Development of a Multi Sexually Transmitted Infections Modelling Software

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I, Fabian Daniel Sailer, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the work.

Abstract

Background Human Immunodeficiency Virus (HIV) and other sexually transmitted infections (STIs) do not operate in isolation; people with risk-taking sexual behaviour in particular are more likely to be co-infected. In this complex landscape policy makers are limited by monetary constraints and still need to find optimal coverage solutions. Disease modelling could help in this context but modelling software accessible to decision makers examining various STIs and HIV is rare.

Methods I developed an STI modelling software, using the programming language Java, consisting of a model for each STI and a graphical user interface. The models were drafted based on literature reviews and subsequently refined by experts, e.g. STI clinicians and policy makers. Afterwards, all models were internally and externally validated. The user interface was developed with user interface development experts and policy makers. The resulting software was validated using the MenSS trial.

Results The software consists of different models, which serve individual purposes. All models are interacting, individual-based discrete event simulations.

Separate disease models, which describe the progression of chlamydia, gonorrhoea, HIV, and syphilis, and their corresponding sequelae describe the progression of the respective infections.

Sexual network models are used to describe the formation and dissolution of partnerships and thereby the occurrence of sexual contacts. A user can choose from four different network models which are included in the software.

Clinical pathway models, which describe interventions, like screening or treatment for all included STIs, reflect the current English setting.

All models have been validated using sensitivity analyses and publicly available data

sources. The user interface has been validated by policy makers.

Conclusion With this modelling software policy makers can compare intervention options, existing and hypothetical, to each other. All parameters, formulas, model structures, and clinical pathways are editable and well documented. The software is not bound to a specific research question but can be fitted for different scenarios to be reused and updated if needed, e.g. if medicinal knowledge changes. For example, by adapting parameters which describe treatment pathways the software can be used in non-English scenarios.

Impact Statement

Based on the research which has been conducted and is described in this thesis one publication has been published in BMJ Open. Different stages of the work have been presented at 14 scientific conferences. A detailed list of the quantifiable output can be found in section *Output*. It raised national and international academic interests with the work being presented on national, European and global conferences. I also aimed to reach out with my work to a broader audience by writing a blog and contributing to a podcast.

This work is the first model to simulate multiple STIs simultaneously while also aiming to be accessible because of the use of graphical user interfaces and thereby facilitating the access of non-disease modellers (e.g policy makers) to this STI modelling software.

The whole work is of intersectional nature which tried to communicate between STI clinicians, disease modellers, policy makers and health economists. It clearly showed the benefits of collaborative research and the improved output after a joint development process.

In the future, policy makers might be able to use this software to find optimal coverage solutions for their local STI landscape and thereby spending the least amount of money for the best possible health outcome, given the constraints.

This work also aimed to bring two worlds, inside and outside academia closer together and to showcase directly how evidence from academia can be used in practice. During the development of the software, I sought contact with decision makers in health care to ensure that the software which I developed was tailored to their needs and could be used in practice after the end of my PhD. During my PhD, I also contributed to an audit report by Public Health England (PHE).

Towards the end of my thesis, I had the opportunity to present my PhD project at PHE. After this presentation, we discussed further usage of this software within PHE.

The overall aim of this thesis was to make disease modelling more accessible. As

the software now has been developed this journey does not end yet because the software which is readily available now has to be integrated into the decision-making processes for sexual health.

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School for Primary Care Research

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My acknowledgements also go to all participants of countless meetings which helped me to understand my research topic better and better.

Lastly, and most importantly I want to thank all my friends, especially my girlfriend Tamara Mütsch for her ongoing support throughout the past years and their way to encourage me to keep researching.

Career Summary

I studied medical informatics for my Bachelor's (2011-2014) and Master's (2014-2016) degree at the University of Heidelberg in cooperation Heilbronn University. During my Master's studies, I developed an interest in health economics and disease modelling, which resulted in me becoming a member of a health economics modelling team at Heilbronn University. In this team, we developed Markov models for diabetes.

Searching for projects on disease modelling for my Master's thesis I contacted the Research Department of Primary Care and Population Health at University College London. They offered me a placement for six months to develop a chlamydia disease model. After finishing this piece of work, I felt that there was still a research gap to be filled. Being fascinated by disease modelling for STIs, I pitched my idea of a multi-STI disease modelling software with the NIHR School for Primary Care Research. Luckily, I was awarded the studentship which enabled me to commence working on my PhD project in October 2016.

Output

Written Output

Journals

Sailer F, Hunter R, Schramm W. Development of a Chlamydia Infection Model for Evaluating Costs and Outcomes of Health Interventions. GMS Med Inform Biom Epidemiol. 2017;13(1):Doc06.

Sailer F, Rait G, Howe A, Saunders J, Hunter R. Methods and Quality of disease models incorporating more than two sexually transmitted infections: A protocol for a systematic review of the evidence. BMJ Open, 2018 May 5;8(5)

Protocols

Sailer F, Howe A, Hunter R, Saunders J, Rait G. Methods and quality of disease models incorporating more than two sexually transmitted infections. PROSPERO: International prospective register of systematic reviews. 2017 Oct 18. CRD42017076837 `https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=76837`

Blogs

Sailer F. SPCR Blog [Internet]. Sex, Infections and Disease Modelling. 2017 May 9 [cited 2017 Nov 2]. https://www.spcr.nihr.ac.uk/news/blog/sex-infections-and-disease-modelling-1

Sailer F. PCPH Blog [Internet]. Google Flu Trends is dead – long live Google Trends?. 2018 Jan 23 [cited 2019 Jan 22]. https://blogs.ucl.ac.uk/pcph-blog/2018/01/23/google-flu-trends-is-dead-long-live-google-trends/

Posters

Sailer F, Schramm W, Hunter R. Development of an easier-to-use Chlamydia Modelling Tool. Poster presented at: UCL Populations and Lifelong Health Domain Symposium; 2017

Jan 17; London, UK.

Sailer F, Saunders J, Rait G, Hunter R. Development of a user-friendly multi-STI modelling tool. Poster presented at: PHE Research and Applied Epidemiology Scientific Conference; 2017 Mar 22; Warwick, UK.

Sailer F, Saunders J, Rait G, Hunter R. Development of a multi-STI model: Getting the full picture of the STI landscape in the UK. Poster presented at: NIHR SPCR Showcase; 2017 Sep 19; Oxford, UK.

Sailer F, Saunders J, Rait G, Hunter R. Development of a multi-STI model: Getting the full picture of the STI landscape in the UK. Poster presented at: UCL HE Symposium; 2018 Feb 08; London, UK.

Sailer F, Saunders J, Rait G, Hunter R. Development of a multi-STI model: Getting the full picture of the STI landscape in the UK. Poster shown at: UCL GP tutors conference symposium; 2018 Mar 16; London, UK.

Howe A, Sailer F, Bailey J, Stephenson J, Barrett G, Hunter R. Measuring the health-related quality of life of women using contraception: a systematic review and analysis of available tools. BJOG, doi: 10.1111/1471-0528.15132

Sailer F, Rait G, Saunders J, Hunter R. Including end users in a decision model development process: A case study using a multi-sexually transmitted infection health economic model. Poster presented at: HESG winter meeting Symposium; 2019 Jan 08; York, UK.

Sailer F, Rait G, Saunders J, Hunter R. Including end users in a decision model development process: A case study using a multi-sexually transmitted infection health economic model. Poster shown at: UCL GP tutors conference symposium; 2019 Mar 01; London, UK.

Sailer F, Saunders J, Greta R Hunter R. Development and validation of decision modelling software for sexually transmitted infections in cooperation with policy makers. Poster presented at: STI/ HIV 2019 World Congress; 2019 Jul 15; Vancouver, CA.

Presentations

Sailer F. Sex, Infections and Disease modelling. Three Minute Thesis presented at: 2017 Mar 24; University College London; London, UK.

Sailer F. Introduction to disease modelling and some advanced techniques. Departmental Seminar presented at: 2017 Apr 7; Department of Primary Care and Population Health, University College London; London, UK.

Sailer F. Development of a multi-Sexually transmitted infections decision modelling tool for use by health care professionals, policy makers and analysts. Elevator Pitch presented at: 2017 May 16; Department of Primary Care and Population Health, University College London; London, UK.

Sailer F. Development of a multi-Sexually transmitted infections decision modelling tool for use by health care professionals, policy makers and analysts. Elevator Pitch presented at: 46th annual scientific meeting of the Society for Academic Primary Care; 2017 Jul 13; Warwick, UK.

Sailer F. Fortgeschrittene Methoden zur gesundheitsökonomischen Evaluierung: Cost-Effectiveness Acceptability Curve, Cost Effectiveness Planes und Net Monetary Benefit. Presentation at Symposium: 2017 Sep 11; PROSIT Disease Modelling Community, GECKO Institute for Medicine, Informatics and Economics, Heilbronn, Germany.

Sailer F. Development of a multi-Sexually transmitted infections decision modelling tool for use by health care professionals, policy makers and analysts. Elevator Pitch presented at: School for Primary Care research trainee meeting; 2017 Sep 18; Oxford, UK.

Sailer F. Development of a multi-STI disease modelling tool. Talk presented at: European Health Economists Association student supervisor conference; 2017 Sep 6; Lausanne, CH.

Sailer F. Short Summary of the Advanced Health Economics Course from York University. Departmental Seminar presented at: 2017 Oct 19; Department of Primary Care and Population Health, University College London; London, UK.

Sailer F. Development of a disease modelling software using a discrete event simulation approach. Departmental Seminar presented: 2018 May 08; PROSIT Disease Modelling Community, GECKO Institute for Medicine, Informatics and Economics, Heilbronn, Germany

Sailer F, Hunter R, Rait G, Saunders J; Development and validation of sexual network model based on published Natsal-3 data; Talk presented at: Health studies user conference; 2018 July 17; London, UK

Sailer F, Hunter R, Rait G, Saunders J; Involvement of decision makers in health care in the development of user interfaces for a modelling software of sexually transmitted infections as a decision support tool; Elevator Pitch presented at:SPCR trainee event; 2018 Sep 24; Oxford, UK

Sailer F. Programming for happy health economists: A case study on developing a

new microcosting tool for the British National Formulary data set. Departmental Seminar presented at: 2019 Mar 27; Department of Primary Care and Population Health, University College London; London, UK.

Sailer F, Saunders J, Rait G, Hunter R. Development of a user-friendly multi STI modelling software: Working with decision makers. Seminar given at PHE England; 2019 Jun 27; London, UK.

Sailer F, Saunders J, Rait G, Hunter R. Development of a user-friendly multi STI modelling software: Working with decision makers. Talk presented at: The International Health Economics Association 2019 Congress; 2019 Jul 15; Basel, CH.

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List of Abbreviations

AIDS acquired immune deficiency syndrome

AMR antimicrobial resistance

ART antiretroviral therapy

ASSIA Applied Social Sciences Index and Abstracts

BAME black, Asian, and minority ethnic

BASHH British Association of Sexual Health and HIV

CE cost-effectiveness

CEA cost-effectiveness analysis

CIN Cervical intraepithelial neoplasia

CPU central processing unit

csv comma-separated values

CUA cost-utility analysis

DES discrete event simulation

DoH Department of Health

DSA deterministic sensitivity analysis

EMBASE Excerpta Medica Database

FSW female sex workers

GDPR General Data Protection Regulation

GP general practitioner

GPs general practitioners

GUM genitourinary medicine

GUMCAD Genitourinary Medicine Clinic Activity Dataset

HCV hepatitis type C

HE health economics

HIV human immunodeficiency virus

HPV human papillomavirus

HR-QoL health-related quality of life

ICER Incremental Cost Effectiveness Ratio

ISPOR International Society for Pharmacoeconomics and Outcomes Research

LGBT lesbian, gay, bisexual and transgender

MenSS men's safer sex trial

MeSH medical subject heading

MMS Markov microsimulation

MSM men who have sex with men

MVC model - view - controller

NCSP National Chlamydia Screening Programme

NICE National Institute for Health and Care Excellence

NHS National Health Service

PHE Public Health England

PID Pelvic Inflammatory Disease

PLOS Public Library of Science

PrEP pre-exposure prophylaxis

PRISMA preferred reporting items for systematic reviews and meta-analyses

PROMs Patient Reported Outcome Measures

PROSPERO international prospective register for systematic reviews

QALY quality-adjusted life year

QALYs quality-adjusted life years

QoL Quality of Life

SAS Statistical Analysis System

SD standard derivation

SF-36 Short Form 36 questionnaire

SI susceptible - infected

SIR susceptible - infected - recovered

SIRS susceptible - infected - recovered - susceptible

sQoL sexual Quality of Life

STATA Statistics and Data

STI sexually transmitted infection

STIs sexually transmitted infections

TTO time trade-off

UCL University College London

UK United Kingdom

UML unified modelling language

USA United States of America

VAS visual analogue scale

VBA visual basic for applications

WHO World Health Organisation

WTP willingness to pay

Research Questions

- Is it feasible to develop a health economic disease model for multiple sexually transmitted infections, which incorporates the most important sexually transmitted infections in England?
- Is this model valid and effective considering decision makers in health care as potential users?

Aims

- To develop a user-friendly multi-sexually transmitted infection model as a decision support tool for decision makers in health care.
- To calculate the economic and health outcomes of sexually transmitted infections with this model in order to compare and evaluate different sexually transmitted infection interventions, either planned or existing.
- To validate this model.

The objectives of this thesis were to:

1. Systematically review the literature on computational disease models which simulate at least two sexually transmitted infections in one disease model to examine employed methodology and the quality of those models.
2. Determine the most suitable modelling approach to simulate multiple sexually transmitted infections in one disease model.
3. Prioritise prevalent sexually transmitted infections in England with respect to their importance for the National Health Service and thereby for inclusion in the model.
4. Create a set of disease models, which are able to interact, reflecting the prioritised sexually transmitted infections.

5. Develop models for clinical pathways to describe existing and hypothetical interventions.

6. Develop a sexual contact network model, which describes the formation and resolving of partnerships in the United Kingdom using available nationwide data.

7. Examine the validity of these models by using internal and external validation techniques.

8. Develop user interfaces for this disease model with an agile development process in cooperation with its future users, e.g. decision makers in health care, to ensure the interface will suit their needs.

Overview

This thesis started with a short summary of my academic career to put the work on my thesis into context, as I did not study a public health or primary care related degree. The previous section listed the aims and objectives of my thesis, whereas the rest of the thesis details how I accomplished each of those. The first chapter lays the foundation for this thesis by showing the necessity of the work. All following chapters map on the objectives stated above.

Chapter I provides the background and context for this thesis. It summarises the relevant research which has been conducted previously and shows research gaps.

Chapter II describes the systematic review I conducted to understand what had already been done in the field of computational multi-STI modelling. (Objective 1)

Chapter III uses the information gained from the systematic review to set up a modelling approach to cope with the complexity of the models and their interactions. (Objective 2)

Chapter IV shows the cooperation with decision makers in sexual health in this research, which was lead by an advisory group. One of the results of this collaborative work is the user interfaces of the modelling software. (Objective 8)

Chapter V begins by describing how I selected which sexually transmitted infections had to be included in the software. I then continue to explain - based on the chosen modelling approach and the selected STIs - how the natural progression of sexually transmitted infections is modelled. I also explain structure of all disease models which are included in the final version of the software and shows the steps I took to validate those models. (Objective 3 and 4)

Chapter VI describes how the natural progress of a disease, as presented in the previous chapter, is influenced by interventions, such as treatments. It also shows which interventions are included in the software and how I validated this part of the model. (Objective

5)

Chapter VII connects the disease models from *Chapter V* and the clinical pathway models from *Chapter VI* with each other. In this chapter, I describe how I developed and validated sexual networks, which are used in the software. These networks simulate the formation and dissolution of sexual partnerships and thereby the occurrence of sexual contacts, which allow the spread of sexually transmitted infections. (Objective 6)

Chapter VIII gives an example of how the software could be used and validates the overall software, by examining real-life study data, which was published from a trial, which examined sexual behaviour change in heterosexual men. (Objective 7)

Chapter IX summarises and concludes the thesis. It reviews the strengths and limitation of the work conducted and showcases potential future usage of the software.

Chapter 1

Background

Sexually transmitted infections (STIs) are a serious threat to health, globally and in England. On average more than a million new cases of chlamydia, gonorrhoea, trichomoniasis and syphilis are registered worldwide every day [1]. This leads to an economic burden for health systems; in 2008 in the United States alone the total costs related to STIs was estimated at USD 15.6 billion [2]. Being aware of the economic and health impact of STIs, decision makers must find optimal solutions to prevent, diagnose and treat STIs within a limited budget. Currently decision makers may not have tools to hand which can support their decision-making process, particularly disease modelling software that simulate multiple STIs with a user-friendly interface might be lacking. The nature of STIs, often being asymptomatic, confronts them with considerable difficulties as effects of the money spent are not immediately obvious. If these asymptomatic infections are left untreated serious long-term sequelae can occur [3]. To avoid infections in the first place prevention measures could be implemented, which cost money in the short term but have the potential to decrease the prevalence and ultimately lead to lower costs in the long term.

The aim of this thesis is to help sexual health decision makers evaluate sexual health interventions by providing a tool to facilitate decision-making in sexual health.

1.1 Overview

The first section of this chapter starts by making an argument for the necessity of this thesis, especially outlining the need for looking at multiple STIs simultaneously and the role of disease modelling in this context.

The second section provides an overview of STIs in general and introduces the relevant STIs for this thesis.

The third section covers how health care in England is managed. Policy decisions on

sexual health have to be made within the constraints, such as finite budget, imposed on the decision-making process. To help the reader understand this system, it is introduced in the second section of this chapter.

The fourth section examines how decisions based on data can be made, e.g. to compare different intervention options by using various methods and tools. Health economics allows us to consider the health impact and economic impact of intervention options. It provides a valuable set of methods to help make decisions in health care. The software developed during this thesis uses health economic methods which are also introduced in this section.

The chapter ends by providing details on concepts of disease modelling which lay the foundation for the following chapters.

1.2 Research Gap addressed by this thesis

1.2.1 Why Is It Important to Look at Multiple STIs Simultaneously?

STIs do not operate in isolation. Studies have shown that the presence of one STI can be an indicator for the presence of another STI. For example, syphilis, gonorrhoea, and chlamydia infections are indicators of having an HIV infection [4]. This correlation is rooted in two mechanisms, the likelihood of infection and biological interaction.

The risk of becoming infected with an STI differs between people. People having a high risk of becoming infected with any STIs are hence at a higher risk of getting infected with more than one STI simultaneously. The risk of becoming infected with an STI depends on the risk-taking sexual behaviour of a person. Factors known to increase the risk of becoming infected are:

- frequent partner changes,
- concurrent partnerships and
- unprotected sex.

We also know that STIs interact with each other, especially HIV, which can establish syndemic relationships with other STI such as gonorrhoea and syphilis. Two mechanisms are responsible for this: the weakened immune system, which facilitates a further infection and ulcers, e.g caused by gonorrhoea, which break open the skin barrier and hence facilitate the access of further pathogens [5, 6].

Seeing the aforementioned mechanisms of interaction between STIs it is important to notice that behaviour change interventions, e.g. towards safer sex practices by increasing condom use in men [7], can have the capacity to decrease the incidence of several STIs simultaneously. Though, the literature on the effect of condom use on the transmission of STIs is still undecided; some studies found an effect of condom use on the prevalence of STIs [8], but a Cochrane review did not report a significantly decreased transmission rate [9]. Other interventions which can potentially have the capacity to decrease the incidence of several STIs include:

- testing schemes for multiple STIs [10],
- safer sex education in schools [11],
- partner notification [12] and

- public awareness campaigns [13].

1.2.2 How Can Disease Modelling Help For Modelling Multiple STIs?

Disease models can be used as decision support tools in health care. [14, 15] Various models have been developed to simulate multiple STIs simultaneously and are presented in Chapter 2.The aim of these models is to provide information to decision makers about the costs and consequences of the intervention in question compared to standard care or current best practice, e.g. prevalence of a disease in a cohort of interest and its impact on treatment costs and disease outcomes. Disease models can facilitate the comparison of different intervention scenarios and the extrapolation of the findings, e.g. from clinical studies, to a population-wide context or over a longer time horizon. Disease models thereby allow decision makers to make objective decisions based on a wider set of data than would be possible in clinical trials. This is because trials most often need to focus on a single aspect of an intervention, for example behaviour change only such as increasing condom use. As a result, trials might also be limited to using a proxy for the outcome as they are not able to directly measure the outcome of interest, such as reductions in STI incidence, due to the sample size required being too large for the trial to be value for money or the outcome being too far in the future so the trial duration would need to be very long. Disease modelling on the other hand allows to bring aspects examined by several trials together and look at them in a wider context and a pragmatic way.

We know from other disease areas that simulating multiple similar diseases can impact on resource use and the intensity of disease management needed. This is an important aspect when discussing cohorts with several simultaneous conditions, e.g. in elderly patients. Zulman et al. discussed in their paper [16] the advantages of including comorbidity into different areas of health research, practice, and policy making. They also underline that for patients who have multiple and interacting conditions there is a need for evidence-based decision-making. This is something I aim to provide in the field of STIs with this thesis.

Another example of a disease model looking at multiple diseases is the model from Aguilar et al. [17] looking at asthma, eczema, and rhinitis. This research acknowledged the benefits of modelling several similar diseases, in this case respiratory disease, in one model and have consequently implemented such a multi-disease model. Key aspects of this model included the analysis of protein interaction to understand the existence and the mechanism of action of comorbidity between the examined respiratory diseases.

Generally, for the treatment of people with multi-morbidity, several treatment models

have been developed and implemented. Grover et al. found in a systematic review [18] that these models have in common that they take a holistic approach and look at the whole patient instead of focussing on one specific disease of the patient. Whereas the systematic review focussed on chronic diseases, aspects of it can be transferred to a multi-STI model as HIV and syphilis are chronic conditions.

This thesis aims to assimilate these learnings from other multi-disease models and translate them into a STI context. Decision makers and ultimately patients in sexual health can then profit from a holistic view on the sexual health of their cohort of interest, instead of looking at STIs separately and ignoring effects on combined disease management or combined resource use.

1.3 Clinical Background

1.3.1 What Distinguishes an STI from any Other Infection?

The World Health Organisation (WHO) describes STIs in the following manner [19]:

"Sexually transmitted infections (STIs) are passed on from one person to another through unprotected sex or genital contact."

There are more than thirty recognised STIs which can be caused by bacteria, viruses, and parasites. They are transmitted primarily via sexual contact. Some sexual practices enable further transmission routes, which can include the oral-oral route or the faecal-oral route [20]. For instance, a common cold (oral-oral transmission route) or shigella (faecal-oral route) can be transmitted during sexual contact. These examples though should not be considered as STIs, because their primary route of transmission is not via sexual contact. Instead, the primary route of transmission is other common scenarios, e.g. sneezing or bad hygiene settings [21].

STIs can also be caused by *congenital infection*. This is the transmission from an infected mother any time during pregnancy (transplacental) through to childbirth (peripartum) to her new-born(s) [22].

1.3.2 Why Are STIs Important?

1.3.2.1 Importance on Personal Level

STIs impact negatively on the overall well-being of a person affecting morbidity and mortality. STIs are an important influencing factor on the global morbidity, especially since some STIs no longer respond reliably to inexpensive antimicrobials, i.e. gonorrhoea [23]. Other STIs such as HIV-infection are an important factor for the global mortality (see Section 1.3.3.3). Some pathogens are known to cause cancer, e.g. human papillomavirus (HPV) which can be the cause of cervical cancer [24], further STIs may result in miscarriage or neonatal death [22]. Non-fatal outcomes can also occur and influence the Quality of Life (QoL), e.g. due to anxiety or stigmatisation, of an individual over an extended period of time [25]. These points illustrate the effect an STI might have on the life of one individual. Considering these effects on a larger population-wide scale, the public health relevance of STIs becomes obvious [21, 22, 26].

1.3.2.2 Worldwide Incidence and Prevalence

The estimated number of new cases of four curable STIs (chlamydia, gonorrhoea, trichomoniasis, syphilis) is shown in Figure 1.1. They sum up to an estimated number of 357 million new cases of curable STIs each year [1].

