	£ 404.63 [31]	0.78 [44]	–
	A	£ 404.63 [31]	0.65 [15]	–
	PwC	£ 404.63 [31]	0.78 [44]	–
	CPP	£ 5725.06 [16]	–	–0.10 [15, 45]
	TI	£ 669.37 [31]	–	–0.15 [15, 45]
	EP	£ 3626.81 [31]	–	–0.1 [15, 45]
F/M	RA	£ 150.00 [46]	–	–0.15 [47]
M	CE	£ 1235.53 [31]	–	–0.077 [48]
	CP	£ 1235.53 (est.)	–	–0.77 [49]
	MI	£ 669.37 (est.)	–	–0.10 [50, 51]
	NC	£ 0	0.87 [50]	–
	LC	£ 0	0.87 [50]	–
	AUC	£ 0	0.87 [50]	–
	AKC	£ 0	0.83 [50]	–
	SC	£ 0	0.83 [50]	–
	E	£ 29.06 [52]	0.83 [50]	–
	P	£ 29.06 [52]	0.83 [50]	–

Social model

Our model uses an open cohort; individuals can leave the cohort and new individuals can enter it. Modelled persons die in line with the UK death table [29]. If a person surpasses the upper age border the model checks whether they still have an active relationship. If not, the person is removed from the model. If they have at least one current partner the partnership is kept in the model until the relationship ends or both partners exceed the age limit. Individuals above the upper age limit will not start new relationships. For each individual that dies, a new individual of the same sex enters the model. This can be either an uninfected person at the lower age border (growing up) or a person with any age of the modelled interval and a random health state (migration). This keeps the modelled population at the same size throughout the whole modelled time.

The social model is best described by looking at the different processes which are simulated. Processes are in-fluenced by attributes of individuals which are randomly assigned to each individual when they enter the simulation. Some of those, e.g. age, change over time, whereas others, e.g. sex, will stay the same. The whole model is parametrised for a UK context. Nevertheless, a user can fit the parameters for any other given context.

Partnership building

To build a partnership, two random individuals are picked out of the cohort. The model checks whether the parameters of both modelled persons match. Therefore it is checked whether at least one of the potential partners has reached his or her maximum number of partnerships, whether their sexual preferences match, whether their sexual activity groups match, and whether their age preference match. If all checks are passed, and neither is already in a long-term relationship, they will start a long-term relationship. Otherwise they start a short-term relationship.

Each of the previous checks examine one attribute of the individuals. Persons have a preferred number of partnerships and a maximum number of partnerships, which is looked at in the first check. The "sexual preference" determines whether this person will prefer relationship with a male or female or has no preference. The sexual activity group is a value which describes how often this person would like to have sex, this value is at 0.7 per day for the highest group, 0.4 for the middle group and 0.2 for the lowest group [30]. A mixing pattern (see Table 5) is applied to allow mixing between the different sexual activity groups.

Table 5: Mixing matrix for sexual activity groups [31]

	High	Middle	Low
High	1.0	0.2	0.1
Middle	0.2	1.0	0.15
Low	0.1	0.15	1.0

Each individual also has a preferred age difference for a potential partner. Males tend to search for slightly younger partners, whereas female are looking for slightly older partners [26]. The confidence intervals around these parameters increase over time.

This partnership building process is started a couple of times each day to keep up the partnership building process. A person can have one long partnership and eventually short partnerships concurrently. Based on the preferences of the duration of a partnership and whether the partnership is going to be a short or long, its length is calculated.

Sexual intercourse

Based on the sexual activity groups of both partners the average frequency of sexual intercourse is calculated. For each day and each couple, a random number is drawn

to see whether they have sex at this particular day. Based on their condom use preferences and the condom security the probability of infection or a pregnancy is calculated.

Screening

Screening can either happen as a screening offer is made for a random modelled person or due to partner notification, as the partner is found to be positive for CT earlier on. Individuals can decline the screening offer. The test result is influenced by infection status and the specifity and sensitivity of the test.

Treatment

Modelled people who know about their chlamydia infection will receive an offer to get treated. This offer is declined by a certain percentage. Based on adherence, efficacy data for treatment success is calculated. In any case a rescreening is offered.

Validation

As the model was built based on other published models, its structure is comparable to already existing models. Nevertheless, the structure of this Markov model contains more health states than any other model we have found during the scoping of the literature.

We conducted a one-way sensitivity analysis, changing each input parameter by plus/minus 90%, 10%, and 2.5%. This analysis examined the effect (among others) on the cost-effectiveness and the total number of infections. The parameters that had the largest impact in the model were "condom use" and "condom security". Furthermore, changes in the gender proportion as well as a different mixing matrix for sexual activity have a high impact on the overall cost-effectiveness.

Changes in the initial distribution over the health states did not change the results, as a warm-up is performed before the model starts evaluation. Other parameters like the mortality table had little to no effect on the overall result.

We could see a higher prevalence of chlamydia in our models than we expected it to be in comparison to real world data.

As the validation part of the software is encapsulated in a module, it can easily be replaced by another validation module. In this version, we only deployed a module for deterministic one-way sensitivity analyses. However, it is possible to enhance the internal validation by replacing this module with another more sophisticated one, e.g. for probabilistic sensitivity analyses.

User interaction

To keep the modelling tool as simple as possible but still allow every parameter to be editable, we put all parameters in two categories. This was based on the results or our expert interviews.