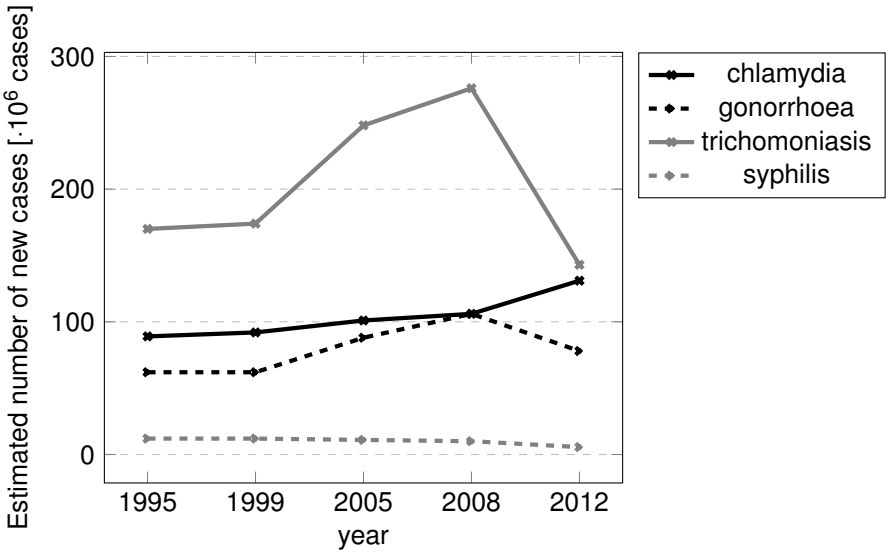


Figure 1.1: Worldwide number of new cases of four curable STIs between 1995 - 2008 [1]

Arguably, the best-known STI might be HIV. Figure 1.2 shows the estimated number of new cases of HIV and deaths due to HIV. The number of new cases decreased within the last couple of years and in parallel treatment improved, which resulted in lower mortality. Therefore, the prevalence is still increasing, despite decreasing number of new cases, see Figure 1.3. Depending on the specific geographic region this pattern of new cases compared to prevalence and deaths varies. The burden of disease of HIV in low to middle income countries is higher [27].

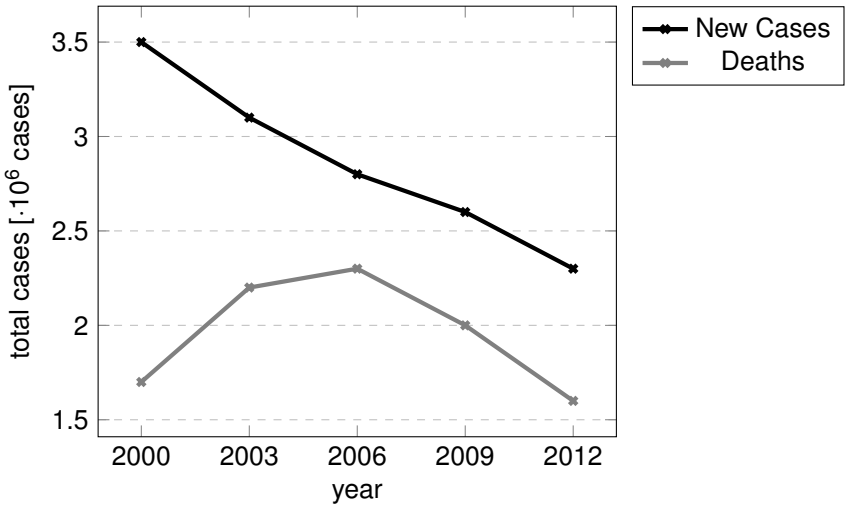


Figure 1.2: Global number of new HIV cases and HIV deaths between 2000 and 2012 [27]

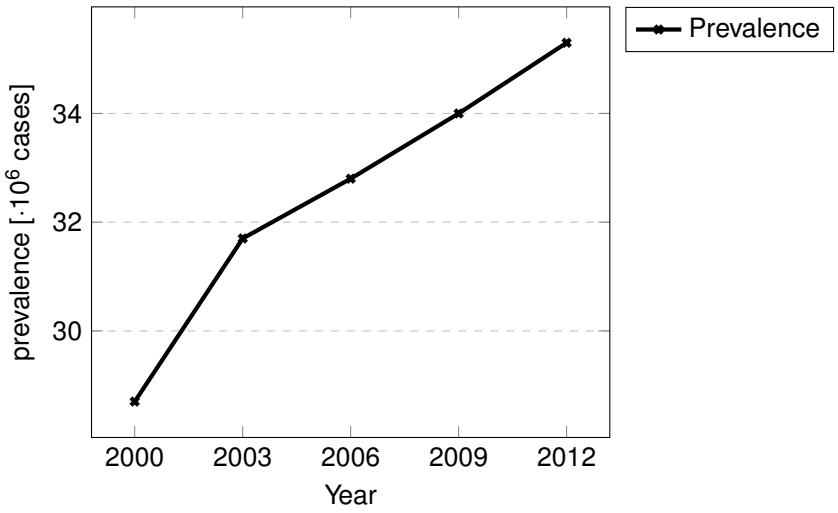


Figure 1.3: Global HIV Prevalence between 2000 and 2012 [27]

More recent data confirm the trend of an increasing HIV prevalence whilst observing a decreasing HIV mortality [28].

1.3.2.3 Under-Estimating of STIs

Not every infected person receives treatment for STIs. There are several reasons for this, one of it being because STIs can be asymptomatic. Infected people might not be aware of their infection and hence do not attend available sexual health services.

Social stigmatisation of STIs can prevent infected people from receiving the best possible treatment as they do not use available sexual health services or may not reveal the symptoms. Also people may attend non-specialist services and may not get the best diag-

nosis or treatment. Additionally, the structure to provide sexual health services for people in need might not be sufficient in some regions.

These reasons lead to under-estimating the real incidence and prevalence. For example, in the United States of America (USA) it is estimated, that 20-50% of all reportable new STI cases are not being reported [1, 29].

1.3.2.4 STI Reporting in England

In England, all STI diagnoses are stored centrally using Genitourinary Medicine Clinic Activity Dataset (GUMCAD) [30]. This electronic surveillance system allows to track the prevalence on a local and nation-wide level in detail. GUMCAD collects patient-level pseudonymised STI data from about 400 sexual health services across England. The collected data contain information on STI tests and STI diagnoses from all commissioned specialist and non-specialised STI services. Some of the collected information is made publicly available in quarterly reports, other information is only available to registered users, such as local authorities.

Whilst being the best available dataset, GUMCAD has some limitations. Due to the pseudonymised nature of its data, it is not possible to create longitudinal dataset of one patient across several clinics. It is not feasible to track the medicinal history of one patient over different clinics. Furthermore, the access to behavioural data is limited within GUMCAD which means that some relevant parameters for modelling purposes cannot be extracted from this dataset [31]. Still, GUMCAD-data are one of the best available information sources for population-wide STI-incidence in England.

We can assume that a majority of all prevalent cases of people who had contact with the English health care system are captured in GUMCAD. I use GUMCAD data in this thesis to input disease models (for example, see Section 4.3.1.1 Table 4.1).

1.3.2.5 Impact of STIs on Health Care Systems and Financing

STIs are a major issue for health care systems all around the globe, with England being no exception. Resulting prevention and treatment costs and long-term sequelae pose a burden for health care systems.

Overall, STIs are among the ten most important reasons for health care visits worldwide [21]. Prevalence and incidence vary between low and high income countries, men and women, different STIs, and even within different countries of comparable wealth and developing status. Consequently, the importance of certain STIs might differ from country

to country [26].

In many countries, the government is in some form involved in financing healthcare. STIs can cause significant expenditures, money which could be spent elsewhere for greater benefit if the STI prevalence was lower in the first place. The economic importance of STIs on a population-wide level and thereby for health care systems becomes even clearer if we look at these costs. The cost to the health care service of STIs in the United Kingdom (UK) totalled to £700 million in 2011 [21, 32, 33]. A more detailed view is given in section 1.4.

1.3.3 Which STIs are Relevant for This Thesis?

The selection process for the relevant STIs presented in this section is described in-depth in section 3.3. This section focusses on epidemiology of the selected STIs.

1.3.3.1 Chlamydia

The pathogen *Chlamydia Trachomatis* can cause two STIs; chlamydia and Lymphogranuloma Venereum. Usually, chlamydia does not cause any severe symptoms but can lead to serious long-term consequences, such as infertility or Pelvic Inflammatory Disease (PID)

Hughes et al. reported that Lymphogranuloma Venereum was very rare in the UK except a series of outbreaks starting in 2003. Lymphogranuloma Venereum has a low prevalence in the overall UK population but can cause localized outbreaks within high-risk groups [34, 35].

Chlamydia positivity numbers reported in the literature agree on 2-3% in the general population and 9-10% in those attending a genitourinary medicine (GUM) clinics [36, 37]. These numbers are confirmed e.g. by a national study of approximately 15,000 people in Great Britain (Natsal-3) [38] in which 1.5% (women) and 1.1% (men) of the participants aged 16 – 44 were tested positive for *Chlamydia Trachomatis*. These numbers are higher for younger adults (16-24 years) and generally higher for women in all age groups.

1.3.3.2 Gonorrhoea

The pathogen *Neisseria gonorrhoeae* can cause a gonorrhoea-infection. Similar to chlamydia infections many infected people do not have symptoms. Gonorrhoea can, if left untreated, lead to serious long-term sequelae.

The prevalence of gonorrhoea in the UK is low, being estimated at a level under 0.1% in the total population [38, 35]. Nevertheless, gonorrhoea is still relevant and causes outbreaks in geographically concentrated high-risk groups [34], e.g. men who have sex with men (MSM) [39].

Within the last couple of years, gonorrhoea was in the focus of research as antimicrobial resistant strains were observed and posed new challenges regarding the treatment of gonorrhoea-patients [23, 40].

1.3.3.3 Human Immunodeficiency Virus (HIV)

acquired immune deficiency syndrome was discovered in the early 1980s [41] and led to a global pandemic in the following decades [42]. HIV, the virus which causes AIDS was first identified by Montagnier and Barré-Sinoussi in 1983 [43] who received the 2008 Nobel Prize in Physiology or Medicine for this discovery.

Clinical progression with HIV can be separated in three stages, these are:

- Primary HIV infection
- Chronic HIV infection
- AIDS

Primary HIV infection occurs within weeks of first acquiring HIV.During primary HIV infection, individuals may be asymptomatic or symptomatic (acute retroviral syndrome). Symptoms can be mild or severe, are non-specific and can include fever, headache, pharyngitis and rash. During this stage, individuals have a high amount of HIV in their blood and bodily fluid and are therefore very contagious sexually. This stage usually lasts no longer than a month. [22, 44]

The "chronic HIV infection" stage begins after the "primary HIV infection" stage is over. This "chronic HIV infection" stage can last, even without treatment, for several years. People who take antiretroviral therapy (ART) as prescribed are likely to never leave this stage at all. This means that people living with HIV can remain well and live a normal life expectancy without ever progressing to AIDS. In this stage many people do not show symptoms. [22, 45]

Without treatment, the immune system is gradually weakened by HIV and people progress to AIDS. AIDS is the last stage of an HIV infection in which the immune system is severely weakened. In this stage, the weakened immune system is not able to fight off further infections and individuals acquire opportunistic infections and cancers such as tuberculosis, *Pneumocystis* pneumonia and Kaposi's sarcoma. If left untreated the mean survival time of people with AIDS is 3 years. [21, 44]

Usually, the mortality increases with each of the HIV stages, being highest for AIDS. Prevention measures as well as early diagnosis and treatment can stop the progression to

AIDS and reduce morbidity and mortality. Therefore, since the beginning of the epidemic, an increasing number of people die with HIV, but are not dying because of HIV. [44, 45]

There are regions in the world with a high HIV prevalence of over 20% (e.g. Swaziland, Lesotho, and Botswana) [27], however the prevalence in England is estimated to be 0.16% by Public Health England (PHE) [46]. PHE estimated that 94% of all people living with HIV in England have been diagnosed. Of those, 98% are on treatment, and of those on treatment 97% do not have a detectable viral load. A non-detectable viral load means that treatment is successful, and they are no longer able to transmit the virus to sexual partner(s). [47]

In England over the past 10 years, the number of people with AIDS or AIDS-defining illness at the point of HIV-diagnosis has decreased. Due to this earlier diagnosis in combination with earlier and better therapy and also fewer undiagnosed people living with HIV, HIV-related deaths are also decreasing over the last decade. [48]

1.3.3.4 Syphilis

An infection with the pathogen *Treponema Pallidum* is called syphilis. Syphilis usually start with mild symptoms but can affect the whole body of an infected person. Syphilis can lead to neurosyphilis, for example, if left untreated [22].

Syphilis, whilst being important worldwide [49] is not highly prevalent in England. The national infection report on syphilis and congenital syphilis 2013 stated an overall prevalence of syphilis of 0.00025% for men and 0.000038% in women, with higher prevalence rates for urban areas. Sporadically localized outbreaks in England within high-risk groups, such as men who have sex with men (MSM) are reported. Congenital infection is possible, leading to severe health issues, however this way of infection is nearly eradicated in England due to low prevalence and a universal antenatal screening programme with 0.0025 cases within 1000 life births [50].

1.4 Organisation of Sexual Health Care in England

The target audience for the software developed in this thesis are decision makers in sexual health. This section gives a brief overview of the involved parties in English health care system, focussing on sexual health care financing and delivery to understand the role of decision makers within the health care system. The National Health Service (NHS) is the most important player in the English health care system. Health services in England are centrally funded by the Department of Health and Social Care, based on a set tariff per patient and type of treatment. Healthcare is devolved to the other countries making up the UK; NHS Wales; NHS Scotland, and the *Health and Social Care Board, Northern Ireland*. I focus on NHS England for the remainder of this section, as this also constitutes the target audience of the software to be developed.

1.4.1 How Is Health Care Organised in England?

From a patient perspective, the most visible part of the NHS is health care providers. These are for example, general practitioners (GPs) or NHS trusts, such as hospitals or the ambulance service. Providers are contracted by commissioners to deliver services.

The main task of commissioners is to set up contracts with the providers. These commissioners can be local authorities, clinical commissioning groups or NHS England. They must decide which providers to make contracts with while not exceeding their budget on one hand and guaranteeing appropriate health care coverage on the other.

The providers are then regulated by national regulating bodies such as the *Care Quality Commission* and *NHS Improvement*. Their main task is to monitor the delivered health care quality. Therefore they are responsible for performance management, governance, and financial regulation and will support service improvements.

Overall, this structure has been summarised by the King's Fund in one sentence: "Commissioners contract with providers, which are regulated by regulators." [51].

The King's Fund [51] derived a summary of the cash flow after it leaves the Department of Health (DoH) from the NHS business plan [52], a National Audit Office report [53], and the DoH annual report [54]. This figure is reproduced in figure 1.4.

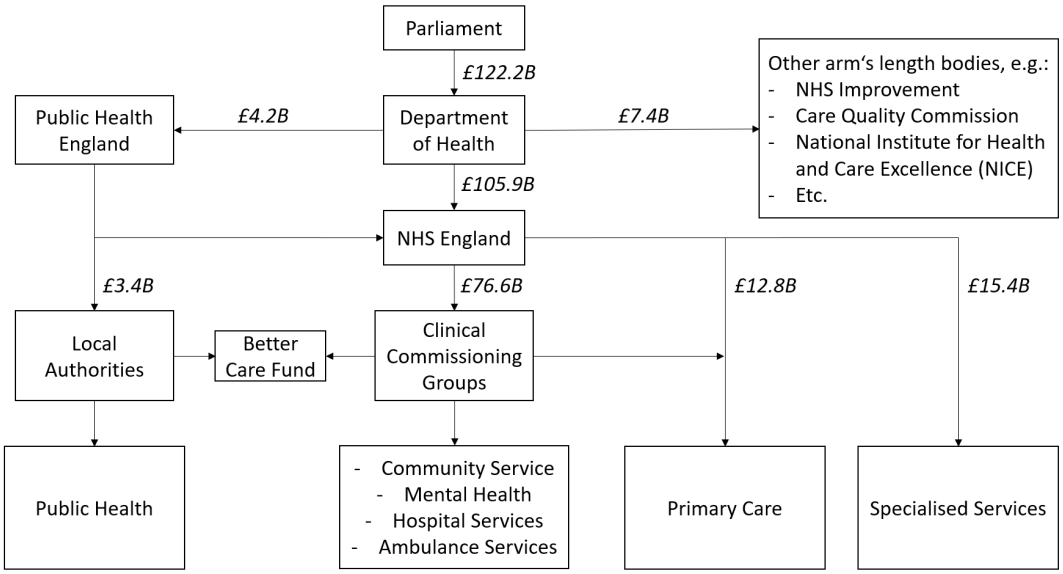


Figure 1.4: Cash Flow in the English Health Care System, reproduced from the King's Fund. [51]

In this cash flow diagram, we can see the regulators in the top right corner, the providers are at the bottom and the commissioners are in the centre of the figure.

In this graph, no money is directly assigned to sexual health services. This is due to insufficient granularity of this diagram. In a hypothetical and more detailed version of this graph, we could see that there is money assigned to different clinical areas of health care, including sexual health, reproductive health, and HIV, in each of those boxes. To understand this bit of the system better, the next subsection will examine the structure of commissioning sexual health reproductive health and HIV.

1.4.2 How is Sexual Health, Reproductive Health, and HIV Managed in England?

The structure of sexual health care delivery in England takes a whole system approach. This means that "commissioning takes a broad view across the full range of responsibilities undertaken by commissioners in local authorities (including public health, social care, education, leisure and recreation) and the NHS. In sexual health, reproductive health and HIV commissioning, relationships are between NHS England through its specialised services, primary care and public health commissioners, clinical commissioning groups and local authority public health and social care departments." as defined by PHE in their guide "Making it work" [55]. PHE aims to put patients in the centre of commissioning so that their needs drive the decisions which will be made. Clear definitions of areas of responsibility

are necessary to allow a frictionless flow of patients through the system.

Based on the aforementioned PHE guide, sexual health commissioning is the aggregation of three commissioning bodies which are: local authorities, clinical commissioning groups, and NHS England. Each of these is responsible for certain areas of care.

Local authorities are responsible for:

- STI testing via public health contract,
- STI treatment via public health contract, and
- contraception.

The following areas of care fall under the responsibility of NHS England:

- HIV treatment,
- HPV immunisation programme,
- STI testing via general practitioner (GP) contract, and
- STI treatment via GP contract.

Clinical commissioning groups commission services including:

- female sterilisation,
- vasectomy, and
- abortion.

These lists are not exhaustive and only give an idea of the different areas of responsibility of these commissioning bodies. To minimise conflicts between those areas two ground rules for the cooperation of these bodies have been set up:

1. A commissioning body is responsible for all costs related to the provision of a service which is within their area of care.
2. The healthcare status of a patient does not affect the responsibility of a certain area of care.

The second rule guarantees that for example the STI tests which HIV patients access through open access offers will be financed through local authorities, whereas the HIV treatment is financed through NHS England. If it makes practical sense exceptions to these ground rules can still be made.

1.4.3 What is the National Chlamydia Screening Programme?

One public health intervention to improve the sexual health of the general population is the National Chlamydia Screening Programme (NCSP) [56]. The NCSP was started in 2002 and is targeted at young adults aged 15 - 24 and aims to:

- prevent and control chlamydia through early detection and treatment of asymptomatic infection,
- reduce onward transmission to sexual partners,
- prevent the consequences of untreated infection
- raise awareness and skills of health professionals to screen for chlamydia, and provide the information young adults need to reduce the risk of infection and transmission

Young adults are given opportunities for chlamydia screenings e.g. at GP visits [57].

To control chlamydia prevalence, the chlamydia care pathway was developed. This is a seven-step process, which when taken together, represent a comprehensive case management for an episode of chlamydia including testing, diagnosis, treatment and partner notification as recommended by the NCSP [58, 59].

1.5 Health Economics

Decision makers in health care must make difficult decisions, balancing working within a fixed, finite budget and maximising the health outcomes for their population. Health economics provides tools to facilitate decision making in this field and is an important part of this thesis. Within this section, I will briefly introduce basic health economic concepts needed for this thesis.

All decisions and calculations in health economic evaluations should always look at two dimensions simultaneously, the costs and the effect of the intervention on the people affected by it. The first subsection examines how we can quantify the effect of the intervention on affected people and the second subsection introduces costs further.

1.5.1 What are Health Outcomes?

Health outcomes describe what we get for the money we spend on an intervention. This can be for instance the difference in life years or the number of prevented myocardial infarctions. Looking at these countable events on their own is not sufficient to describe the overall well-being of an individual. In these cases, it is beneficial to be able to quantify the health of a person.

Hence, it makes sense to have a look at the widely accepted WHO definition of health:

"a state of complete physical, mental and social well-being, and not merely the absence of disease and infirmity" [60]

A similar term which is often - mistakenly - used interchangeably with *health* is *quality of life*. Quality of life is defined by the WHO as:

"An individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns." [60]

But QoL covers more than just the health status of a person. It also includes factors which are not directly related to health, for example income, educational status, and housing. These factors are linked to each other. This means that a worse health state might decrease a person's ability to work and therefore also decrease their income. The lack of financing might affect their housing status and arguably even their educational level.

Including all factors which influence the overall QoL to assess the overall QoL in clinical trials is not practicable. This is due to the fact that factors such as housing and education

migh tnot be influenced by the examined intervention at all. Instead the health-related quality of life is used in health economics more frequently. This concept encompasses all aspects of the QoL which are part of a person's health. Some may question what the difference between *health* and *health-related quality of life (HR-QoL)* is.

The health status tries to quantify the objective difference between the current physical, psychological, and social status of a person compared to a status, where all these aspects are "perfect". The HR-QoL adds another layer of complexity to this as it tries to assess the subjective impact of the potential impairments on a person's overall well-being. The latter is frequently used as an important parameter of health economic studies [61, 62].

1.5.1.1 How to Measure Health-Related Quality of Life?

After clarifying the differences between health, QoL, and HR-QoL, I will look at methods which allow us to transform the abstract concept into a measurable outcome which can be used for further calculations. In this subsection I only give a very brief overview over the methods and tools used to quantify the health status of a person.

Measuring vital parameters, such as blood pressure and body temperature, does not assess the subjective impact of the potential impairment on the overall health-related well-being of a person. Therefore, other ways to quantify the HR-QoL need to be found.

Patient Reported Outcome Measures (PROMs) [63] are tools which allow people or their caregivers to describe their health status. One popular way of doing it is questionnaires, which can be disease specific or not disease specific. If they are specific for one condition, relevant aspects which might influence the HR-QoL and which are related to the disease in question are covered by the questionnaire. Using a translation algorithm, the answers can be translated into a number, which is called utility value. The utility is anchored at 0 and 1, with 0 being equivalent to *death* and 1 being equivalent to *perfect HR-QoL* [64].

The problem with disease-specific PROMs is that they need to be developed for each disease individually. It is a lengthy process before an academic consensus is reached on what this questionnaire might look like. In many disease areas more than one questionnaire is being used as a total consensus could never be reached. It is without further research not possible to compare the measurements of two different questionnaires to each other [65].

In health economics different diseases need to be compared to each other. As a result, it is inevitable to consider opportunity costs, see Section 1.5.2. This can only be done with a generic HR-QoL measuring tool, which allows comparisons between different diseases

as it was assessed using the same tool. The disadvantage of such a tool is that it may not address specific disease related issues and therefore might not be sensitive enough.

The EQ-5D questionnaire [66] is a commonly used generic measure of HR-QoL. It assesses the health of a person in five distinct dimensions. These dimensions are:

- mobility,
- self-care,
- usual activities,
- pain/ discomfort and
- anxiety/ depression

There are two main versions of this questionnaire. One gives three options for each of those dimensions, which is the EQ-5D-3L. This version has a total of 243 (= 3^5) different health states a person can be in. Therefore, especially in healthier cohorts people tend to report the best possible health state. This results in a ceiling effect and not being able to observe small changes in the overall health status [67, 68]. To avoid this problem the more detailed EQ-5D-5L can be used which offers five answers for each category and thus offers better measurement properties [69].

The answers to the EQ-5D questionnaires can be translated with country-specific value sets into a number, which is anchored at 0 (= death) and 1 (= perfect health), as described above.

For some conditions such as sexual health, vision loss, hearing loss, and tiredness the EQ-5D is not very sensitive [70]. To address this issue, bolt-ons [71] have been developed which add another independent dimension to the EQ-5D questionnaire to pick up relevant information.

Besides the EQ-5D there are other questionnaires, like the Short Form 36 questionnaire (SF-36) which were developed to assess the HR-QoL. There are further tools, like visual analogue scale (VAS) or time trade-off (TTO), which also allow researchers to calculate utility values.

A problem with most general methods used to assess HR-QoL is that they are not very sensitive to sexual health issues [72]. Therefore specific questionnaires such as sQoL must be used to adequately capture these effects [73].

1.5.1.2 Quality-Adjusted Life Years

The previous section showed how HR-QoL can be quantified. This gives us one utility value for a single point in time. If time trends need to be observed, multiple measurements need to be made. To compare the HR-QoL over an extended period it has to be extended by a time component.

The utility value is multiplied by the number of years a person is in this state of health to calculate the quality-adjusted life years (QALYs). This value does not only account for the actual utility value but takes the time a person is in this state of health into account. It thereby allows the comparison of the well-being over an extended period [74].

1.5.2 Costs

In health economics opportunity costs are important. This means that money is limited, and any pound spent on one treatment cannot be spent for another treatment. Consequently any benefits of the treatment which was not chosen are lost. It means that we always have to ask the question: *What else could I use this money for?* Or: *Could I spend this money more effectively?* In health economics, costs, more specifically opportunity costs, are presented in analyses besides health outcomes such as QALYs.

This section gives a brief overview of different cost types and perspectives which could be adopted for the analyses [75].

1.5.2.1 Perspectives

Health economic analyses should include "all relevant costs". It depends on the adopted perspective about which costs are considered to be relevant and which are not. For analyses in England, the most important perspective is a "health and social care cost perspective". This perspective includes all costs related to the condition in question [65].

Other perspectives, which are frequently used, are:

- societal perspective and
- payer perspective.

The **payer perspective** includes all costs which occur related to the diseases and which are covered by the payer in question, e.g. a health insurance company.

The **societal perspective** includes all costs which are related to the disease, but is not restricted to health costs, and includes further costs such as productivity losses.

Depending on the adopted perspective and therefore the variety of included costs, the

cost-effectiveness threshold (see section 1.5.3.1) can be adjusted. The default perspective which is used in this software is the health and social care perspective. Other perspectives can still be adopted by amending the costs and utilities associated with each event in the model.

1.5.2.2 Cost Types

Depending on the perspective, different costs need to be included in a health economic analysis. These costs can be put in different cost type categories.

We can differentiate between direct and indirect costs. Direct costs are directly associated with the disease, whereas indirect costs are not. For example, a cast for a broken arm is categorised as a direct cost, whereas a taxi which is needed because the patient cannot drive on their own any more is an indirect cost [65].

Another distinction can be made between disease-related costs and non-disease related costs. Disease-related costs are linked to the disease, which is in the focus of the intervention, in contrast to non-disease related costs which are not [65].

Depending on the level of detail of the data, different costings can be done differently. The least detailed way of doing it is also the one with the least requirement towards data. In this case, a person/ patient costs a pre-defined amount of money per day. The better the quality of the data, the more in-depth the costing can be. The most detailed version is micro-costing when e.g. the costs of the prescribed drugs are added for each patient [76].

1.5.3 Different Types of Health Economic Analyses

In this subsection, outcomes which are calculated by the software developed during this thesis and presented are laid out. These results are shown to the user after the end of the simulation. One of the key outcomes in health economics is the Incremental Cost Effectiveness Ratio (ICER). It compares the cost and the effectiveness of two interventions to each other [65, 77]. Equation 1.1 shows how it is calculated.

$$ICER = \frac{\Delta costs}{\Delta QALYs} = \frac{costs_{new} - costs_{old}}{QALYs_{new} - QALYs_{old}} \tag{1.1}$$

Instead of quality-adjusted life year (QALY)s, other measures of the effectiveness, such as "number of infections", can be used. If QALYs are used the calculated ICER can be used to compare it to the cost-effectiveness threshold suggested by the National Institute for Health and Care Excellence (NICE).

1.5.3.1 Cost-Effectiveness Plane

The relationship between costs and utilities can be illustrated in a cost-effectiveness (CE) plane, see Figure 1.5. The origin of the graph usually depicts the reference intervention, i.e. the current standard of care. A point right of the origin shows more effective intervention, i.e. those with higher total QALYs and vice versa. A point which is further up shows a more expensive intervention, a point further down a cheaper intervention.

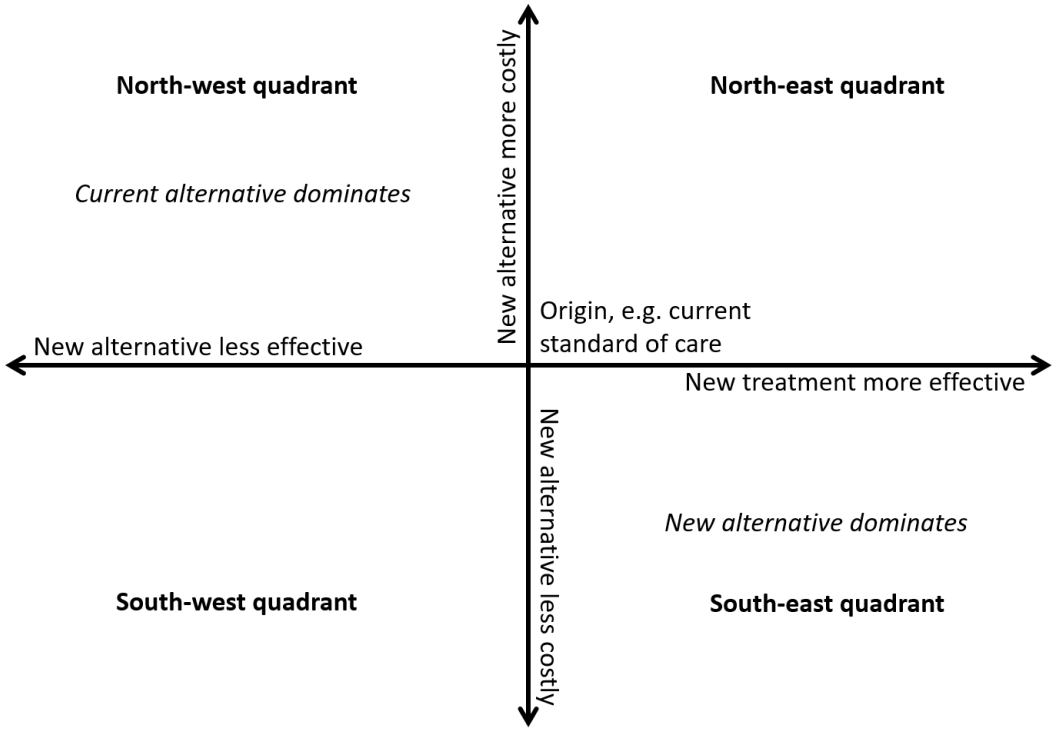


Figure 1.5: Explanation of the structure of a cost-effectiveness plane.

The x-axis (effectiveness) and y-axis (costs) split this plane into four quadrants. The north-west quadrant shows interventions which are more expensive and less effective than the intervention in the origin. They are dominated by the reference treatment and we would never choose them. On the other hand, interventions in the south-east quadrant are less expensive and more effective. We would always prefer these interventions as they dominate the intervention in the origin.

The case is more complex for interventions in the south -west quadrant and especially in the north-east quadrant. Nowadays most interventions end up being more expensive but also more effective (north-east quadrant). In these cases further health economic methods need to be employed.

Cost-Effectiveness Threshold. One of these additional pieces of information which can be used is the cost-effectiveness threshold. This threshold quantifies how much a decision maker is willing to pay for an additional outcome gained. In England, the threshold of a standard intervention is between £20,000 and £30,000 per QALY. Exceptions to this threshold are made for rare diseases, neonatal care, and end of life care treatment [78]. If the ICER does not exceed the threshold it is likely that a certain intervention will be funded.

This threshold, or more precisely the range of acceptable cost-effectiveness, has been subject to various discussions. Work by Devlin and Parkin suggests that the threshold is not the only factor NICE bases their decisions upon. Other factors include the burden of disease and the existence and availability of alternative treatments. In their paper they used a binary choice analysis to examine whether or not a single threshold could be found. They concluded that with increased cost per QALY the probability of NICE rejecting the proposal decreases, but no single value could be found. [79]

While some authors suggest that the way NICE handles the threshold as a range of decreasing probability of acceptance, other authors such as McCabe favour an actual single threshold. They argue that above this threshold other criteria can be considered and for interventions with a potential significant impact on the budget can be evaluated with a lower threshold. [80]

Similarly Claxton et al. also suggest that the threshold should be decreased to account for technologies with a huge impact on the overall NHS budget. They argue with the opportunity cost of one additional QALY. Or in other words, how much money we can pay for an additional QALY without losing the opportunity to spend the money somewhere else in the healthcare system more efficiently. They tried to find a single value for the threshold and concluded that the likelihood of it being smaller than £30,000 is 97% and of it being smaller than £20,000 is 89%. [81]

The last paragraphs of this subsection briefly introduce other types of health economic analyses, some of which can be calculated by the software and some are listed in here to give background information for the systematic review conducted.

1.5.3.2 Cost-Utility Analysis

A cost-utility analysis (CUA) compares the costs of intervention and their QALYs. The aforementioned methods, like CE planes and CE frontiers as well as the cost-effectiveness threshold, are tools which can be used in a CUA [65, 82].

1.5.3.3 Cost-Effectiveness Analysis

A cost-effectiveness analysis (CEA) is similar to a CUA, with the main difference being that the health outcomes are not QALYs, but countable units of measurement, such as number of infections. Other units are possible as well, e.g. unintended pregnancies, or deaths averted [65, 82].

Cost per Infection. This is one sort of cost-effectiveness analysis, especially relevant when examining infectious diseases. To calculate this number the total costs are divided by the number of incident infections in the relevant interval [65, 82]. It can also be important to see how much money one needs to spend to prevent infections, this is described by the cost per averted infection. This number is used to compare how much money has to be spent to prevent one infection. It is calculated as shown in Equation 1.2.

$$cpi = \frac{c_1 - c_2}{i_1 - i_2} \tag{1.2}$$

with

cpi = cost per averted infection

c_1 = costs in intervention

c_2 = costs in control

i_1 = infections in intervention

i_2 = infections in control

1.5.3.4 Budget Impact Analysis

A Budget Impact Analysis usually follows a CUA or CEA. A Budget Impact Analysis evaluates whether the previously examined intervention is affordable in the given setting taking the available resources into account. A Budget Impact Analysis for example calculates how much it would cost to implement the given intervention on a population-wide scale [65, 82].

This type of analysis and the two following analyses as well have been added to give background information on the systematic review. My software is not capable of calculating these analyses.

1.5.3.5 Cost-Benefit Analysis

A cost-benefit analysis puts a monetary value on the outcome of an intervention. It compares the costs which have been spent on some intervention with the monetary value of its

outcome. It is difficult to find monetary values for health outcomes which is why this type of analysis is used rarely to evaluate health interventions [65, 82].

1.5.3.6 Cost Minimisation Analysis

This is an older type of health economic analysis, which is not used widely anymore. It has been used to find the cheapest alternative using the assumptions that the outcome of all interventions is considered equal. Hence the cheapest option is also the best option [65, 82].

1.6 Disease Modelling

Disease Modelling can be performed in many different ways. I will provide a brief overview of most important approaches for this thesis which are Markov models [83], mathematical models using linked differential equations [84], and discrete event simulations [85] in Chapter 5.

In all approaches, the disease has to be described in a way that software can process. Therefore a common approach is to define health states. Some approaches avoid using health states by looking at attributes of an individual, e.g. CD4 count for HIV-modelling. Models can describe the progression of the disease either by changes in health states, changes in the values of the individual's attributes or a combination of both.

If health states are used the definitions for all health states must be mutually exclusive [83]. This is to guarantee that one individual can only be in one health state at each point in time. The health states must also cover all possible aspects of the disease at the same time [83]. To avoid ambiguity health states also need to be unique. This is defined as any randomly picked pair of health states must consist of two distinct health states. This feature is also called "being pairwise distinct". Both requirements result in the fact that any given individual being in exactly one health state at any given point in time.

Health states can be connected by transitions. Transitions allow individuals in the model to move from a certain health state to another health state [83].

1.6.1 Model Structure

A common structure for disease models is the so-called "susceptible - infected - recovered (SIR)" structure [84]. These can be used to simulate infectious diseases. An SIR model consists of three health states:

- Susceptible; if the individual has not been infected so far,
- Infected; if the individual is currently infected, and
- Recovered; after the individual recovered from the disease.

This model type usually assumes that individuals will develop immunity after their first exposure to the infective pathogen. This means that individuals can transit from *Susceptible* to *Infected* and from *Infected* to *Recovered*. Other transitions are not possible.

Not all infectious diseases can be described using an SIR structure.

Similar approaches, like susceptible - infected - recovered - susceptible (SIRS)-models, assume that individuals can lose their immunity and therefore transit from *Recovered* to *Susceptible*. This puts them under the risk of getting infected again.

Another model structure assumes that there is no immunity at all. In these susceptible - infected (SI) models [84] individuals will transit after being *Infected* directly back to *Susceptible*.

These model types, SI, SIR, and SIRS, only define the structure of the model. The specific implementation varies on whether they are realised as discrete event simulation (DES), Markov models, or mathematical compartmental models. In all three approaches, the transitions between these states are handled differently. Different infections can be modelled with these structures by using different transitions.

Models can use a structure differing from the aforementioned SIR-like structures. In this case, experts must be found to find a valid structure which fulfils all requirements towards health states.

1.6.2 The Modelled Cohort

In many infectious disease models, the population of the model is interacting. This means that the proportion of infected individuals in the model influences the reproduction number of the disease, which describes the speed by which the infection spreads within the given cohort [84]. The spread of an infection can be simulated by a rate which depends on the number of infected individuals in the model or by simulating individuals separately in the model. In contrast to this, it is possible to simulate diseases using a non-interacting approach, where the reproduction number does not depend on the number of infected individuals. This simplification is useful for non-transmissible diseases such as diabetes or cancer.

In some models, the number of individuals in the model stays the same over the whole modelling time. The distribution of individuals over the health states in the model can still vary. These models are called closed cohort models and can be used for example to examine the effect of an intervention on a specific cohort. The opposite of closed cohort models are models in which the number of individuals included increases or decreases over time. These are called open cohort models. Open cohort model can be useful to simulate the effects of birth, migration, or to observe long-time trends over several generations [83, 84].

Depending on the research question, disease models might vary the length of simu-

lated time. The length of simulated modelling time is also called the time horizon of the disease model [83].

1.6.3 Terminology

The last subsection clarifies some terms to prevent potential misunderstandings in the following chapters.

1.6.3.1 Patient

Not all infected people are patients. In this thesis, I use the word patient for people who have any form of contact with a health service. That means that infected people are not automatically patients unless they use or visit some form of health service.

1.6.3.2 Individual

In this thesis, I differentiate between people and modelled people. A person is an entity from the real world, whereas a modelled person refers to its virtual representation. To underline this difference, I use the term individual to refer to a modelled person in the software. Whenever the term person is used, it is about a real-life human, e.g. participants from a study.

1.6.3.3 Agent-Based Model

Simulated objects can also be called agents. The term agent is broader than the term individual, as it also includes other acting entities within the model, such as health care providers. An agent-based modelling approach is an individual-based approach which is driven by simulated decisions and effects of various simulated entities (= agents), in the model.

1.7 Summary

In this chapter I have covered the background to the STIs discussed in this thesis, the organisation of health care in England, health economics and general aspects of disease modelling. Hence this chapter builds the foundation for the remainder of the thesis.

Using the background provided in this chapter I will look at the existing literature on simultaneous modelling of multiple STIs in the next chapter.

Chapter 2

Systematic Review

2.1 Rationale

There is a solid evidence base on disease models for single STIs. For example, during the development of the disease models included in my software, I counted 82 models for chlamydia. But there is less literature on STI models for more than one STI in the same model.

This chapter explains the methodology and the results of the systematic review which was conducted for this purpose. The systematic review was supported by a total of three second reviewers. Other than that I conducted the systematic review alone, supported by my supervisors who had a consulting role.

Interactions of STIs and interventions which target more than one STI underline the need for more information on the effect of multiple STIs within the same network of individuals. Disease modelling can be a tool to provide this information, which is why I was intrigued by the small number of multi-STI models a piloting search returned.

I am aware of one software which has been specifically developed to simulate multiple STIs simultaneously. This software is STDSIM [86] which has been developed by Bakker et al. at the beginning of this century to model the spread of HIV and connected STIs in sub-Saharan Africa. This software was not parametrised for an English context and was also not capable of calculating health economic outcomes. I wanted to see whether other similar software for England is readily available.

2.1.1 Objectives

This systematic review tried to achieve two main goals; these were:

1. To identify disease models, which can simulate multiple STIs simultaneously.

2. To examine the methodology that was used to develop the models.

The first goal demonstrated the research gap and thereby helped to understand the necessity, or lack thereof, for this thesis. The information which was gathered to answer the second goal was used to develop the multi-STI modelling software.

The PRISMA [87] framework was used to report this review.

2.2 Protocol and Registration

The protocol has been published in BMJ Open in 2018, see [88].

The systematic review was registered with the international prospective register for systematic reviews (PROSPERO), the registration number is CRD42017076837 (`https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=76837`).

2.3 Methods

2.3.1 Eligibility

2.3.1.1 Inclusion Criteria

The inclusion criteria for this systematic review were kept broad to identify studies. One of the **aims of an eligible article should be to report on the STI model** in question. This guaranteed that the reviewers could extract information with sufficient detail from this article. Therefore, any article which did not provide enough detail to extract the relevant data was excluded.

Eligible articles must simulate STIs on a cohort or population level.

The described models should allow horizontal sexual transmission of the simulated STIs. This meant that the models should simulate a sexually active group of individuals. This did not necessarily have to be the whole sexually active proportion of a population, the model could also focus on relevant sub-groups of it, e.g. female sex workers (FSW), MSM, or young people.

Relevant articles must describe an STI model which simulates at least two distinct STIs simultaneously, whereas an actual interaction of the STIs was preferred but not required for inclusion.

The review was not restricted to a specific intervention. If the aforementioned eligibility criteria were fulfilled, any model was accepted. This included models looking at behaviour change interventions, models for examining new STI treatment, and models which did not

simulate any intervention at all. If models projected the current prevalence without considering a change in an intervention or without any intervention at all these models were still eligible. All modelling approaches were included.

Any article type was potentially relevant, providing that the description of the model was detailed enough.

Articles in any language were included, providing that they offered an English title and abstract. This restriction was necessary as otherwise the search strategy would have to be translated into all potentially relevant languages. If the full text was not written in English, it was translated for further examination.

2.3.1.2 Exclusion Criteria

STI models which looked at the interaction of pathogens in a single patient (in-host interaction) were excluded.

Models which solely considered non-sexual horizontal transmission, such as needle sharing, as a way of communicating the disease were excluded. If non-sexual horizontal transmission pathways were considered in addition to a horizontal sexual pathway the article was still eligible. Models, which solely simulated mother-to-child transmission (vertical transmissions) were excluded.

Models which only simulated different strains of the same STI were excluded. Articles which looked at the interaction of an STI with a non-STI, e.g. HIV and tuberculosis, were excluded.

Some models solely simulated the interaction of an STI with a sequela. If a model simulated an STI and sequelae, this article was still excluded if no other STI was included in the model. For example, many HIV-models also simulated AIDS. As AIDS is a sequela to HIV infection, these articles were excluded provided that no other STI is included in the model.

Articles which described qualitative work or case reports were always excluded. Articles types which were included could be but were not limited to:

- health economic analyses,
- clinical trials with modelling component,
- governmental documents,
- theses, and

- modelling studies.

2.3.2 Information Sources

For this review, nine databases were searched. These were Cochrane, Dart Europe, Embase, Medline, New York Academy of Medicine Grey Literature, OpenGrey, PLoS, and ProQuest. More information on these databases can be found in Appendix A.4. The variety of databases guaranteed that I picked up different types of articles, ranging from grey literature to scientific journals, and theses.

2.3.3 Search

The search was divided in three smaller searches for different areas, these were:

- "interacting" articles
- "STI" articles
- "model" articles

Potentially relevant articles were expected in the overlap of the results of these searches, Figure 2.1 shows this.

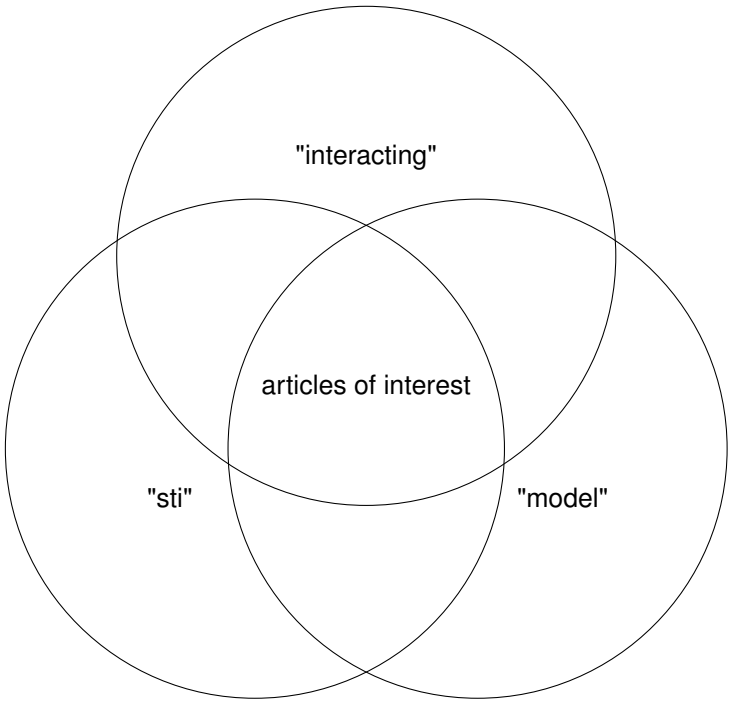


Figure 2.1: Visualisation of the search strategy. Each circle displays one area of interest, the overlap of all three circles contains the papers relevant to this systematic review

For each of these searches, a set of search terms was aggregated. These were amended for each database according to their syntax and, if applicable, thesaurus. The complete list of search terms for Medline and Embase can be found below. The search strategies for all other included databases can be found in Appendix A.1.

2.3.3.1 Medline and Embase

This was the baseline search strategy. All other strategies were derived from this one. Medline and Embase were performing full-text searches in the title and abstract that were complemented by searches for medical subject heading (MeSH) terms. No filters or limits were applied to the search.

Terms 1 - 8 are the search terms used to find articles describing an interacting feature, terms 9 - 31 are the terms used to find articles which deal with modelling, and terms 32 to 64 are the terms used to find articles about STIs. Term 65 combines the results.