The first category includes parameters that users might want to change regularly. Those can be changed using the input mask shown in Figure 5. This mask is preloaded with some default values, suggested by the authors. Parameters, which could be changed on the GUI mostly dealt with the screening and treatment process, as shown in this list:

- Cohort demographics,
- Screening uptake (male/female, age group),
- Number of test offered per year,
- Test and treatment parameters (sensitivity, specifity, adherence, efficacy, testing duration, treatment duration), and
- Partner notification per index case.

The second set contains parameters where users are less likely to have additional information on or want to change, e.g. transition probabilities for health state changes. Parameters of the second set can be adapted by changing their value in property files by using a text editor.

After the modelling calculations are finished users can examine the development of the prevalence for each health state. The ICER, and the total number of infections are reported. Figure 6 shows the result user interface after a sample calculation.

Discussion

In this study, we present a new chlamydia model that can be controlled by the user via GUIs. The model is available from the authors upon request. We show that it can perform complex modelling calculations while providing a graphical user interface. We demonstrate that it is possible to design a disease model in such a manner so that it can be adapted to changes in medical knowledge, hence increasing the potential field of usage and customisability of the model. Nevertheless, the efficiency of the proposed GUI has not been tested and other also effective ways for building user interfaces exist. This situation was not within the focus of this study, but it should be tested in further research.

The validation has shown that the model is consistent with current knowledge about chlamydia and chlamydia modelling. We justify the higher prevalence in our model with the absence of unknown cases.

The model is based on a multitude (n=159) of parameters, some of which are hard to find literature on and therefore had to be estimated. As every parameter needs a daily estimate due to the cycle length, the actual values of the parameters can be hard to interpret. For example the asymptomatic duration of chlamydia for women (on average 365 days) translates into a rather cryptic daily transition probability of 98.89% of staying in this health state for the next cycle. The face validation of these probabilities is not possible and non-modellers might be objected by those.

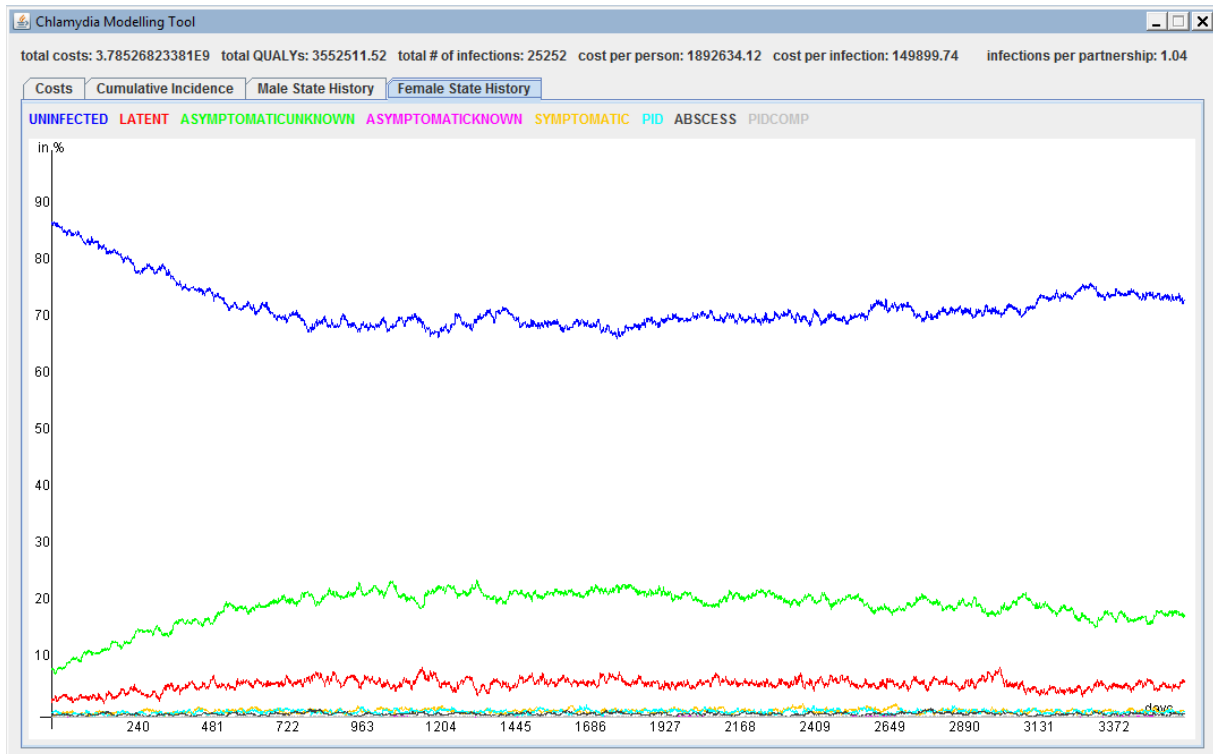Figure 5: Input mask with the parameters users want to change most often

Figure 6: User interface to display all outcomes of interest of a calculation

The modelling tool is currently implemented in a computationally resource intensive way. This means that the calculations take a long time to finish. The progress bar showing the current state of the modelling process and the display of the current prevalence of CT help the user to wait for the results. Further projects though should try to reduce calculation time so that the results can be obtained in a shorter amount of time.

Future work

As the feasibility of hiding complex disease models behind GUIs was proven by this paper this work is currently being continued. Subsequent research should focus on the question whether these results are transferable to an even more general approach. A first step would be to develop a generic model which covers multiple STIs and also examines interactions and coinfections of those.
It should be an aim to implement this kind of modelling software in the workflows of policy makers in medicine.

The targeted dissemination of these results could ease the life of decision makers.

Notes

Competing interests

The authors declare that they have no competing interests.

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