1. interact*.mp
2. coinfect*.mp
3. parallel.mp
4. simultaneous*2.mp
5. coexist*.mp
6. multi*.mp
7. "more than".mp
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. (compart* adj3 model*).mp
10. (mathematic* adj3 model*).mp
11. (comput* adj3 model*).mp
12. *decision support techniques/
13. *models, theoretical/
14. *models, statistical/
15. exp models, economic/

16. *nonlinear dynamics/
17. "agent based model*".mp
18. (decision*1 adj1 support*).mp
19. (quant* adj3 model*).mp
20. "discrete event".mp
21. "markov* model*".mp
22. STDSIM.mp
23. "micro simul*".mp
24. "agentbased model*".mp
25. "theoretical model*".mp
26. "statistical model*".mp
27. "economic model*".mp
28. "nonlinear dynamics".mp
29. microsimul*.mp
30. "individual based model*".mp
31. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32. exp Sexually Transmitted Diseases/
33. "sexual* transmit* infect*".mp
34. "sexual* transmit* disease*1".mp
35. STD*1.mp
36. STI*1.mp
37. HIV.mp
38. "human immunodeficiency virus".mp

39. Hepatitis.mp
40. "Genital Herpes".mp
41. HSV.mp
42. HSV-1.mp
43. HSV-2.mp
44. "acquired immune deficiency syndrome".mp
45. mycoplasma.mp
46. gonorrhoea.mp
47. syphilis.mp
48. Chlamydia.mp
49. "Lymphogranuloma Venereum".mp
50. Chancroid.mp
51. "Treponema Pallidum".mp
52. Trichomon*.mp
53. "Human Papillomavirus".mp
54. "Genital Warts".mp
55. "Pelvic Inflammatory Disease".mp
56. PID.mp
57. "Condylomata Acuminata".mp
58. Cervicitis.mp
59. Epididymitis.mp
60. Urethritis.mp
61. Infertility.mp
62. "vener?al disease*1".mp

63. "vener?al infect*".mp

64. 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63

65. 8 and 31 and 64

I piloted this search strategy and saw that already known and relevant articles, for instance the previously mentioned STDSIM-model, which were manually selected beforehand were picked up by this search strategy. In addition to the listed search terms, I decided to track potentially relevant citations of already included articles and add these to the list of articles which I wanted to screen.

The search of all databases including the import into EndNote was carried out on 27 November 2017.

2.3.4 Study Selection

I searched all databases using their corresponding and previously introduced search strategies. After this, the results were aggregated, and duplicates were removed from the overall dataset. The remaining duplicate free data set was used for the title and abstract screening.

Title and abstract screening was carried out by myself (FS), Alice Howe (AH) and Florian Tomini (FT). FS screened the whole dataset whereas AH and FT each screened 10% of all abstracts. The second reviewers were chosen based on their experience in the academic fields of STIs and health economics (HE). There was no overlap between the articles AH and FT reviewed. All articles for the second reviewers were chosen randomly. Any conflicts were discussed with Rachael Hunter (RH) to resolve those. If the proportion of disagreement between the second reviewers and my decision would have been over 5% I planned to raise the proportion of articles to be screened by a second reviewer. This was to ensure that the systematic review is of sufficient quality.

For the full test screening, the second reviewers were FT and Ekaterina Bordea (EB). They screened 20% of all articles. Conflicts were resolved by RH.

All reviewers piloted each phase of the screening on selected articles to synchronize their understanding of the protocol and the topic and to ensure an equally high quality of their work.

2.3.5 Data Collection Process

During the data extraction, EB and AH acted as second reviewers. Some content which had to be extracted was captured in free text fields, such as the *input parameters*. Therefore, the results of all reviewers were cleaned, i.e. spelling was corrected, before the results were compared. RH moderated arising conflicts.

2.3.6 Software and Tools

To conduct this systematic review, I used tools and software, some of which I developed specifically for this purpose.

EndNote was used for reference management and manual de-duplication using the following fields:

- year,
- title, and
- authors.

The "Web search" function of Endnote was used to find available full text, providing that the full text was available to me, either via open access or through my University College London (UCL) library access.

Copies of the EndNote database were made after each step during the data preparation and cleaning to safelv store the progress.

2.3.6.1 Microsoft Access

The main documentation of the systematic review was done in a Microsoft Access[1] database. It tracked which reviewer rejected or accepted articles during the title and abstract screening or the full-text screening. This allowed automated searches for conflicts.

Several queries were developed which randomly selected references for the second reviewers at each stage of the review (title and abstract screening, full-text screening, data extraction). To ensure that both second reviewers did not review the same articles, a random sample of 20% was drawn, which was divided into two equal parts.

Other Access database queries generated lists of conflicts to be moderated by the third reviewer.

An input form for the quality assessment of the articles was developed directly in Access. For the remaining parts of the review key information on the references were exported

[1] `https://www.microsoft.com/Microsoft/Access`

to Microsoft Excel and manually distributed to the second and third reviewers.

2.3.6.2 Microsoft Excel

The Microsoft Access database was run as an offline database on the local network drive within the UCL network of FS. FS was the only person who could directly use it. To allow all other reviewers to effectively input data into the database, Microsoft Excel data input forms were developed. These were distributed alongside pdf files of the studies, which had to be reviewed. After the review these files were returned to FS, who uploaded them into the database.

These Excel files for title and abstract screening, full-text screening and data extraction were structured in the same way. Each file consisted of the input form and the data sheet. In the input form reviewers could input the extracted information or their eligibility decision. The data sheet was pre-filled with data on the articles to screen. Macros written in the programming language "visual basic for applications (VBA)" to show the reviewers necessary information on the input sheet. Another macro was programmed by me to copy their decisions into the data sheet. At any stage, while working with these Excel files, reviewers could save and close the Excel file. They could pick up their work upon opening the file at the automatically detected point where they last left.

After the reviewers finished their review, they returned the Excel file to FS. Subsequently, the data from the data sheet of the Excel file was imported into the Access database.

I tested the extraction and conversion to Excel to ensure that it works properly. My supervisors piloted the Excel files using the input sheet before it was used in the systematic review.

2.3.7 Data Items

I decided to not contact authors for potentially missing data in the studies. This was to avoid a biased quality score if some models had the opportunity to give further details, whereas others do not. As such, I decided to only use the publicly available data for each model.

For each article, I extracted its year of publication, title, list of authors, and where it was published. I collected information on the following items:

- Modelling approach,
  - Entity-level,
  - Open cohort versus closed cohort,

  - Interacting versus non-interacting population,

- Time handling,
- Data origin,
- Cohort size,
- Time horizon,
- Modelling software,
- List of included STIs,
  - Interaction,
  - List of sequelae of STIs,
- Interventions,
- Economic component,
- Year in which the study has been conducted,
- Input,
- Country,
- Output, and
- Customisability.

The complete data extraction form is listed in Appendix A.2.

During the data extraction, the quality of the examined article was also assessed. For this, I used the percentage scale published by Kopec et al. [89] for modelling studies. This scale uses 17 dimensions, which are grouped in the following five categories:

- conceptual model,
- parameters,
- computer implementation,
- evidence from examining model performance, and
- evidence from examining the consequences of model-based decisions.

Each of the 17 items has a different value which can either be scored as ‘none’ (=0 points), ‘partial’ (=1 point) or ‘complete’ (=2 points). Some dimensions were not applicable to some models. At the end, the sum of all gained points is divided by the sum of all points the model could have gained. This results in the percentage as an indicator of the quality of the model.

The quality assessment form was an input form in the Microsoft Access database which was used. I developed data extraction sheets, using Microsoft Excel, which were distributed to the reviewers. More information on this is given in section 2.3.6.

2.4 Results

2.4.1 Study Selection

Figure 2.2 shows the PRISMA chart of the systematic review. A total of 15,538 articles were found in the nine before mentioned databases. After duplicate elimination and removing references without abstract attached to it, 11,739 distinct articles were identified as eligible for title and abstract screening. 11,555 of those were excluded during the title and abstract screening. Each second reviewer screened 1,173 articles. There was a total of 44 conflicts between FS and the second reviewers (either FT or AH), therefore the disagreement rate was below 2%. RH received the 44 conflicting titles and abstract without knowing which reviewer decided in favour or against considering the article for the full-text screening. In 28 out of these 44 cases (= 63.6%) RH decided the way FS did. This results in a total misclassification rate of ($\frac{45-33}{2 \cdot 1173}$ =) 0.5% of FS. In the 15 cases where RH decided differently from FS, FS voted to include the article in nine cases, showing a tendency to be over-inclusive. Therefore, I decided to not screen further articles by a second reviewer.

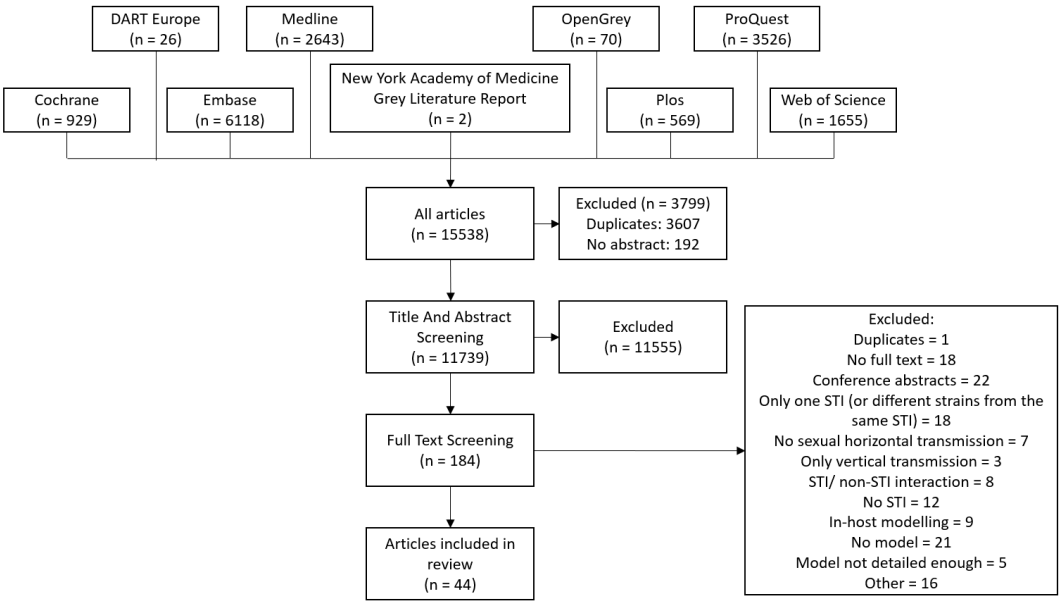


Figure 2.2: PRISMA chart of the systematic review.

In the remaining 184 articles, I found another duplicate which has not been picked up by the duplicate search before the title and abstract screening.

Both second reviewers reviewed 16 articles each. During the review, a total of three conflicts arose. These were sent in a pseudonymised manner to RH so that RH did not know which reviewer decided which way. In one conflict RH agreed with FS, in one case

FS was over-inclusive and in the last case FS was over-exclusive. Based on these numbers, I decided to not increase the proportion of articles to be screened by a second reviewer.

A total of 140 articles were rejected during the full-text screening, most of them as they were only conference abstracts (n=22), did not describe a model (n=21), or described only a single STI (n=18). This left 44 articles for data extraction.

The remaining 44 articles were eligible for inclusion in the systematic review. FS extracted data from all articles, whereas EB and AH extracted data from five articles each. Before aggregating the results from the data extraction FS cleaned the data set. Upon merging the data two minor conflicts showed up, one was a difference in the extracted cohort size the other one was a difference in the extracted time horizon of the model. Both conflicts were sent in a pseudonymised way to RH, who resolved them.

2.4.2 Results of Individual Studies

Table 2.1 summarises the results of the systematic review.

Table 2.1: Overview of the results of the systematic review, sorted by year of publication and surname of first author

Ref.	Year	Inc. Gr.	STIs	Modelling Approach	Entity-Level	Open Cohort	Time Handling	Cohort Size	Time Horizon (days)	Modelling Software	Intervention Favoured	Economic Comp.	Country/ Region
Kault et al. [90]	1991	unclear	HIV Gonorrhoea	mathematical modelling	Cohort	Closed	Continuous	unclear	unclear	unclear	none	No	unclear
Stigum et al. [91]	1997	High	gonorrhoea chlamydia HIV	mathematical model	Cohort	Closed	Continuous	3060	until equilibrium	unclear	none	No	Norway
Chesson et al. [92]	2000	High	HIV syphilis	mathematical modelling	Individual	Closed	Continuous	unclear	365	statistical software	none	Other	USA
Law et al. [93]	2000	High	chlamydia gonorrhoea syphilis HIV	spatial analysis and disease mapping	Cohort	Other	Unclear	4553	0	statistical software	none	No	USA
Kacker et al. [94]	2001	Low	HIV syphilis chlamydia chancroid Mycoplasma	Markov model	Individual	Open	Discrete (Fixed)	unclear	5 years/ 25 years	TreeAge	Yes	BIA	Uganda

Table 2.1: Overview of the results of the systematic review, sorted by year of publication and surname of first author

Ref.	Year	Inc. Gr.	STIs	Modelling Approach	Entity-Level	Open Cohort	Time Handling	Cohort Size	Time Horizon (days)	Modelling Software	Intervention Favoured	Economic Comp.	Country/ Region
Korenrom et al. [95]	2001	Low	HIV syphilis chancroid herpes gonorrhoea chlamydia	dynamic transmission model with stochastic events	Individual	Open	Continuous	unclear	8395	STDSIM	Yes	No	Uganda
Korenromp et al. [96]	2002	unclear	HIV syphilis chancroid gonorrhoea chlamydia	discrete event simulation	Individual	Unclear	Discrete (Flexible)	unclear	lifetime	STDSIM	Yes	No	unclear
Kuehne et al. [97]	2002	High	HepC HIV	Markov state transition	Cohort	Closed	Discrete (Fixed)	unclear	lifetime	TreeAge	Unclear	CUA	USA
Blower et al. [98]	2004	High	HIV herpes	mathematical model	Individual	Unclear	Continuous	unclear	18250	unclear	none	No	USA
Turner [99]	2004	High	gonorrhoea chlamydia	mathematical model	Cohort	Open	Continuous	unclear	unclear	unclear	Yes	No	UK
Campos et al. [100]	2006	High	HIV HepC	deterministic state-transition Markov model	Cohort	Closed	Discrete (Fixed)	unclear	lifetime	DATA 4.0; TreeAge	Yes	CoI	USA

Table 2.1: Overview of the results of the systematic review, sorted by year of publication and surname of first author

Ref.	Year	Inc. Gr.	STIs	Modelling Approach	Entity-Level	Open Cohort	Time Handling	Cohort Size	Time Horizon (days)	Modelling Software	Intervention Favoured	Economic Comp.	Country/ Region
Orroth et al. [101]	2006	Low	HIV chancroid syphilis herpes gonorrhoea chlamydia trichomonas	micro-simulation	Individual	Closed	Discrete (Flexible)	unclear	7300	STDSIM	none	No	Uganda
Sutton et al. [102]	2006	High	HepB HepC	mathematical Unclear	Cohort	Closed	Continuous	12826	1825	unclear	none	No	UK
Matser et al. [103]	2007	High	HIV HepC	Markov Model	Cohort	Open	Discrete (Fixed)	unclear	14600	R	none	No	Netherlands
Okango et al. [104]	2007	Lower middle	HIV Herpes	semi-parametric spatial joint modelling	Other	Closed	Other	1800	1	WinBUGS	none	No	Kenya
Abu-Raddad et al. [105]	2008	Lower middle	HIV herpes	deterministic compartmental model	Cohort	Closed	Continuous	unclear	10950	unclear	none	No	Kenya
Bayoumi et al. [106]	2008	High	HIV HepC	dynamic compartmental model	Cohort	Closed	Discrete (Fixed)	unclear	3650	unclear	Yes	CUA	Canada

Table 2.1: Overview of the results of the systematic review, sorted by year of publication and surname of first author

Ref.	Year	Inc. Gr.	STIs	Modelling Approach	Entity-Level	Open Cohort	Time Handling	Cohort Size	Time Horizon (days)	Modelling Software	Intervention Favoured	Economic Comp.	Country/ Region
Vickerman et al. [107]	2008	Upper middle	Herpes HIV	dynamic Markov health-state transition model	Individual	Closed	Discrete (Fixed)	300	lifetime	unclear	Yes	CBA	South Africa
White et al. [108]	2008	Low	chancroid HIV Herpes Syphilis Gonorrhoea chlamydia	individual-level stochastic model	Individual	Closed	Discrete (Flexible)	unclear	7300	STDSIM	Yes	No	Benin
Dorey [109]	2009	un-clear	hypothetical	mathematical model	Cohort	Open	Continuous	1000	18250	unclear	none	No	unclear
Xiridou et al. [110]	2009	High	HepB HepC	mathematical model	Cohort	Open	Continuous	26000	unclear	unclear	none	No	Netherlands
Mahiane et al. [111]	2010	Upper middle	HIV herpes	Mathematical Markovian models	Individual	Closed	Discrete (Fixed)	3750	1	unclear	none	No	South Africa

Table 2.1: Overview of the results of the systematic review, sorted by year of publication and surname of first author

Ref.	Year	Inc. Gr.	STIs	Modelling Approach	Entity-Level	Open Cohort	Time Handling	Cohort Size	Time Horizon (days)	Modelling Software	Intervention Favoured	Economic Comp.	Country/ Region
Vickerman et al. [112]	2010	Upper middle	gonorrhoea chlamydia syphilis HIV	dynamic deterministic compartmental mathematical	Cohort	Closed	Continuous	3000	2555	unclear	Yes	No	South Africa
Foss et al. [113]	2011	Lower middle	HIV herpes	Dynamic deterministic models	Cohort	Closed	Continuous	unclear	1825	unclear	Unclear	No	India
Johnson et al. [114]	2011	Upper middle	HIV herpes chancroid syphilis gonorrhoea chlamydia trichomonas	mathematical model	Cohort	Closed	Unclear	unclear	7300	unclear	none	No	South Africa
Kravchenko et al. [115]	2011	High	HPV HIV	Transitional probability-based Markov model	Cohort	Closed	Discrete (Fixed)	396	unclear	SAS	Unclear	No	USA

Table 2.1: Overview of the results of the systematic review, sorted by year of publication and surname of first author

Ref.	Year	Inc. Gr.	STIs	Modelling Approach	Entity-Level	Open Cohort	Time Handling	Cohort Size	Time Horizon (days)	Modelling Software	Intervention Favoured	Economic Comp.	Country/ Region
Mushayabasaa et al. [116]	2011	Low	HIV gonorrhoea	deterministic mathematical model	Cohort	Open	Continuous	5000	500	unclear	none	No	Sub-Saharan Africa
Quinlivan et al. [117]	2012	High	HIV trichomonas	mathematical modeling	Individual	Closed	Continuous	unclear	unclear	unclear	none	No	USA
Feng et al. [118]	2013	unclear	HIV Herpes	mathematical model	Individual	Open	Continuous	unclear	4000	unclear	none	No	unclear
Geskus et al. [119]	2013	High	HIV HPV	Two-state Markov models	Individual	Closed	Discrete (Fixed)	612	lifetime	unclear	none	No	Spain
Lungu et al. [120]	2013	Low	Herpes HIV	deterministic system of ordinary differential equations	Cohort	Closed	Continuous	800	lifetime	unclear	Yes	No	Sub-Saharan Africa
Newman et al. [121]	2013	un-clear	hypothetical	mathematical model	Individual	Closed	Continuous	unclear	unclear	unclear	none	No	unclear
Schackman et al. [122]	2013	High	HIV HepC	decision analytic model decision tree	Individual	Closed	Unclear	1954	unclear	TreeAge	No	CUA	USA

Table 2.1: Overview of the results of the systematic review, sorted by year of publication and surname of first author

Ref.	Year	Inc. Gr.	STIs	Modelling Approach	Entity-Level	Open Cohort	Time Handling	Cohort Size	Time Horizon (days)	Modelling Software	Intervention Favoured	Economic Comp.	Country/ Region
Vrienda et al. [123]	2013	High	chlamydia HIV	Transmission model combined with economic analysis	Cohort	Closed	Continuous	unclear	7300	Wolfram Mathematica 8	Yes	CCA	Netherlands
Carvalhoa et al. [124]	2014	High	HIV HepC	mathematical model	Cohort	Open	Continuous	500	600 years	XPPAUT	Yes	No	USA
Martin et al. [125]	2014	Upper middle	HepC HepB HIV	deterministic compartmental model	Individual	Closed	Continuous	unclear	lifetime	MATLAB	Yes	No	South Africa
Pinto et al. [126]	2014	High	HIV HepC	mathematical model	Cohort	Open	Continuous	500	1000	unclear	Yes	No	Portugal
Alveya et al. [127]	2015	High	HIV herpes	transmission dynamics mathematical model	Cohort	Open	Continuous	unclear	1600 years	unclear	none	No	USA
Deshmukh et al. [128]	2015	High	HIV HPV	Markov model	Cohort	Closed	Discrete (Fixed)	unclear	lifetime	TreeAge	Yes	CUA	USA
Ghebremichael et al. [129]	2015	Low	HIV herpes	joint response and marginal models	Cohort	Unclear	Continuous	794	unclear	unclear	none	No	Tanzania

Table 2.1: Overview of the results of the systematic review, sorted by year of publication and surname of first author

Ref.	Year	Inc. Gr.	STIs	Modelling Approach	Entity-Level	Open Cohort	Time Handling	Cohort Size	Time Horizon (days)	Modelling Software	Intervention Favoured	Economic Comp.	Country/ Region
Jewell et al. [130]	2015	Upper middle	HIV herpes	microsimulation model	Individual	Closed	Continuous	100000	7300	unclear	Yes	CUA	South Africa
Saab et al. [131]	2015	High	HIV HepC	Markov model	Cohort	Closed	Discrete (Fixed)	unclear	lifetime	unclear	Yes	CUA	USA
Sanchez-Gonzalez [132]	2016	Upper mid-dle	HIV HepC	mathematical model	Cohort	Closed	Continuous	unclear	lifetime	Mathematica 8.0	Yes	CoI	Mexico
Zahnd et al. [133]	2016	High	HIV hepC	individual-based model	Individual	Closed	Continuous	unclear	lifetime	R	none	CoI	Switzerland

2.4.3 Risk of Bias

Figure 2.3 shows the quality distribution of the percentage scale by Kopec of all included articles. Percentage values were rounded down to the closest percentage in the graphic, e.g. the bar at 30% contains all models which had quality values ranging from 30% up to 39.9%.

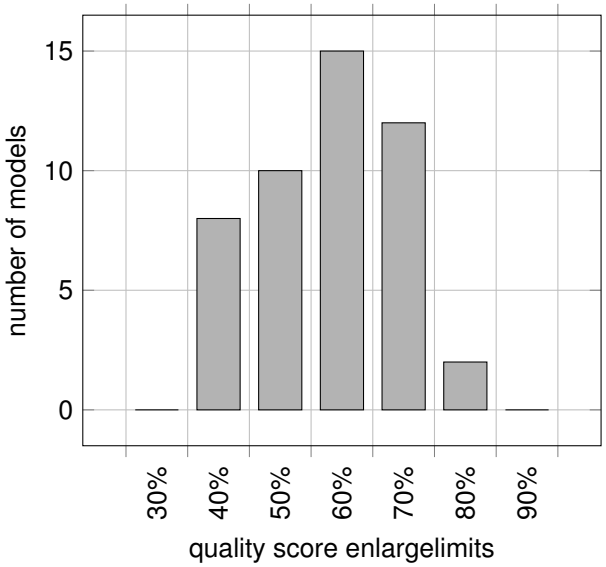


Figure 2.3: Distribution of the quality of all included models. Quality was assessed using the quality score of Kopec et al. [89]

2.4.4 Additional Analysis

2.4.4.1 STIs

Figure 2.4 shows how often STIs have been included in all models of the review. The included STIs could interact and influence each other in a majority (68.1%) of all models. All other models simulated multiple STIs in parallel, without the individual STIs influencing each other.

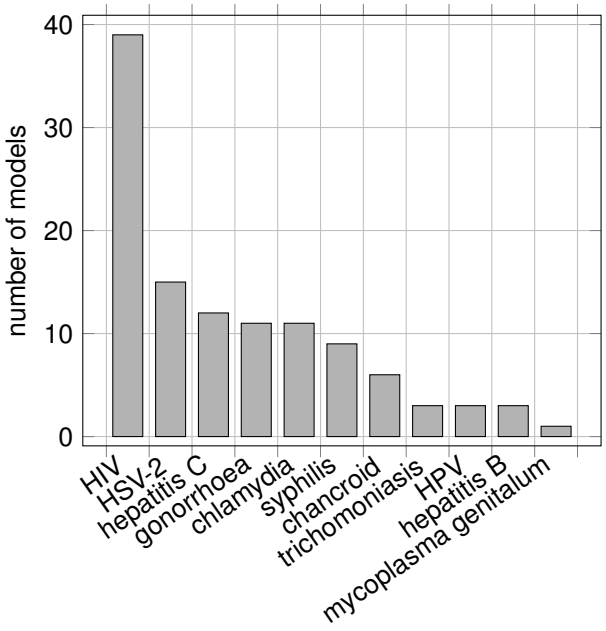


Figure 2.4: Number of times each STI was modelled in the papers included in the systematic review

Figure 2.5 shows all models which simulate up to three different STIs simultaneously. All models included HIV. HIV is also included in all models which simulated more than 4 STIs simultaneously, as shown in Figure 2.6.

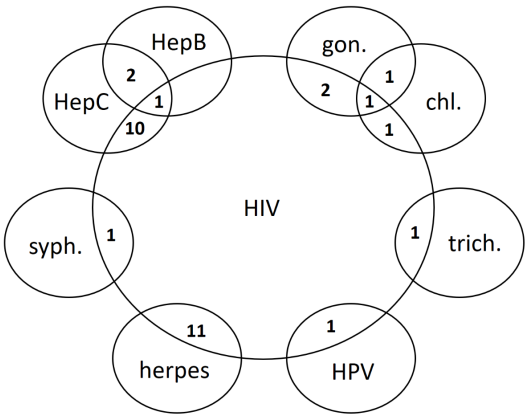


Figure 2.5: STIs which have been modelled together in models for up to 3 different STIs.

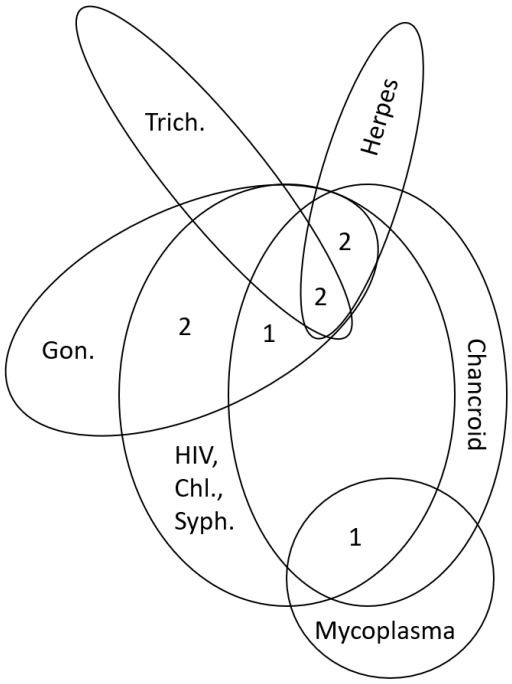


Figure 2.6: STIs which have been modelled together in models for over 4 different STIs.

Figure 2.7 shows the regions which were simulated by the models. I identified the United States of America and Sub-Saharan Africa as regions which were simulated the most by all models.

Figure 2.7: The regions for which the models have been developed.

50% of all models (n = 22) simulated sequelae. Figure 2.8 shows which sequelae have been included how many times.

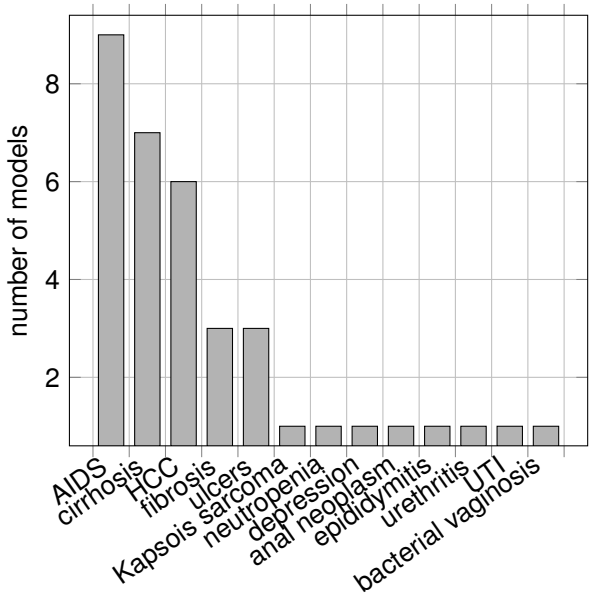


Figure 2.8: Sequelae which were modelled in models included in the review.

2.4.4.2 Metadata

The bar chart in figure 2.9 shows that the number of multi-STI models being developed per year is increasing. The reported year refers to the year of the development of the model which is not necessarily the year of the publication.

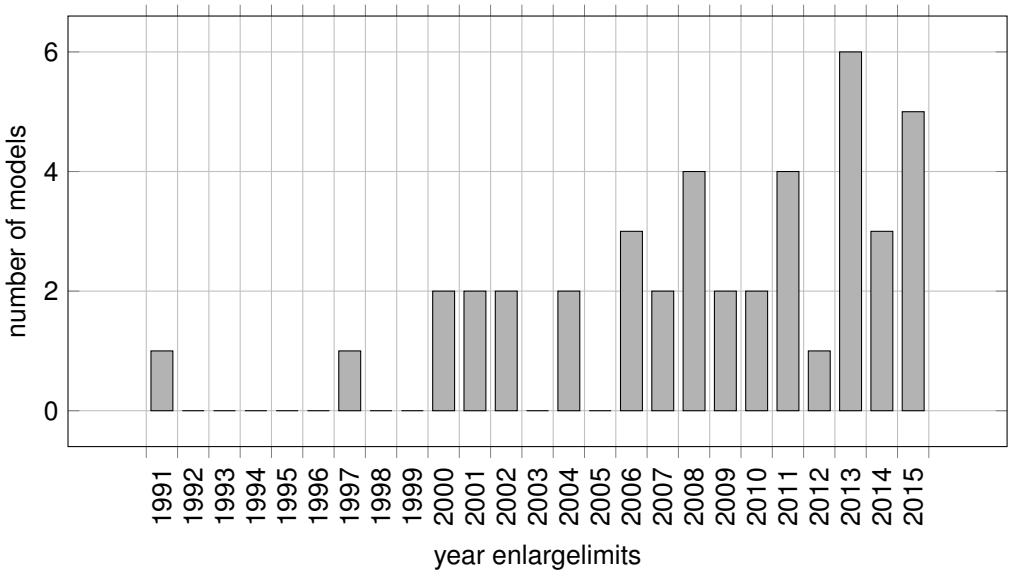


Figure 2.9: The year when the modelling study was conducted.

2.4.4.3 Technical Approach

Figure 2.10 shows which approaches have been used to simulate multiple STIs in one model, whereas Figure 2.11 shows the software which has been used to develop or run the models. In some cases, the authors only reported that they used statistical software but did not specify the name or version, these cases are summarised as "statistical software" in the graph. There were 24 studies which did not report the use of any software. These models were not included in the Figure 2.10.

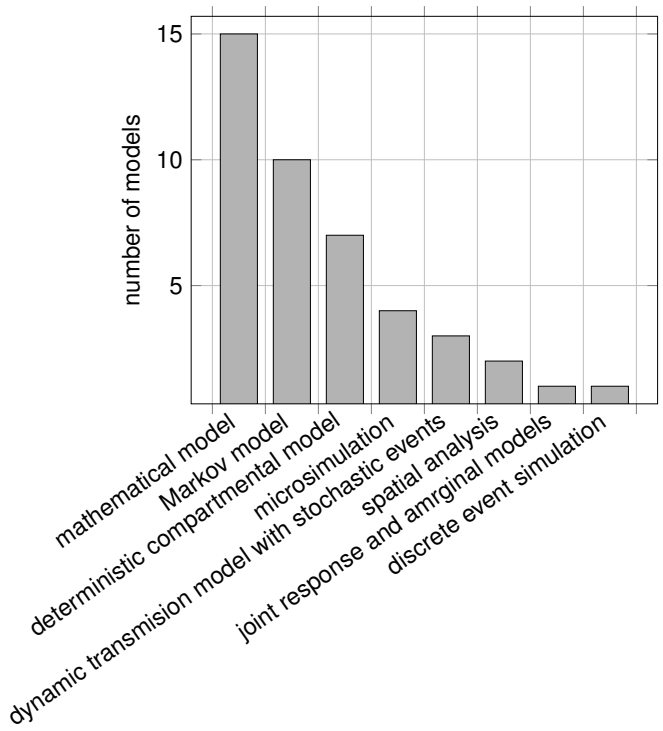


Figure 2.10: The modelling approaches which were used by models included in the systematic review

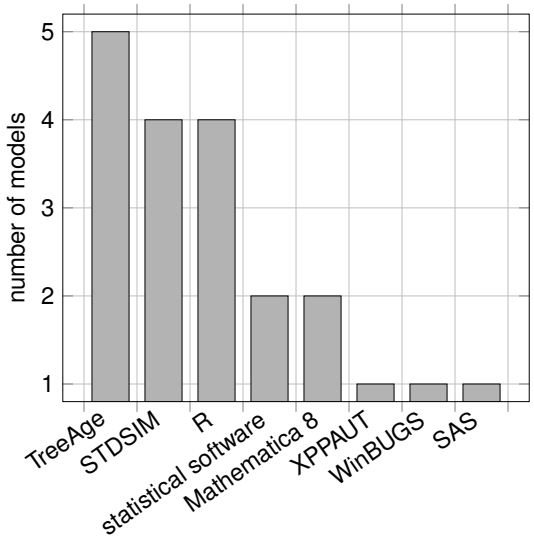


Figure 2.11: The software which has been used to simulate multiple STIs by models in the systematic review

2.4.4.4 Evaluation

Half of the models did not examine any intervention (n=22). Of those models which considered an intervention 82% (n=18) favoured the intervention. These models examined interventions such as behavioural change, or improved treatment and screening strategies.

Most models (70.5%) did not have an economic component. Of those (n=13) with an economic component, Figure 2.12 shows the types of economic evaluations which were calculated.

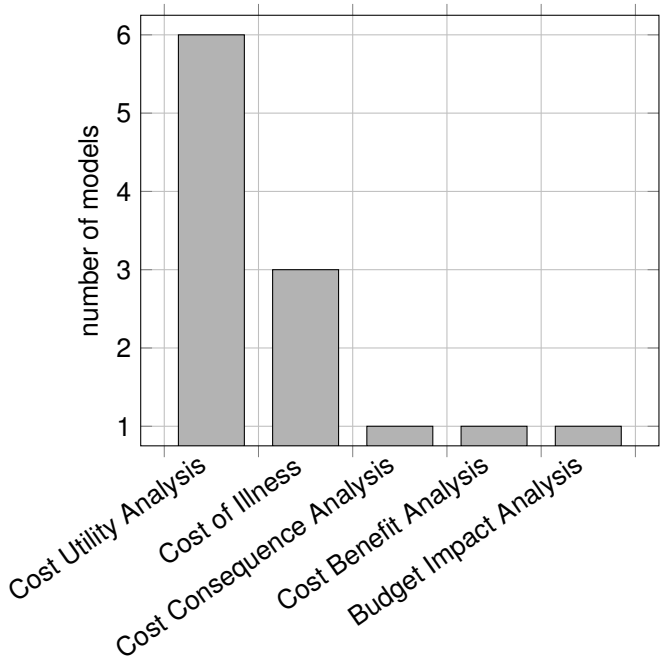


Figure 2.12: Type of Economic Evaluations used by the models included in the review

2.5 Discussion

2.5.1 Summary of Evidence

I identified 44 papers which were included in the review. The majority of those papers dealt with HIV. Most papers looked at two or three STIs simultaneously. Just under a third (29.5%) of all models included an economic component.

A majority of models did not include an economic component. Most models were developed for a non-English context, with a special focus on sub-Saharan Africa and the United States of America. All reviewed models were not suitable to be used as a multi-purpose disease modelling software to support decision makers in England.

The software STDSIM [134, 86] is similar to the software I develop in this thesis. STDSIM has a different focus as it includes STIs that are not relevant in an English context. Furthermore, STDSIM is used to simulate a different geographic setting (sub-Saharan Africa). STDSIM is also not capable of calculating health economic results. Therefore, STDSIM cannot be used as a decision support software for commissioners in a English sexual health context.

Therefore I concluded that it was necessary to develop a multi-STI modelling software. The insights into other models I gained during this review influenced the model development process.

2.5.2 Strength and Limitations

The review used nine different databases, each of which added at least one article to the review. This shows that the search strategy identified a variety of relevant articles. To obtain these articles, a high number of false positives had to be screened and rejected manually.

The review process was supported by an Access database, which supported the review process, especially while merging the decisions of each stage of the review and of the data extraction.

I decided to not contact authors to gather further information on the model. This might have improved the quality score of some models, compared to how they were scored without the full information. Most models used appendices to give further information to the reader. The quality score was applied in a way that criteria which were not applicable did not negatively impact the quality score of the model. It was therefore not compelling to ask authors for further information.

2.5.3 Further Observations

Nearly all models in this review included HIV. This might be since HIV suppresses the immune system and thereby indirectly interacts with all other STIs by facilitating further infections. Including HIV also makes sense from an economic perspective as its treatment is one of the most expensive treatments which is available for STIs. Other STIs are therefore modelled to examine their suitability as HIV indicators. The high number of models which includes HIV underlines its importance for multi-STI modelling in general and confirms my decision of including HIV in the software.

The most relevant STI model for this thesis which I identified in this research was STDSIM. This software focusses on the spread of four STIs in sub-Saharan Africa. It does not have any economic component and could therefore not be used for the purpose of informing decision makers in the NHS with health economic data.

We did not find any eligible article published in another language than English. This raises the question of whether the search was biased towards English articles and we subconsciously excluded e.g. Russian and Chinese articles. This potential bias had to be considered when reviewing the results. Some Chinese and Russian articles were picked up by the searches but excluded during the review process. Thus, I conclude that I did not systematically exclude these countries, but in fact, no eligible articles were published there. Based on the health care systems in both countries which are isolated from other systems, it might be the case that disease modelling is less important there than it is, e.g. in the USA.

The quality assessment has shown that the quality of a model does not necessarily depend on its publication year. I found that some papers lacked space, even considering appendices and supplementary material, to report on all relevant sections, which decreased the perceived quality of the model. In these cases, it is hard to distinguish between the actual quality of the model and the quality of the reporting of the model. Whereas I aimed to assess the first one, the quality of reporting certainly influenced it. Some models indicated that further work, e.g. sensitivity analyses, are planned but had not reported on them yet. Therefore, the quality of some papers might rise after they publish additional information.

Overall, there was lots of agreement between the reviewers. As not all articles have been reviewed by two reviewers it is worth having a closer look at the error which might have been made during the review process. Assuming constant error rates, the number of articles which were missed out were calculated and resulted in an estimated total of five

articles which have potentially been missed.

2.5.4 Influence of systematic review on subsequent work

The results of this systematic review influenced the model development process in multiple ways. This includes the selection of modelling approaches, the parametrisation of models and the validation of models. The influence of the systematic review on the work conducted in this thesis is detailed in the next paragraphs.

The most important outcome of the systematic review was to confirm, that no one else has conducted the work I planned to conduct. At the same time it was good to see that other researchers have already developed multi-STI models, whereas none of the models was applicable for the use case my model was planned for. This was due to the fact that other STIs were modelled, or the model was set in a different geographical region. Nevertheless, this meant that I had other models to compare my model to.

During the review I found that a majority of the models was only mentioned in one paper and not used multiple times. Regarding the time spent to develop these models these resources could be used more efficiently if models could be reused. To address this issue the plan to make the model reusable for different research questions was confirmed. To achieve this re-usability a key aspect from my viewpoint is the inclusion of future users in the modelling process to make the model relevant to them. Few models in the review reported on actually doing this.

During this review I found that certain modelling approaches seemed to be more suited to simulate multiple STIs on an individual level. In particular these were “Markov microsimulation models using Monte Carlo techniques“, “Mathematical compartmental models using differential equations“, and “discrete event simulations“. I used this information to develop a prototype for each modelling approach, to compare the approaches, and to decide which modelling approach to use in my multi-STI-model.

During the development of all sub-models included in the multi-STI model I used the models found in the systematic review to compare my results to and to find input for parameters. Firstly during the development oft he model structures, I validated those with existing structures of models found in the review. When I had to find parameters for said structures I looked at the evidence used by other models to start the parameter search, including backtracing of references, for my model.

Lastly I found that the way tests and treatments are modelled in the models included in the review was often done in a very simplified manner. The simulation of tests and

treatments is from my viewpoint, compared to other parts of the model, such as the natural progress of a disease, a bit which can be influenced easier. Therefore I assumed that there is potential interest in a model which simulates tests and treatments in sufficient detail.

Overall the systematic review accelerated the development of my work as I did not need to “reinvent the wheel“ and could find inspiration in the work of other researchers. At the same time it uncovered gaps in multi-STI models which I assumed existed, when I started working on this thesis. Through this review I could confirm that these gaps existed and address those in my model.

2.5.5 Conclusion

The systematic review showed that no suitable model for simulating multiple STIs simultaneously in an NHS context currently exists. Some of the models are similar to the STI model I develop in this thesis but have either been developed for a different geographical area, such as Sub-Saharan Africa, or do not have a sufficient health economic component to allow the health economic comparison of multiple intervention strategies.

The systematic review also showed that it is inevitable to choose an individual based modelling approach, when developing a multi-STI disease model. This important learning will be taken into the next chapter and discussed further.

Chapter 3

Modelling Approach

3.1 Aims and Objectives

The aim of this chapter is to describe how the modelling approach for the multi-STI modelling software works.

Before developing a model, it is crucial to find an appropriate modelling approach. This approach should be able to answer the research question in sufficient detail. In this case, it is necessary to acknowledge the peculiarities of simulating multiple diseases in parallel when selecting the modelling approach [15, 135].

3.1.1 Overview

Simulating multiple STIs simultaneously in challenging on several levels, which can best be addressed by choosing an individual-based approach. Three key points to consider when modelling STIs are:

- The natural progress of the disease.
- The spreading of the disease within the population
- The influence of health care on the natural progress of the disease.

The *natural progress of the disease* describes, for example, the progress from *incubation period* to *asymptomatic infection*. In Chapter 5 I will explain how I developed models for the natural progress of all STIs included in the software. As the disease models only simulate the progress of the disease within one individual another part of the overall model needs to simulate infection processes. Therefore the sexual contacts, which could possibly lead to an infection, must be modelled. I simulate sexual contacts using a sexual network model described in Chapter 7. Lastly, the infections can be influenced by interventions, e.g.

treatments. In Chapter 6 I explain how these treatment pathways are incorporated into the software.

Three modelling approaches were identified in the systematic review, see Chapter 2, to be capable of simulating infectious diseases on an individual level. These are *Markov based microsimulation using Monte Carlo simulation techniques*, *mathematical compartmental models with a stochastic component*, and *agent-based discrete event simulations*. A brief introduction of these modelling approaches is given in Section 3.2.1.

To decide which approach I should use in my model, I decided to develop a prototype for each modelling approach, which is explained in Section 3.3.

In Section 3.3 I describe why I decided to use discrete event simulation (DES) as a modelling approach during this PhD project. Section 3.4 covers technical questions on how to develop a DES. Section 3.5 describes how a single simulation is calculated and which steps are necessary to complete it. Section 3.6 extracts key performance indicators, such as computational speed, of the modelling approach. This is also the first step towards the validation of the overall multi-STI modelling software.

The work presented in this chapter was done by me, with my supervisors having a consulting role.

3.2 Background

3.2.1 Disease Modelling Approaches

This section introduces the relevant disease modelling approaches for the development of this multi-STI modelling software and lists software which is typically used to simulate diseases.

3.2.1.1 Mathematical Compartmental Models

In this model type, the health states are called compartments. The number of people in each compartment is described by a state variable. The derivative of the state variables describes how many individuals enter or leave a compartment over time. If it is a closed cohort model, individuals leaving one state will appear in another. This means that the differential equations describing the number of individuals having a certain value of the state variable are linked to each other [84].

For example, the models by Mushayabasaa et al. [116] and Foss et al. [113] which I identified during the systematic review (see chapter 2) used this approach to model the interaction of HIV with another STI. This modelling approach accounts for the infective

pressure, which is the probability of uninfected individuals getting infected, of a pathogen towards the whole modelled cohort, the equations can also include the proportion of individuals being infected to calculate the number of new infections.

The number of factors considered in an equation is not limited, whereas the complexity of the model increases with the number of included factors.

The equations describe the proportions of the population being in a compartment and therefore do not allow individualised statements. A standard implementation of this modelling approach is not able to follow single individuals over time.

The implementation of this modelling approach is deterministic, which means that the same model structure with the same input always yields the same results [83].

In other implementations of the modelling approach, it is possible that it can be individual-based, allowing to follow specific individuals over the course of the simulation. Like every individual-based approach, such a solution is probabilistic [85].

3.2.1.2 Markov Simulation

Another approach of implementing a multi-STI disease model was chosen by Matser et al. [103] and Deshmukh et al. [128] who used a Markov simulation in their models. This approach is similar to the aforementioned mathematical compartmental models. In their standard implementation both approaches simulate the cohort as a whole with parts of the cohort transiting between health states. This method of implementing a Markov model is also deterministic.

The main difference between mathematical compartmental models and Markov models is the way they handle time and transitions. In mathematical models, time is a continuous input parameter. In Markov models time proceeds in steps of fixed length, so-called Markov cycles. At the end of each cycle, a proportion of the modelled cohort can transition to another health state [83].

The size of this proportion depends on the state transition formulas. These formulas can only depend on the attributes of a cohort and on the current health state, but not on previous health states. This restriction is called Markov property.

Equations in mathematical compartmental models describe how many people transit from one compartment to another in the model at any given point during the modelled time. In Markov models, the formulas describe the proportion of the cohort which will make a transition to another health state at the end of the current cycle [83].

If a Markov model is run as a microsimulation it becomes individual-based and is no

longer a deterministic approach. Similar equations can be used, but they now no longer describe "the proportion of the cohort making this transition" but "the probability that a single individual transits". To determine whether a specific individual will make a transition a random number is drawn. If this number is smaller than the probability calculated by the aforementioned formula this individual will transit to the next health state, otherwise not [83].

Running a Markov microsimulation (MMS) needs more computational power than running a plain Markov model. Firstly, random numbers have to be drawn for each individual in each cycle and afterwards compared to the individual's transition probability. This is more complex than calculating the proportion which makes the transition. Secondly, modellers tend to simulate the outcome multiple times to average out random effects of a single model run.

3.2.1.3 Discrete Event Simulation

Discrete Event Simulation (DES) uses a different approach than the aforementioned two approaches. In its standard implementation, DES is a stochastic, individual-based approach [85]. This approach was chosen by Korenromp et al. [96], as highlighted in the systematic review.

Events describe everything which happens during a model run, e.g. state changes. These events are stored in an event queue. The events in this queue are sorted chronologically and processed in this order. Events which have not yet been executed can be modified, postponed, or deleted.

Events which affect other events in the queue are called "competing events", as they compete on which one to execute first, thereby not allowing or altering the effects of the execution of the other event. A death-event competes with all other events. After the execution of this death-event, all other events of this person must be deleted from the queue and will therefore not be executed.

Events can either affect one individual in the model, e.g. a change in health state, or they can involve more than one individual, e.g. a sexual contact.

Two time points are important in the life cycle of an event: the creation time of the event and the execution time. At the creation time, the event is generated. By using a time-to-event-formula it is calculated how many modelled time units, e.g. days, must pass until the event will be executed. The execution of an event might lead to the creation of further events. For example, a "sexual contact"-event might lead to the creation of an infection-

event.

As this modelling approach only requires calculations when something happens, the model "jumps" on the time axis from one event to the next.

3.2.1.4 Modelling Software Package

There are modelling software packages and languages available which can be used to develop disease models, including R, TreeAge, WinBUGS, Excel etc. The advantages and disadvantages of these are briefly summarised in the next paragraphs.

Excel[1] is a licensed spreadsheet editing software. It is widely used, and a majority of all researchers have already used it, as its technical barrier of using it is considerably low. Although Excel itself is not a free software it is most often included in the standard office software at universities. Other third-party software, like open office is also able to read and write Excel-files, but this may result in compatibility issues.

R[2] is a free to use programming language. It is commonly used in research and hence has an active community. R can include a user interface and has good plotting options.

MATLAB[3] is, as R, a programming language and hence has the same benefit towards efficiency and transparency of its calculations. Unlike R the commercial use of MATLAB is not free.

TreeAge[4] is a licensed modelling software. It is a visual development tool which is not open source. This means that the transparency of its calculations is not always given. Nevertheless, TreeAge is still required by some health technology assessment agencies for evaluations.

WinBugs[5] is, like TreeAge, a licensed software which is not open source, and hence suffers from a lack of transparency. The community around WinBUGs for disease modelling is also smaller than the communities of the other options.

Java[6] is a powerful programming language with various included and externally developed code libraries. It is one of the most used programming languages for applications worldwide. Even though I could not find other modellers using it prior to my thesis, Java can be used for disease modelling, as I have shown in my Master's thesis [136]. Software development companies use Java to develop software which is more complex than the multi-STI

[1] https://www.microsoft.com/en-us/p/excel/cfq7ttc0k7dx
[2] https://www.r-project.org/
[3] https://www.mathworks.com/products/matlab.html
[4] https://www.treeage.com/
[5] https://www.mrc-bsu.cam.ac.uk/software/bugs/the-bugs-project-winbugs/
[6] https://java.com/en/download/faq/whatis_java.xml

modelling software described in this thesis. Additional external libraries to enhance the default capacity of Java are available. Multi-threading to parallelise tasks can be incorporated easily. In my software, this was used to parallelly execute two or more simulation runs at the same time, ideally using different cores on the computer's central processing unit (CPU). This helps to speed up simulations and cut the runtime of the software. Java also enables the straightforward development and integration of graphical user interfaces for software.

3.3 Selection of Modelling Approach

To justify the preferred modelling approach, this section summarises the development of prototypes to decide on the approach which I will use for the development of my software. A full description of the prototypes and more results are presented in Appendix B.

Mathematical compartmental models with a stochastic component are similar to Markov based Monte Carlo simulations. Whereas these two approaches differ when they are used to simulate diseases on a cohort level, their individual-based realisations are similar. The same formulas could be used to run both approaches. As a result, I decided to not further look at mathematical compartmental models, but only at MMS and DES.

3.3.1 Methods

To decide whether to use MMS or DES, I developed a prototype for each modelling approach. These prototypes simulated a simplified scenario of a single STI connected with a corresponding sequela. The model structure is shown in Figure 3.1.

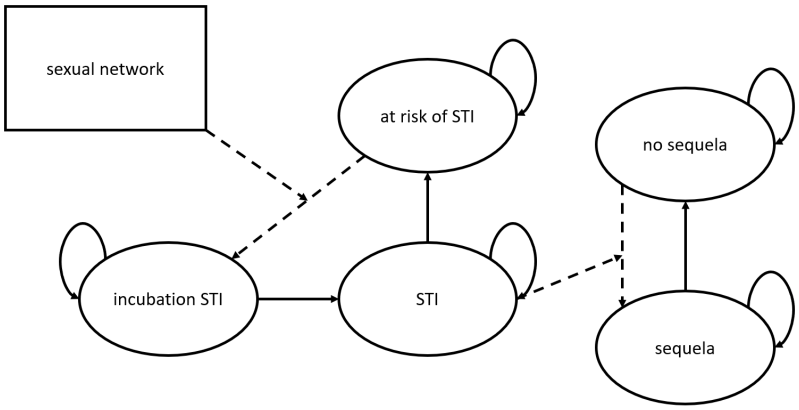


Figure 3.1: Model structure of a fictional STI to simulate with the prototype.

Each individual can be in one of the three health states describing the hypothetical STI. These are *no STI*, *incubation period of STI* and *STI*. Infections are simulated through a sexual network. If an infection happens, a health state change of the individual from *no STI* to *incubation period of STI* will occur. Individuals stay in this health state for up to two days. After that, they will transit to the *STI* health state in which they will stay for at least five days, but not longer than 30 days.

Each individual is represented by one entity in the STI model and another one in the sequela model. Looking at both entities gives the holistic view on the health state of the individual. Any combination of health states of both models is possible.

As long as one entity of an individual is in the health state *STI* their corresponding entity in the sequela model can transit from *no sequela* to *sequela*. They will stay in this health state for a maximum of 28 days.

The sexual network used was kept simple. It does not differentiate sexes or partnership building preferences. In this sexual network, two individuals are picked at random to initiate contact. This happens at a rate of one contact per 20 individuals at any given modelled day. This value was chosen after piloting simulations to find a level of promiscuity which matches reported numbers.

The same sexual network was connected to different prototypes the disease models. One prototype used a DES approach to describe the aforementioned setting the other one used an MMS approach.

3.3.2 Results

The comparison of both prototypes has shown that in the examined scenario a DES approach is advantageous, which is why I decided to use DES for my disease model.

The parametrisation of the DES-prototype was more intuitive, as time-to-event durations could be used within the prototype without further adaptions. For the MMS-prototype the average time per health state had to be recalculated into daily transition probabilities. This parametrisation difference can be seen for example in the input for the duration of the hypothetical sequelae which ought to last 14 days on average. In the DES model this transition is simulated by the following time-to-event formula: `14 days +/- random component;`. The same transition is modelled in the MMS prototype by a daily transition probability of 4.83%. Arguably the parametrisation is also easier to understand for a third party, who was not involved in model development.

The modelling results of both prototypes were not significantly different. DES calculated its results between 67% and 74% faster than MMS, depending on the input parameters, see table B.4 in Appendix B.2.1.

A more detailed view on the results of the prototype comparison is given in Appendix B.2.1.

3.4 Model Structure

Having taken the decision to use DES, I needed to structure the overall modelling approach. Additional information on this and supplementary technical documentation is available in the appendices C and D.

3.4.1 Why is it beneficial to simulate several STIs in separate models?

A general disease model, which covers all possible health states of an individual in one model would be complex, if not impossible to construct. For example, a general STI model covering the most important STIs in England would consist of hundreds of health states which are the sum of all combinations of the different manifestations of the health states of chlamydia, gonorrhoea, HIV, and syphilis. Conservatively assuming that these models consist of five health states each, this would lead to a total of (5^4 =) 625 health states. Additional health states for sequelae would still need to be included, leading to more than 1000 health states.

If we hypothetically consider a general STI model, we can also see further problems with this approach. Especially in sexual health, there are some diseases or sequela which only affect one sex. For example, PID will not affect men whereas epididymitis will not affect women. It would be possible to set up one general STI model for men and one for women. This would lead to two complex structures which have to be simultaneous. To allow infections as a result of heterosexual intercourse, these two models would also need to interact. This would further increase the complexity of the resulting model.

These problems can be avoided by splitting the overall model into several sub-models, one for each disease. The overall health state of an individual is in this approach defined by the aggregate of all health states that the individual is in in each sub-model. Individuals are only simulated in sub-models they are eligible for, e.g. women will be in the PID model, but not in the epididymitis model.

When modelling multiple diseases in several interacting sub-models the health states of all models must still be unique to avoid uncertainties and confusion. In most of the cases, this is not a problem. For example, a chlamydia model will include health states like *chlamydia* and *no chlamydia*. Whereas a gonorrhoea model might consist of states like *no gonorrhoea* and *gonorrhoea*. The states "*No X*" does not imply that the individual is healthy, it just recognizes the absence of a specific condition. An individual can be healthy in one dimension, whereas it can be ill in other dimensions at the same time. Therefore all

four aforementioned states are pairwise distinct.

Generally, if we want to avoid the need for extensive adaptions in the disease models no sequelae should be included in the disease models. It is advantageous to describe STIs, like chlamydia or gonorrhoea, in individual disease models and all possible sequelae in separate models.

3.4.2 How to include sequelae in the overall model?

As soon as sequelae, such as PID are included the situation becomes more complex. A possible approach would be to add a health state *PID from chlamydia* to the chlamydia model and *PID from gonorrhoea* to the gonorrhoea model. But these two states are similar, e.g. they require the same treatment. To avoid double-counting and confusion it is best to extract PID into a third model.

The PID-model can refer to chlamydia or gonorrhoea health states, e.g. the number of episodes of these infections, and other attributes the user selects. In doing so these three models can be linked to each other. This allows accounting for an elevated risk of developing PID after multiple episodes of different infections or the increased risk due to co-infection [137, 138]. The general idea of the connected disease models is presented in Figure 3.2.

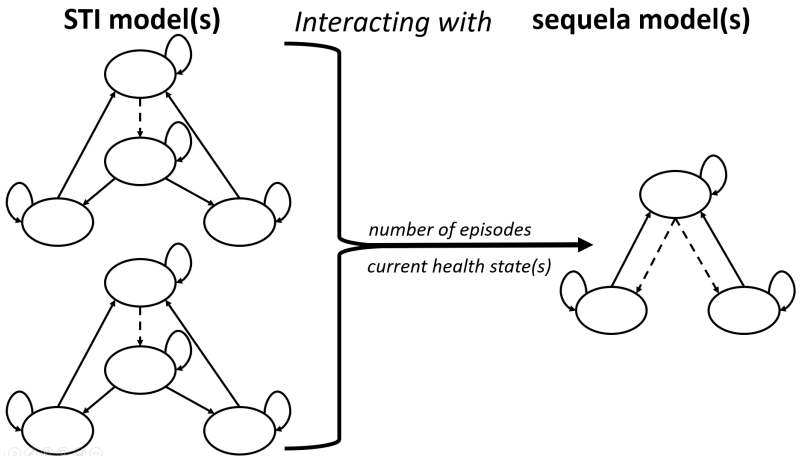


Figure 3.2: Different STI models can affect the same sequelae model. In doing so sub-models are linked with each other.

The STI models do not store information on which sequelae are connected to them. The sequelae models gather their information from all main disease models to calculate their time-to-event formulas. This way all dependencies connected with one sequela are all in the same place which makes it easier to change parameters and to amend or remove a

sequela model.

The modelling approach to simulate all diseases separately is a flexible and modular way to design the interaction of different STI models. By splitting one large model into several smaller models, new models can be added more easily. Existing transitions can be removed without the need to re-evaluate every transition in the model, as every model is responsible for its transitions and does not influence other models directly.

3.4.3 How to Handle Large Numbers of Events During a Simulation?

All events are stored in the same event queue, as all three parts of the model communicate with each other. With a high number of individuals in the model and several STIs to examine at the same time, there are many events in this queue. The execution of some events yields the need to delete or update other events in the queue. The bigger this main event queue is, the more time it takes to edit or delete from the queue. If the health state of one individual changes, and therefore an event of this individual needs to be deleted from the queue, the whole queue has to be searched for the event to be deleted. We also know that at the same time most events in the main event queue do not affect this particular individual, as they are other individuals' events.

There are multiple ways to overcome this problem and speed up the modelling process. One way would be to index the events not only by the time but also by the individuals. Events are executed in chronological order. After the execution, the individual index could be used to find other events of this individual. This data structure could help in editing the events of one individual without needing to examine at all events of all individuals.

Another option is to have a separate queue for each individual, in which only events of this specific individual are stored. This approach has the disadvantage that after each event the simulated time could proceed by one step. Therefore we would need to synchronize the proceeding of simulated time between all individual queues.

I chose a hybrid approach which is presented in Section 3.4.5.2, which combined the advantages of both aforementioned approaches while countering their disadvantages. In this hybrid approach a main queue stores pointers to individual queues. The pointers in the main queue are never updated, so that time-consuming searching and subsequently updating in the main queue is not necessary. Whenever a pointer to an individual queue from the main queue is processed, the algorithm checks the corresponding individual queue for events to be processed, i.e. is the current simulated time greater or equal to the processing time of this event. After processing an event in an individual queue all events in the indi-

vidual queue are checked and updated. If changes occurred in the individuals queue new pointers are added to the main queue. This hybrid approach has the advantage is one central queue to handle the proceeding of time and all time-consuming calculations are done in the smaller individual queues.

3.4.4 Selection of Modelling Software

I agree the findings of Holman et al. [139] that programming languages, like R, MATLAB and Java are better suited for a project of this complexity. The transparency and efficiency of these programming languages in combination with their ability to include user interfaces were clear advantages over the other software packages. I finally decided to use Java.

The ability of Java to allow a straightforward implementation user interfaces was an argument for its use. The software can be used by non-modelling experts therefore the modelling software should be easy-to-use and have a low technical barrier towards using it. To facilitate the access of future users to the software, graphical user interfaces can help, if implemented correctly and set up carefully.

Due to my background (see Section "Career path" at the beginning of this thesis) I had previously learned how to write code in Java. Therefore I was familiar with the language and could start with the development of the disease modelling software, without the need to learn a new programming language.

In my systematic review, I found that no other model which was included in the review was developed using Java. The degrees of freedom while using Java in combination with my experience using this programming language made me decide to develop the software in Java. A technical deep dive is given in Appendix C.

3.4.5 Results

3.4.5.1 Threefold Model Structure

As outlined above, simulating STIs can be divided into three smaller problems. Each of those is simulated in a separate model, but all models can cooperate and communicate with each other as they use the same event queue. This threefold structure is displayed in Figure 3.3.

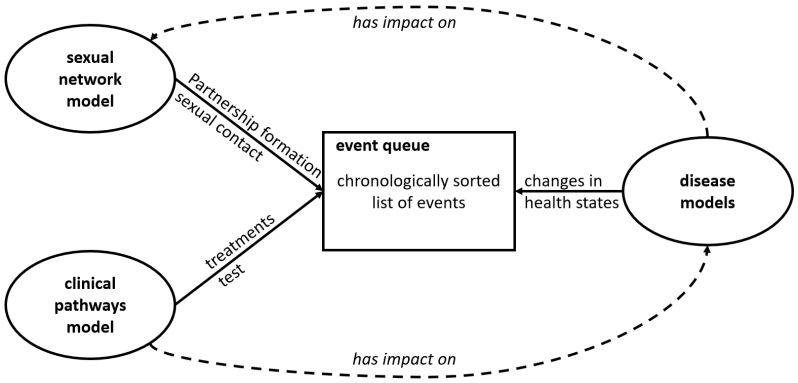


Figure 3.3: Schematic of the structure of the interaction of the three parts of the model. Each part of the model can contains of several sub-models. All sub-models communicate with each other using the same event queue.

The disease model describes the natural progress of the disease in question within one individual. It depends on the output of the sexual network model as the sexual contact simulated by the sexual network might lead to an infection process thereby triggering a state change. The disease model keeps track of the health states of each individual for each distinct STI and sequela. The disease model puts events, which trigger health state changes, in the event queue.

The sexual network model describes the transmission dynamics within the modelled cohort. It is responsible for the formation and dissolution of sexual relationships and thus simulating sexual contacts. The sexual network puts events like *sexual contact* in the event queue.

The clinical pathway model initiates events describing *treatment*, *testing* and other interventions. To fulfil this task the clinical pathway model relies on the information stored and simulated by the disease model. It might influence the health state of individuals, as successful treatment can lead to a cure from disease.

3.4.5.2 Different Event Queues for Different Tasks in the Software

This queueing solution implemented in the software consists of one main queue and one queue for each individual.

The main queue does not store events, it only contains references to the queues for each individual. These references are also called pointers. After the creation of a new event, a new pointer is added to the main queue. This pointer tells the software to look into the queue of a specific individual as an event might occur there in this cycle. The pointers in the main queue are never updated. This saves processing time as it is

not necessary to search the whole queue to update pointer events. If a pointer indicates to look at an individual queue, the event time of the first event in the individual queue is compared to the current simulated time to see whether this particular event from the individual queue has to be executed or whether it was a "false alert". "False alerts" can occur as the individual queues are updated whereas the main queue is not. The main queue can contain deprecated information, such as pointers which are not needed any longer, as the event they referred to has been updated or deleted. Whenever events in the individual queues are updated a new pointer is added to the main queue without altering or removing the old pointer.

The individual queues are responsible for handling the events of all individuals separately. These queues are notified by the pointers in the main queue. The role of the main queue in this approach is only to direct the attention of the software to individual queues where something could potentially happen. This individual queue is kept up to date at all times, but as the queue is shorter it does not take as much time to go through and update or delete relevant events.

3.4.5.3 Example on the Interaction of Multiple Queues in the Software

An example to demonstrate the mechanism of interaction between both queues is provided in Figure 3.4.

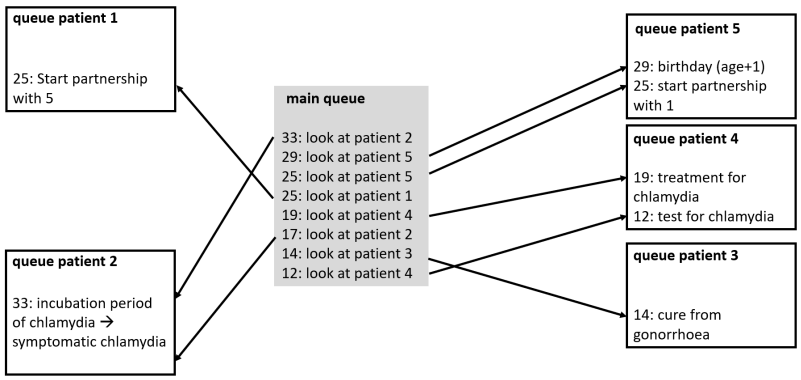


Figure 3.4: An example of the interaction of the main event queue and the individual queues.The main event queue stores pointers to all events in all individual queues. The individual queues store the events which affect a specific individual.

Looking at the main queue in the example we can see that it only contains pointers to the individual queues. The arrows show the individual queues the pointers point at. It also contains "false notifications", like at day 17 the pointer to `individual 2`. This means that an event which was previously referenced by the pointer has been deleted from the

individual queue of `individual 2`. Therefore, the reference is void and does not lead to the execution of an individual event. The events which are stored in the individual queues contain events from all parts (disease models, clinical pathway models, sexual network models) of the model. The sexual network model calculated the beginning of a sexual relationship between `individual 1` and `individual 5` on day 25, which is why we can find this event in both queues. The sexual network model is also responsible for the ageing of `individual 5` on day 29. The clinical pathway model is responsible for the screening of `individual 4` and the beginning of his treatment, as well as the successful treatment of `individual 3` for gonorrhoea. The progress from *incubation period of chlamydia* to *symptomatic chlamydia* in `individual 2` is triggered by the disease model.

As explained above, for every event in the overall model, a pointer in the main queue and an event in the queue of the individual is generated. For events from the sexual network, the situation is more complex as these events affect two individuals at the same time, e.g. to have sexual contacts or to start a partnership. To solve this problem, one individual initiates the partnership. All events regarding this partnership are stored in the queue of the individual. If the partner of this individual dies, the individual event queue must be updated, e.g. all events processing the partnership with the deceased individual have to be deleted.

3.4.5.4 Formulas

To keep the software as flexible as possible no part of the model is described directly in the software code. This allows re-parametrisation of the model without the need to compile the software code again. Thereby the user can edit parameters of the models and amend the structure of the model to update it, e.g. when medical knowledge changes over time. An essential part of the structure of a DES are time-to-event formulas. They describe when events in the model will happen. Next, I will explain how I kept these formulas flexible and editable.

Why are the Formulas to Calculate the Time-to-Event in JavaScript and Not in Java as the Rest of the Software? The easiest approach to include formulas into the model would be to write those formulas directly into the program code. In doing so these formulas would be a fixed part of the software code. As the code is written in Java a change in any formula would also lead to the need of compiling the code again. Compiling is the process of translating “human-readable” code into a code, which can be understood by computers. If anything in the "human-readable" code changes, it must be translated again so that new parts of the code can be understood by a computer as well. If the time-to-event formulas

were included directly in the code it would hamper future users ability to amend the time-to-event formulas in the model as compiling requires programming knowledge and further third-party software, e.g. a software development environment, to compile the code.

A different kind of programming language, called interpreted language, are programming languages which interpret the code during the runtime of the program. At the start-up of the program, the user does not know whether the code will run without major technical issues as no compiler has checked it before. Therefore, the program might crash, e.g. due to a misspelt attribute name. Nevertheless, it is beneficial to use an interpreted language to describe time-to-event formulas, as the formulas can be changed at any time and do not need to be compiled before usage.

It was beneficial to write the main parts of the model in Java, as I explain in section 3.4.4. To enable the user to write their own formulas during the runtime of the model there were two main options. One was to develop another programming language to describe formulas and a module within the software which could understand this language. Another option was to use an already existing language and interpreter which is already included in Java. The self-developed language to describe time-to-event formulas would likely have limited syntactical possibilities compared to already existing languages. On the other hand, the processing of this language could be optimised towards the offered operations. This could potentially result in a slightly faster runtime. All things considered, it seemed practical to use an existing language.

As I already decided on Java, see section 3.2.1.4 for more on this, as a programming language for the software it was necessary that Java offers a built-in interpreter for this language. As seen before, the language had to be an interpreted language. This left me with the following options:

- Python,
- JavaScript,
- BASIC, and
- Forth.

Upon comparison, none of these options was superior. So I decided to use JavaScript, due to its syntactical similarity to Java.

How are Time-to-Event Formulas Read and Interpreted During the Runtime of the Software? During the runtime of the model JavaScript code chunks are read from the files, which describe the time-to-event formulas. These formulas are then interpreted by the Java code. These formulas can depend on attributes (e.g. age, sex) of the simulated individuals and are therefore woven into the model.

To use the attributes of an individual within these formulas the name of the attribute must be spelt exactly in the way the attribute was defined in either the *booleanAttributes.txt* or *doubleAttributes.txt* (see Appendix D.1.1 and Appendix D.1.2 for a detailed explanation).

Before a code chunk is interpreted by the Java interpreter, all occurrences of attributes in this code chunk are replaced by the current value of the attribute. As attributes and health states might change over time the same formula might calculate different results for the same individual at different time points. Additionally, formulas can have a random component.

All occurrences of the word `random` will be replaced by separately drawn random numbers between 0.0 (inclusive) and 1.0 (exclusive). If a formula contains more than one time the word `random`, different values will be drawn for each occurrence. If the same formula is executed twice, different random values will be drawn for each `random`-place holder in the formula so that upon the second calculation a different result might be calculated.

To replace the attributes by their values the names of the attributes are searched for within the formula and all occurrences of this attribute name are replaced within the formula.

A detailed example of the processing of a JavaScript formula within the software is given in the appendix in Section C.2.

3.5 Modelling Process

Previously in this chapter, I explained how the software works and which parts of the software are responsible for different parts of the disease modelling. I will now explain steps included in a simulation run. The flowchart in Figure 3.5 shows those.

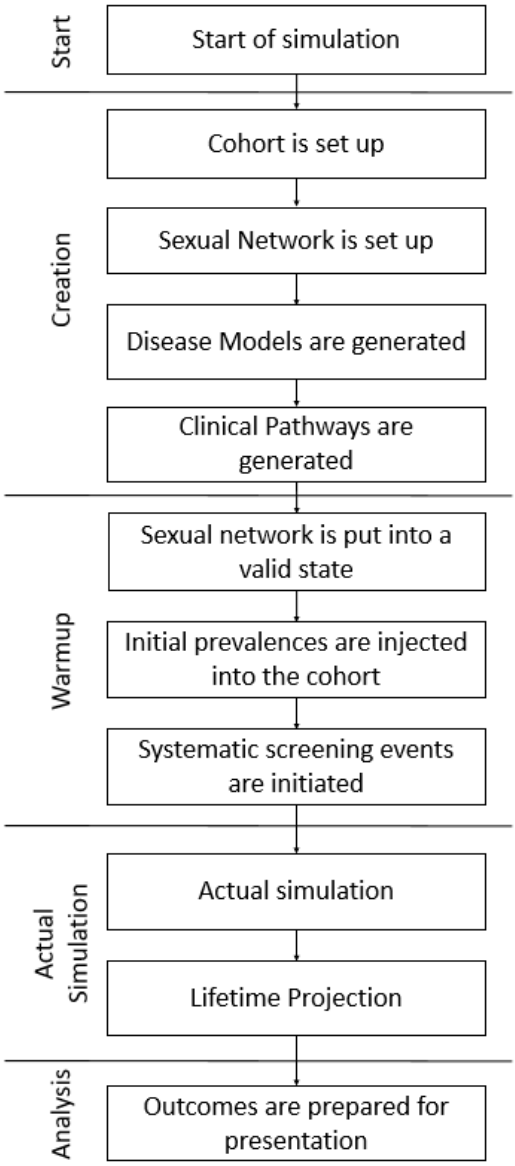


Figure 3.5: Flow through the different stages of a simulation run, from startup until analysis.

3.5.1 Start

A simulation can be started in two ways, either manually or as part of a sensitivity analysis.

A manual start, which is what most users will do, will examine a specific research question. To assist a user with inputting data, I developed a user interface, see Chapter

4. Most often this will start multiple simulations to compare different intervention options. For each treatment option a set of parallel simulations will be started to calculate mean outcomes and confidence intervals around them.

For a sensitivity analysis, multiple simulations are started in parallel to examine the impact of selected input parameters. This is done by looking at the impact on the output of changes on these parameters.

The following paragraphs describe the process of one isolated simulation. In a normal model run this happens in parallel for over 100 simulations.

3.5.2 Creation

After the start of the simulation all required individuals are generated. There are two main ways of doing so.

One is to generate a random cohort based on the `booleanAttributes.txt` and `doubleAttributes.txt` files. If the user made amendments via the user interface those changes are woven into the content of both `*.txt`-files. Based on this information a cohort is generated.

Another way is to load a defined cohort from an input file. The description of individuals enlisted in this file is then used to generate individuals which reflect this cohort. This option can be used if patient level data is available, e.g. while conducting a study.

All files which describe the sexual network are read and translated into a processable form. If applicable the sexual network chosen for this simulation is enriched by information the user gave in the user interface. The disease models, which are described in *.txt and *.js files are also translated into a version which can be used by the modelling tool. See Appendix D for a detailed description of the required input files.

All inputted clinical pathways are also translated into a form which can be used by the software.

3.5.3 Warmup

The software cannot start its simulation directly after the "Creation" step as at this point no partnerships are modelled. This would lead to rapid extinction of all simulated STIs because no infections can occur. A warmup period is needed in which a network of partnerships is being generated. During this phase, no individuals in the model can get infected, as the STIs have not been seeded yet. This shortens the warmup because fewer events have to be processed.

The warmup period lasts half of the maximum length of the longest partnership type. This time is calculated after the partnership types have been defined by the user. It ensures that over the whole simulated time horizon roughly an equilibrium between the formation and dissolution of all partnership types is achieved.

Seven days before the warmup ends the simulated STIs are seeded in the model. For each STI a random proportion of the population is put into health states based on the initial distribution stated in the corresponding `model.txt` file. If a specific cohort was loaded from a file, then the individuals' health states as defined in the file.

When the warmup ends, the first set of systematic screening events is generated and put into the event queue to start the clinical pathway model.

3.5.4 Simulation

During this phase, the model is run for the previously stated amount of modelled time. All described disease sub-models for all included STIs and sequelae are included, and partnerships can start and end during this phase as well. Systematic screenings are offered, and people can be tested or treated. During this phase data, like number of active partnerships, STI prevalence, and costs, is stored in a database.

3.5.5 Lifetime Projection

Before the simulation starts users can select whether they want to have a lifetime projection of the simulated cohort. It is only possible to select this option, when a closed cohort is simulated, which means that dead individuals are not replaced.

If the option for a lifetime projection was selected the software will continue to run until the last individual in the model dies. This means that after the "simulation" phase ended no new partnerships will be started and no contact events will be calculated. No tests will be offered any more either. This "lifetime projection" phase can be important to see how many sequela events related to the "simulation" phase will occur during the remaining life span.

For example, PID depends on the number of episodes of chlamydia an individual has had in their life. This might lead to episodes which occur a long time after the simulation ended. As these are related to the simulated STIs during the actual simulation it can be relevant to include them in health economic analyses.

If the user decided to not include a lifetime projection in the modelling process this phase will be skipped. The software will, in this case, proceed with the analysis phase immediately after the simulation phase.

3.5.6 Analysis

During the modelling process, every event that has been executed is stored in a database. Other outcomes are calculated after the modelling run and stored in the database. The database can be exported after the analysis phase to conduct further examinations. These exports will be saved as "comma-separated values (csv)" files so that they can be processed with any standard table calculation program.

During the analysis, all previously collected raw data from the database is prepared to be presented to the user in graphs and tables on the user interface. This includes health economic evaluations, STI prevalence over time, the number of partnerships over time, and the overall event counts.

3.6 Validation

In this section only the technical correctness of the modelling approach is being validated. The inputted model, e.g. disease models and sexual networks are validated in their respective chapters.

It is an important point to understand how the software behaves if it is challenged with more complex input. The calculation times are of special interest, in this case, to see whether the tool scales appropriately or whether a more complex input will lead at some point to an unbearable runtime of the simulation.

A first step towards understanding the complexity scaling is to look at the scaling of the disease modelling component of the modelling tool. I conducted two different series of simulations, one with an increasing number of disease models, and another one with an increasingly more complex disease model.

3.6.1 More Models

In this scenario, I started with one simple disease model, which only consisted of two states, healthy and sick. I simulated a cohort of 5,000 individuals over a period of five years. The same sexual network model was used in all simulations. I ran each model ten times and averaged the time it took to load the models and the time to complete the simulation. In the next simulation, I included another disease model, consisting of two health states and ran the simulation again ten times. Subsequently, I included up to 25 parallel models. Figure 3.6 shows the increasing number of non-interacting models for up to four models.

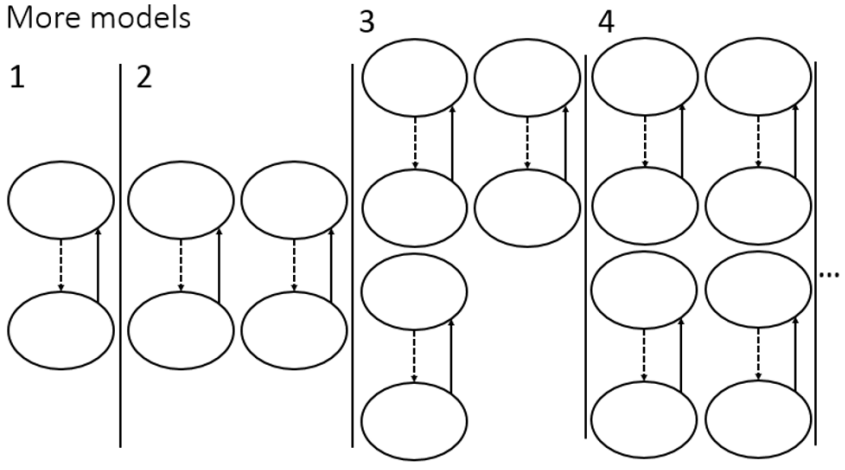


Figure 3.6: Stepwise increment of the number of included models to simulate more models during validation.

The duration of the simulation phase and of the creation phase of the model in relation

to the number of models is shown in figure 3.7, whereas the time for a single model defined baseline value of 1,227ms for creating and 62,235ms for simulating. These values are represented as 100% in the graph. The remaining values are presented in relation to the baseline value.

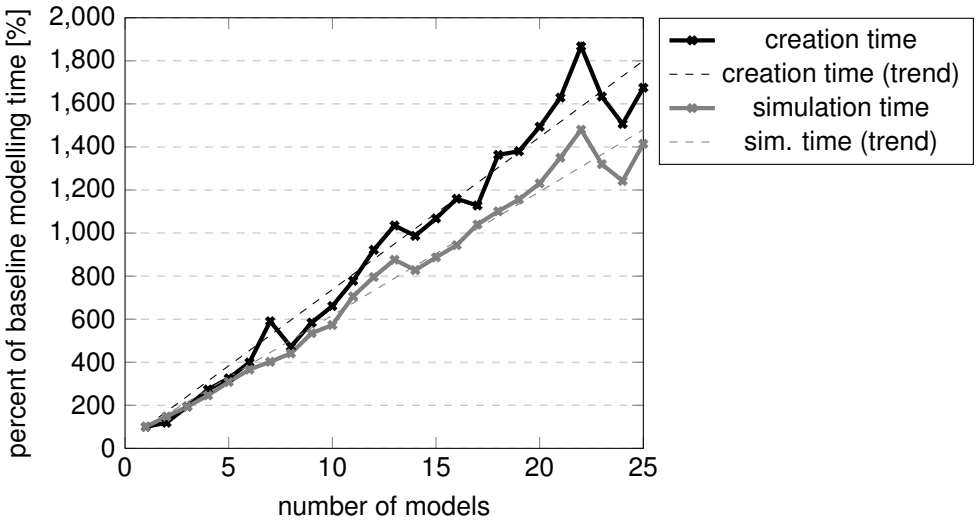


Figure 3.7: Time needed to create and simulate more models

The time of the creation phase and the simulation phase increases linearly with the total number of models included in the model. For each additional model, the simulation phase of the model increases by 14%, whereas the creation time increases by 12%. Fluctuations in the graph, as well as derivations from the linear trend lines, are explained by random effects of the model which could not be averaged out due to a too low number of model runs.

3.6.2 More Complex Models

In this second series of experiments, I took the same model as a base model as I used in the previous validation series. This time I did not increase the total number of included models but increased the complexity of this model. In order to do so, I added health states to the model, one after another. The new health state was connected bi-directionally to all other existing health states except the uninfected state, see figure 3.8. The number of included health states was increased incrementally up to 25.

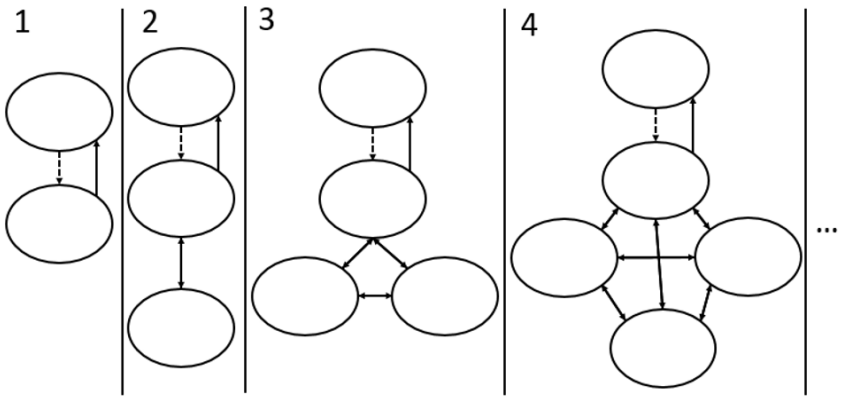


Figure 3.8: Stepwise increment of the complexity to simulate more complex models during validation.

Each model was simulated ten times to calculate the average duration of the creation phase and the simulation phase which are shown in figure 3.9, with the time of the model run with no additional health state being the baseline value of 1,742ms for creating and 64,818ms for simulating. These values are presented as 100% in the graph, all remaining values are presented in relation to the baseline.

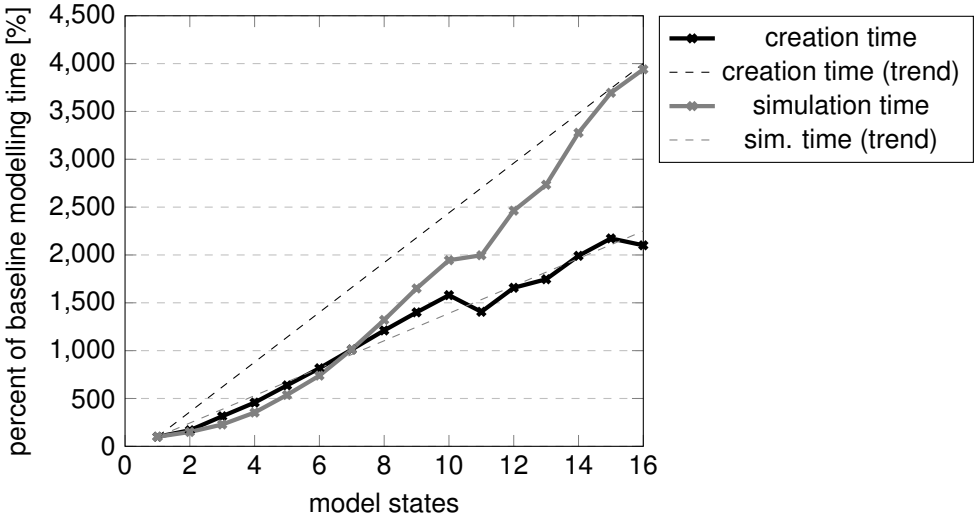


Figure 3.9: Time needed to create and simulate more complex models

The increase in duration of the simulation phase for a greater number of models is linear, however, for more complex interacting models it is polynomial. Since increasing number of health states yield more transitions, and thereby more time-to-event formulas to be calculated. These numbers increase by a non-linear factor as calculated in Equation 3.1.

$$t = 1 + (m-1) \cdot (m-2) \tag{3.1}$$

With `t` being the resulting number of transitions in a model with `m` as the total number of states. This relationship is also visualised in Figure 3.9.

It is evident that the simulation time of the model roughly follows this trend as well. In a real world setting these time-consuming calculations are avoided as most models consist of far less than 25 health states. The health states in a typical model are not completely and mutually connected, which means that not every health state is connected to every other health state. This leads to a lower total number of transitions in typical models.

As we can see in Figure 3.9, the initiation time of the model increases linearly with an increment of 25% per additional state included in the model.

3.7 Discussion

In this chapter I have presented a technical solution to how to simulate multiple STIs simultaneously using a discrete event simulation approach.

3.7.1 Selection of Modelling Approach

There is no "one size fits it all" modelling approach for all disease modelling problems. The guideline from International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [15] recommends developing the model structure first before deciding on the modelling approach [135]. After this step, the data for the model should be collected. If there is missing data, studies must be conducted to impute data into the model [140]. As the development of the model structure was not finished by the time I had to decide on my modelling approach I had to change the order of the steps in the ISPOR process. I revisited my decision on using DES as a modelling approach after finalising the model structure and found that I would still use the same modelling approach.

Work from Kretzschmar et al. [141] and Roberts et al. [142] underline the importance of individual based modelling to accurately reflect the spreading pattern of STIs but highlight the uncertainty around input parameters at the same time. This uncertainty is one of the reasons why all models, regardless of the modelling approach, need to be calibrated to real world data and secondly to reflect all model assumptions thoroughly. Failure to do so might likely lead to a misinterpretation of results and subsequently even to incorrect recommendations for policy makers. In this context it is crucial to choose the correct modelling approach, whereas they also suggest that no modelling approach is superior to another one by default.

3.7.2 Model Structure

3.7.2.1 Challenges in Event Time Updating

If an individual transitions into another health state, all transitions which depend on the previous health state will either be deleted or updated. This must be considered while developing all time-to-event formulas otherwise individuals might get stuck in certain health states. To clarify this, we have a look at two interacting sub-models, presented in Figure 3.10:

I set up a hypothetical example to showcase a potential problem which might occur during event updates, if interacting models are not set up carefully. The transitions between health states in this hypothetical example are defined as follows:

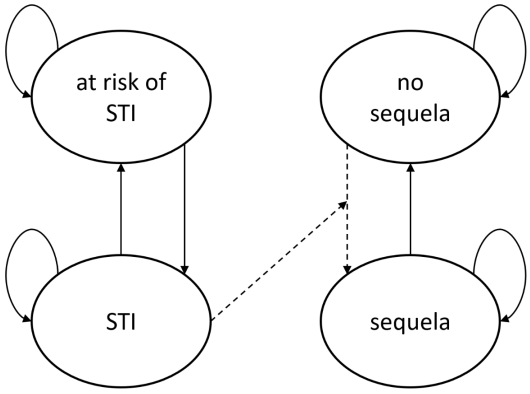


Figure 3.10: Example of how the health state in one sub-model can influence the transition probability in another sub-models

- **No STI** $\rightarrow$ **STI** Not necessary, as infection events are triggered by the sexual network model and not by the disease sub-models.
- **STI** $\rightarrow$ **No STI** After 10 days the disease will cure by itself
- **No Sequela** $\rightarrow$ **Sequela** After 7 days of being in *STI* the infection occurs, otherwise none
- **Sequela** $\rightarrow$ **No Sequela** If the individual is infected, the sequela will cure in 5 days.

In this example, individuals can be put in a state of perpetuity. The above-mentioned formula for sequela to no sequela does not cover all possible health states an individual can be in as this paragraph will demonstrate. After being cured of the STI, all events depending on *STI* in the queue will be updated. This includes the transition from *sequela* to *no sequela*. First of all, this event will be deleted out of the event queue to be replaced by a new event covering the same transition, but no new event will be added to the queue because the transition formula did not cover all possible cases. Therefore, the individual will stay indefinitely in the sequela state without the possibility of cure, as the event had been deleted instead of replaced.

This example shows that the time-to-event formulas must be defined carefully, to avoid definition gaps. Especially, when a certain sequela depends on health states from different STI sub-models, definition gaps might occur.

3.7.2.2 Exception on Event Updating

In certain cases, a single event, which depends on several other disease models, can be postponed multiple times without being executed once. With the help of another hypothet-

ical scenario, I will explain this further. In this situation, there is a sequela (*SEQ*) and two STIs (STI_1, STI_2). An infection will last 28 days or 23 days with with STI_1 or STI_2. The sequela depends on both of them and will start after a certain number of days depending on which STI or combination thereof is present as the following formula shows:

`if (`STI_1 `is present and` STI_2 `is not present)` $\rightarrow$ 20 days

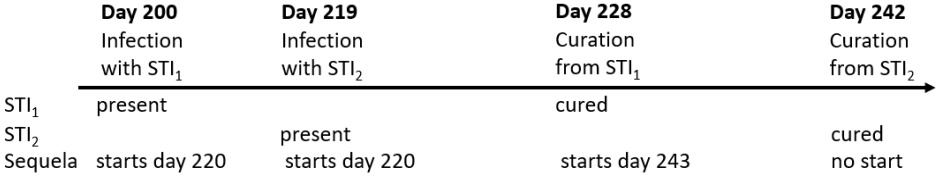
`else if (`STI_1 `is not present and` STI_2 `is present)` $\rightarrow$ 15 days

`else if (`STI_1 `and` STI_2 `are both present)` $\rightarrow$ 10 days

`else` $\rightarrow$ no event

As this formula depends on both STIs the time-to-event will be updated at each change of health state in the models for STI_1 or STI_2. If we now examine another hypothetical situation (see Figure 3.11 for a timeline of this problem) where an individual will be infected with STI_1 on day 200 the disease model would calculate a time-to-event of 20 days. This means the sequela would occur on day 220. On day 219 the same individual gets infected with STI_2, so that the event time of the sequela event has to be updated. The time to event is 10 days, which is added to the current day (219), so that the new event time will be day 229. At day 228 the infection with STI_1 is cured, which is why the time to event for the sequelae event has to be recalculated again. The new event time would be day 243 (=228+15). But on day 242 the individual is completely cured. Consequently, the event will be deleted from the event queue. In this example, we can see that, that the individual has been infected with at least one STI for 42 days continuously, but no sequelae event has been processed. Furthermore, the individual was infected with STI_1 for 28 days and with STI_2 for 23 days, whereas the time to event of the sequela event for each STI on its own should be 20 days for STI_1 and 15 days for STI_2. These situations need to be avoided in the model.

Figure 3.11: Timeline of an example conflict while updating event times - without optimised event updating

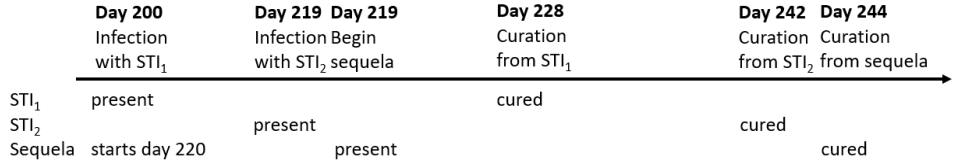


To avoid this unrealistic postponing, the disease models will only update event times if

their new event time is earlier than the old one. In all other cases, the old event time will be kept unless the whole event has to be deleted.

In the example above, this would lead to an altered chain of events compared to the previously described event sequence. At the time of infection with STI_2 the algorithm checks whether the new event time for the sequela event is later than the current one. If this is the case the event would not be updated. This leads to infection with the sequela. Assuming that the sequela lasts for 25 days we can now look at a new timeline in Figure 3.12.

Figure 3.12: Timeline of an example conflict while updating event times - with optimised solution



The deletion of events is not affected by this algorithm. If all risk factors included in a time-to-event-formula are not present this event will still be deleted from the queue.

3.7.3 Formulas

3.7.3.1 Usability

The above-mentioned solution has the advantage that users can change the formula which is an important part of the model without the need of changing the actual disease modelling software code. Still, the user needs to know the syntax of a programming language (in this case JavaScript) to be able to modify these formulas. In Chapter 4 I present the user interface for this multi-STI modelling software, which helps users to input the software in an intuitive way, without the need to write JavaScript code chunks.

3.7.3.2 Errors in Imported Code Chunks

Currently there is no way of checking the code for potential logical errors, e.g. wrong attribute names, before the code snippets are loaded into the program. These errors will lead to errors during the loading of a model file structure. The user interface does not allow input which cannot be interpreted. More sophisticated users might be tempted to edit the `*.js`-files directly without using the user interface. This might lead to processing errors in the JavaScript chunks and thereby to an interruption of the execution of the simulation algorithm.

3.7.3.3 Calculation Time

The detour of interpreting Java Script code snippets in the Java code is time consuming. Therefore, a solution which would have the formulas in Java code would be faster.

3.7.3.4 Safety

A disadvantage of the current solution is that the JavaScript code snippets are directly interpreted. Malicious users could take advantage of this by developing fake models with the purpose of processing code which could be potentially harmful to the computer on which the software will be used.

To avoid potential harm to the computer, the Java Script code chunks which set up the model have to be checked before running the model.

3.7.4 Different Types of Risk of Infection

The risk of a person of getting infected with an STI consists of three main factors, the **pathogen risk**, the **individual risk** and the **network risk**, which are all reflected in the software.

The **pathogen risk** describes the probability of infection if an uninfected person has unprotected sex with an infected person. This risk is reflected in the infectivity of the disease, which can be inputted by the user for each health state individually.

The **individual risk** is modelled using several parameters describing the behaviour of an individual. All of them are used in the sexual network models. For example, the likelihood of condom usage is an important behavioural parameter which influences the **individual risk** of a person.

Even a strictly monogamous person might catch an STI if their partner is infected. This is described by the network risk. The **network risk** describes the risk of getting infected after having sex with an individual from this network. It is linearly proportional to the prevalence of a disease in the network, which is described in the initial prevalence of the disease in the modelled sexual network.

3.7.5 Validation

This validation only looks at the Java code which runs the DES. The default disease models, sexual network models, and treatment pathway models, which I have developed, have been validated (internally and externally), see Section 5.2.4, Section 7.2.4, and Chapter 8.

The increased time for simulating more models and more complex models meet the expectations. As more models lead to more events in the event queue and more events to

be processed the increase in creation time and runtime was not surprising. Nevertheless, it was good to see a linear increase in the calculation time, which suggests that the model scales well even if it is faced with a high number of models. It scales less well for more complex models, especially if those include many transitions.

I saw in this experiment that the execution time is mainly driven by the total number of events to be executed in the model. After acknowledging this, I decided to not conduct any clinical pathway or sexual network complexity tests, as I had no reason to assume that the model would behave differently for more complex pathways. As described earlier in this chapter the same technology and methodology have been used to develop and simulate all models of the software (the sexual network models, the clinical pathway models, and the disease models). They communicate and interact with each other using the same event queue. Therefore, it was reasonable to assume a similar, linear increase of the calculation time if the total number of events was increased in any other way.

These results do not give the full picture of the disease modelling tool. As no realistic social model and no clinical pathways were included in this validation the impact of those could still be significant and increase the calculation and loading time. Furthermore, these tests did not look at the impact referencing other disease model's health states in time-to-event formulas has. This is an important factor in the final model, as transitions depend on certain disease states of other disease models.

3.7.6 Conclusion

In this chapter I discussed different modelling approaches which could be used in a multi-STI model and found that in this specific case discrete event simulation (DES) might be the most suitable approach. I presented a way of structuring a complex DES model in separate parts. Chapters 5, 6 and 7 will elaborate further on the individual model parts. Before that Chapter 4 looks at the involvement of stakeholders in the development of the different parts of the model.

Chapter 4

Stakeholder Involvement in the Model Development Process

4.1 Aims and Objectives

In the previous chapter I presented the modelling approach used in this multi-STI modelling software. To develop a model which is useful to decision makers it was important to include them as stakeholders in the model development process.

The aim of this chapter is to describe the stakeholder involvement in the modelling process. To ensure that their voices were heard, and their requirements met, decision makers were included in deciding on the scope of the software as well as the user interfaces of the software. At a later stage, during the development of the individual disease models, sexual networks and clinical pathways models, decision makers and sexual health physicians were again included in the development process.

Letting future users decide on the scope, meaning the considered STIs, sexual networks and modelled treatments, was necessary so that the software was useful to them and would be more likely to be implemented in existing processes.

That said, a software which can calculate relevant results is, in itself, unlikely to be used in practice. Therefore, the development of intuitive and easy-to-use user interfaces was aspired to facilitate the access of potential users to the software.

4.1.1 Overview

This chapter describes how the scope of the software was defined and how user interfaces for the software were developed. Subsequently, the implemented user interfaces are presented to the reader.

The inclusion of decision makers was a multi-stage process accompanied by an advisory group. The advisory group consisted of a user interface development expert, a STI-clinician, a decision maker in sexual health an me.

The inclusion of decision makers started with a questionnaire, followed by face-to-face interviews, and subsequently led to the definition of the scope of the software and the implementation of the user interfaces. The user interfaces were also validated in a last step.

The purpose of the initial questionnaire was to develop an understanding of the needs and expectations of decision makers towards a potential multi-STI software. Accordingly, the questionnaire included questions, which for example helped to understand which interventions should be able to be modelled by the software.

The main aim of the interviews was to sharpen our understanding of the work of decision makers, the processes they work with and the gaps a multi-STI modelling software could fill. It was crucial to understand the work of decision makers to identify areas where the software could help them, and to understand how the software could be integrated frictionless into their working life.

In these interviews we also developed a set of user interface drafts. This was done by iterative improvements, beginning with an initial set of mock-ups that was set up by the advisory group and based on input from the questionnaires.

4.1.2 User Interface Development

User interfaces are the connecting element between users of a software and a software itself. They can be text-based so that a user has to type commands to interact with the software. If the software displays graphical items which can be used i.e. to control the software, they are called graphical user interfaces. Graphical user interfaces are usually more intuitive and easier to handle for inexperienced users [143].

The inclusion of stakeholders in the development of user interfaces is a common principle in software development. This can be done by user interface mock-ups, so called wireframes, which are iteratively improved in cooperation with future stake holders [144].

I did not see any examples in my systematic review of collaborations with decision makers in the development of user interface to facilitate decision makers using the disease models.

Usability is only partially based on the user-interface of the software. It also depends on other factors, such as organisational structures and the way in which the software is

embedded into processes of the organisation, the design of user interfaces do matter [145].

I applied principles from user interface development to develop user interfaces which aim to facilitate sexual health decision makers utilising disease modelling.

4.2 Methods

With the help of this advisory group, a questionnaire was distributed to potential users (see Section 4.2.2) and face-to-face interviews were conducted (see Section 4.2.3) to gather input on the functional scope and the user interface of the software. The results from these studies were subsequently translated into computer code and included in the model (see Section 4.2.4).

4.2.1 Role of the Advisory Group

The inclusion of decision makers was facilitated and moderated by an advisory group. The advisory group was composed of people from a breadth of experience from different academic and clinical fields. The advisory group consisted of a decision maker in health care, a software development expert, a sexual health clinician and me.

The work of the advisory group was divided into three phases.

1. In the first phase, a questionnaire was developed. Before the questionnaire was used it was piloted and improved. After this, the questionnaire was distributed, and the responses were gathered. Section 4.2.2 describes the questionnaire study.

2. After the questionnaire was closed the advisory group second phase analysed the questionnaires. Based on these results, interview guides for semi-structured interviews were developed. This interview guide was piloted and improved before it was used with the participants of the study. Subsequently, participants of the questionnaire study who indicated their interest to co-operate further were invited to in-depth face-to-face interviews. The face-to-face interviews were primed with a first set of user interfaces which was developed by the advisory group. The face-to-face interview are described in Section 4.2.3.

3. With the help of the interview guide and the user interface drafts, I conducted a series of interviews with stakeholders. The advisory groups reviewed the transcripts of those, derived the scope of the software from those transcripts and validated the resulting user interface in the third phase.

After this last phase, the advisory group was dissolved. The translation of the drafted user interfaces into computer code was done by me. The implementation of the user interfaces is described in Section 4.2.4.

4.2.2 Questionnaire Study

The advisory group developed the questionnaire in a way to understand the target audience and their needs and expectations towards a decision support software as well as their working environment. A copy of the questionnaire can be found in the appendix in Section E.1.

The questionnaire was designed to be as short as possible, so that decision makers could participate despite their busy calendars.

The advisory group identified core areas for the development of user interfaces, which were:

- working life/ workflow of target audience,
- STIs,
- relevant populations,
- relevant interventions, and
- relevant results.

For each of those areas, questions were formulated to address the most urgent issues.

The link for the questionnaire was distributed via existing mailing lists of STI commissioners in England and within the STI and HIV department within PHE. I could use these mailing lists as members of the advisory group had access to them. The initial call for participation was distributed to 19 people. The recipients of the email were considered as the target audience for the software as they were decision makers in sexual health in England.

A short presentation was recorded to introduce the general idea of the software and the purpose of the questionnaire. Participants could, but were not forced to, view the video of the presentation[1] before they started answering the questionnaire.

Among other questions stakeholders were asked to rank these ten STIs according to their importance for their work, with 1 being the top priority and 10 being the least prioritised STI from their perspective. To input the question on which STIs were relevant to the work of decision makers a pre-selection was made.

[1] `https://www.youtube.com/watch?v=tr5mLM4I_r8`

After the questionnaire was closed, its results were analysed in the advisory group. Quantitative analyses were run using Microsoft Excel.

The questionnaire was piloted with my supervisors before distributing it to relevant stakeholders.

4.2.2.1 Pre-Selection of Included STIs

In the questionnaire decision makers could decide on the key STIs to be included in the software out of a pre-selected list. The selection was already narrowed down to to avoid decision makers with an overwhelming and maybe not even exhaustive list of "all" STIs.

The pre-selection process was done by my supervisors and me. We decided to only include the - from our perspective - most relevant STIs in the questionnaire. Therefore I tried to find out which STIs are relevant for England.

What Makes an STI Relevant in a Certain Setting? Not all STIs are globally equally relevant. Local circumstances, such as prevalence and incidence, influence the local relevance of a STI. Thus the local relevance of a specific STI may vary in different geographical areas and cannot be defined globally. For this thesis I specifically looked at the relevance of STIs from an English perspective. STIs which are relevant in other regions in the world may receive less attention in an English context and vice versa.

The relevance of an STI cannot be assessed directly. Consequently, proxy measures to determine the relevance are necessary. I used prevalence and incidence complemented by expert opinion to determine the relevant STIs.

Prevalence and Incidence: The prevalence of a disease depends on several factors. These include available treatment options, duration of the disease, whether the disease is curable, and also incidence. Higher incidence usually leads to higher prevalence as well. Other factors, such as the time of the infection, time of incubation period, whether treatment for the disease exists etc., influence the prevalence as well. In Figure 1.3 (Chapter 1), I showed an example of the rising global HIV prevalence whilst having a global decrease in HIV incidence. This is because HIV is a life-long condition and treatment options are getting better. As a result people now live longer with HIV. This example shows that incidence is not the only factor impacting prevalence and looking at one of the two may not be sufficient.

Prevalence and incidence of an STI within a geographical region of interest is a good indicator of whether this STI is relevant in this setting. But low reported prevalence and incidence might not necessarily imply low infection numbers. It might reflect reporting or insufficient test coverage. From an English perspective, this is less of a problem as GUMCAD

[30] centrally stores STI diagnoses from the whole country, as discussed in Chapter 1, so that the reporting of confirmed STIs in England is expected to be good.

Expert Opinion: Experts, who have experience working with STIs, e.g. physicians in GUM clinics can give empirical evidence on the relevance of STIs on a local level. They see first-hand which STIs are more common in their area and which STIs affect their patients more severely. Therefore, they are useful people to arbiter about which STIs are relevant or not.

Methods for Preselecting STIs for Questionnaire: I decided which STIs should be included in the software in a three-stage process.

In the first step, I looked at the number of new cases per STI as reported in the GUMCAD quarterly reports and ranked all STIs.

In addition to the expert opinion of one of my supervisors, who is a GUM physician, a clinical GUM expert from a local hospital was asked to comment on the relevance of various STIs from their perspective.

The number of new cases and expert opinion were considered when I selected the ten most relevant STIs in England. This step was done in cooperation with my supervisors due to their experience in STI research. This list was used to input a question in the aforementioned questionnaire.

4.2.3 Face-To-Face Interviews

The advisory group developed an interview topic guide for the semi-structured face-to-face interviews, which can be found in Appendix E.2. The topic guide was developed by reviewing the answers to the questionnaire and additionally included areas which were not addressed by the questionnaire but were considered as relevant by the advisory group.

Several questions were included to understand processes at the workplace of the interviewees to learn how the software could be integrated into these processes. We also wanted to get more information on the experience interviewees had with other STI models so that we could learn some lessons from that.

The interview was split into two parts. The first part used the interview topic guide to understand the needs of decision makers towards STI-modelling software. In the second part of each interview, we looked at user interface drafts. The first set of these drafts was developed by the advisory group. These drafts were then iteratively refined in the interviews.

The first user interfaces were drawn on paper. This method was chosen as it facilitates communication with a potential user as criticism is communicated more freely. This connection is reasoned by the perception of the user that effort has been put into this project and therefore feedback can be more direct [146].

After the first couple of interviews, the paper user interfaces were translated into wireframes. Wireframes are user interfaces which can be navigated on the computer as they are connected (=wired) with each other. They therefore give a better impression of what the software will look like than paper prototypes [147].

Each interviewee was asked to "think aloud" while certain they were asked to finish some tasks. "Thinking aloud" is a well-established technique which challenges participants with certain tasks while they report everything verbally that they are thinking during the process of solving the task [148]. The tasks in this context were for example "Run a simulation", "Raise the specificity of a chlamydia test", or "lower the price for ART". No audio or video was recorded during the interviews, but notes were taken. These notes were shared with the interviewees afterwards.

All notes of the interviews were discussed in the advisory group to identify common topics and relevant issues addressed by the interviewees.

Before the interviews were conducted a round of piloting interviews was held with my supervisors to test the topic guide. The interviewees of the actual interviews were chosen randomly from participants of the questionnaire who volunteered to be interviewed.

4.2.4 Implementation of the User Interfaces

Based on the wireframes, which were developed during the face-to-face interviews, user interfaces for the software were developed.

The user interfaces were developed in Java [149] using JavaFX [150] and SceneBuilder [151].

4.2.5 Validation of the User Interfaces

The members of the Health Economics Analysis and Research Team (HEART) at UCL validated the software and reported all arising issues, such as spelling mistakes. To accomplish this, a prototype of the software, which only contained the user interfaces - without any models connected to it - was distributed to HEART. HEART was selected as their members have experience in conducting health economic trials. It was therefore easy to explain the purpose of the software and its intended functionality to this group so that the validation be

conducted rapidly. Their feedback was gathered using an online form, which was open for a month.

4.2.6 Ethical Approval and Dissemination

UCL ethics approved the questionnaire and the face-to-face studies, ethics number: 12221/001.

The questionnaire was published online using EUSurvey (`https://ec.europa.eu/eusurvey/home/welcome`). and open from 21.05.2018 until 27.06.2018.

Interviewees were given an information sheet (see appendix, Section E.3) before they were interviewed and before a face-to-face interview was started written consent was given by the interviewee.

4.3 Results

4.3.1 Questionnaire Study

Counting the recipients of the initial distribution list, 19 people received an invitation to fill in the questionnaire. A total of nine responses to the questionnaire were recorded (response rate: 9/19 = 47%). Four responses came from PHE, the remaining five were from local authorities. We did not expect many responses to the questionnaire due to the low number of eligible people who could potentially fill in this questionnaire.

Job descriptions of the participants included (duplicate-free list):

- sexual health commissioner
- advanced public health practitioner
- sexual health lead
- sexual health facilitator

Working in these jobs the participants are responsible for a variety of tasks (duplicate free list):

- commissioning sexual health services,
- monitoring sexual health services,
- supporting commissioners,
- dealing with queries on quality standard/ chlamydia care pathway,
- monitor delivery of service,
- deciding on models of delivery,
- developing new service models, and
- provide analysis, data, and practice examples.

4.3.1.1 List of STIs to Include in Questionnaire

My supervisors and I made a preselection on which STIs to include in the questionnaire. The results of this selection process are presented in this section, the results of the relevance ranking of STIs based on the answer from the questionnaire are presented in the next section (Section 4.3.1.2).

Table 4.1 shows the number of new cases (as of 2016) of all STIs which were included in the PHE report on "All STI diagnosis & services by gender & sexual risk, 2014 - 2018" [152].

Table 4.1: Absolute number diagnosed of STIs in 2016 as reported in GUMCAD

STI	new cases (2016)
chlamydia	204,424
candidiasis	84,284
genital warts	63,459
gonorrhoea	36,577
herpes	33,041
Molluscum contagiosum	9,374
trichomoniasis	7,209
syphilis	5,955
HIV	3,109
scabies	2,395
hepatitis B	1,210
hepatitis C	871
chancroid/ LGV/ donovanosis	811
Mycoplasma genitalium	205
hepatitis A	100

Table 4.2 summarises the expert opinion on various STIs. The first column lists the name of the STI the expert commented on. The second column summarises the experts comment which was given about this STI and the third column states whether the expert recommended to include this particular STI in the software or not.

Table 4.2: Summary of the STI selection and corresponding reasoning given by STI expert

STI	expert opinion	expert select?
chlamydia	most common STI in England	yes
genital warts	high prevalence, serious outcomes possible	yes
gonorrhoea	low prevalence, relevant for certain cohorts, not overall	yes
HIV	Most publicly discussed STI	yes
mycoplasma infection	evidence that Mycoplasma Genitalum is important for PID	yes
syphilis	only sporadic in England, important for certain subgroups	yes
Trichomonas Vaginalis	high prevalence; might lead to PID	yes
hepatitis viruses	only Type B (connection to HIV), many ways of transmission	unclear
candidiasis	interaction with HIV, high prevalence, no serious outcome	no
chancroid	only sporadic in England	no
cytomegalovirus	lots of different transmission routes, no serious clinical effects	no
Gardnerella Vaginalis	no clinical seriousness	no
herpes	high prevalence	yes
intestinal protozoa	affects gut, other transmission routes more common	no
Klebsiella Granulomatis	only sporadic in England	no
lice	steadily declining prevalence	no
Molluscum Contagiosium	lots of different transmission routes, no serious clinical effects	no
scabies	no clinical seriousness	no
Ureaplasma Infection	no clinical seriousness	no

All STIs which were not excluded by experts were considered in our pre-selection, these were (in alphabetical order):

- chlamydia,
- genital herpes,
- genital warts / HPV,
- gonorrhoea,
- hepatitis B,
- hepatitis C,
- HIV,
- mycoplasma infection,
- syphilis, and

- trichomoniasis.

In the questionnaire, decision makers were asked to rank these STIs according to the relevance for their work, see next section.

4.3.1.2 STI Selection

Figure 4.1 describes the importance of the included STIs according to the responses of the questionnaire. The figure shows the mean rank of all included STIs, with lower number indicating a more relevant rank and thus a higher perceived importance for the participants. Respondents did not suggest adding further STIs.

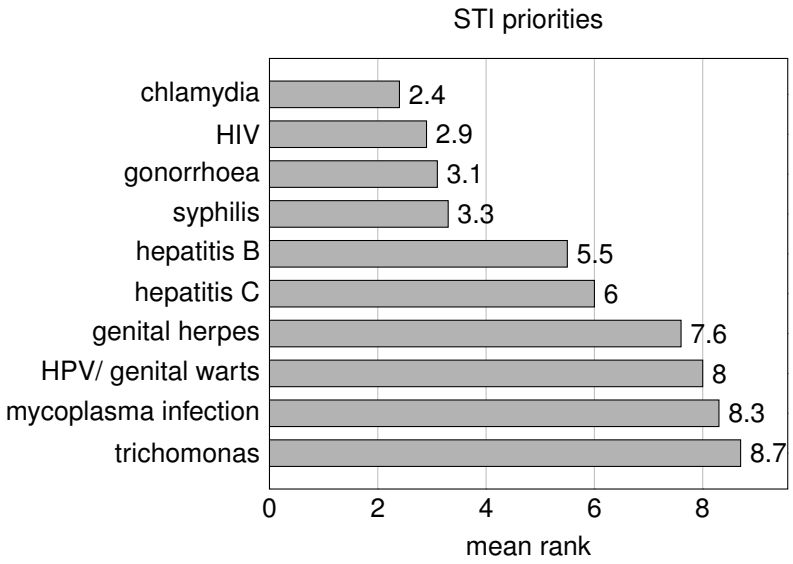


Figure 4.1: Mean ranks of ten STIs, as selected by participants (lower rank equals higher priority)

The results show a drop in the mean rank of the STIs between syphilis and hepatitis B. The four STIs with the lowest mean rank (chlamydia, HIV, gonorrhoea, syphilis) were more important to decision makers than the rest.

4.3.1.3 Sexual Networks

The participants were asked to identify the most relevant populations for an STI model from a pre-defined list and the results are shown in Figure 4.2. Some participants suggested networks which were not included in the list. These were an older generation sexual network (one vote) and women who have sex with women (one vote).

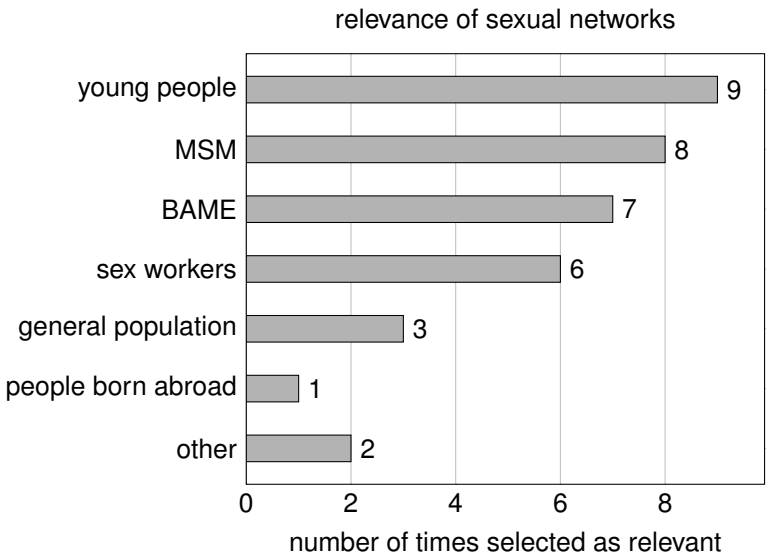


Figure 4.2: Relevance of various sexual networks for the work of participants [absolute number of participants who voted for that option]

Based on this vote we included sexual networks for young people, MSM, and black, Asian, and minority ethnic (BAME) in the software. It was necessary to develop a general population network to derive the aforementioned networks, which is why we developed and subsequently included a general population network in the software, too.

4.3.1.4 Health Promoting Interventions

Participants were asked to select the top priorities of their current work, and what they expected top priorities would be in two years' time (Figure 4.3).

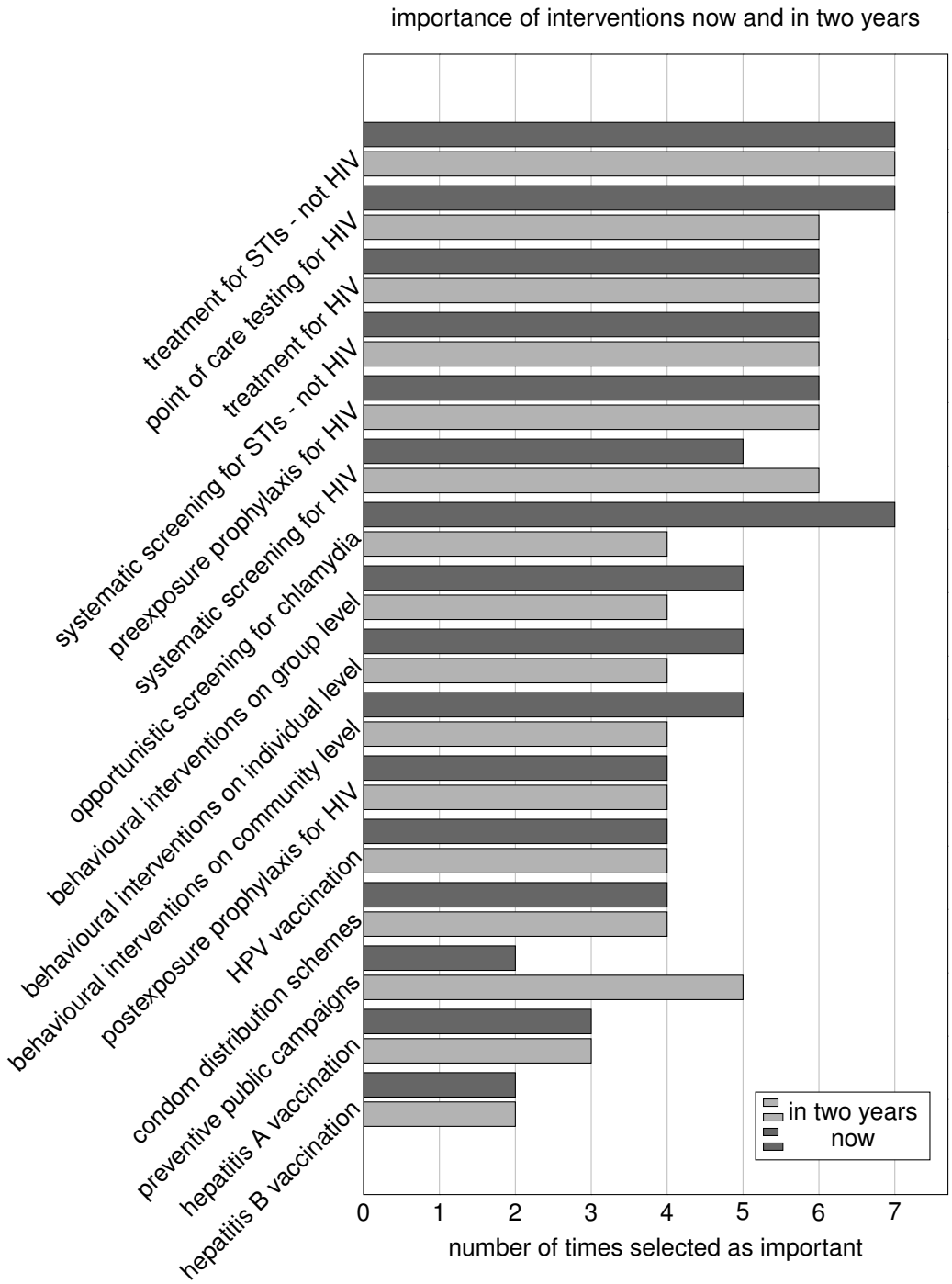


Figure 4.3: Importance of various sexual health intervention now in comparison to the estimated importance in two years (absolute votes)

Besides the interventions which were explicitly listed, no interventions were included using the "other"-option.

In the free text field, some participants indicated that they were disappointed that there is a lack of financing for interventions, i.e. to fund the following interventions:

- pre-exposure prophylaxis (PrEP) as a routine service,
- sex education, and
- more opportunistic screening (online and self-care model).

4.3.1.5 Usage of the Software

We asked participants how they would like to see the results of the simulations. Figure 4.4 shows how often each option was chosen. No participant wanted any other options. Based on the indecisive result, we decided to include all output options.

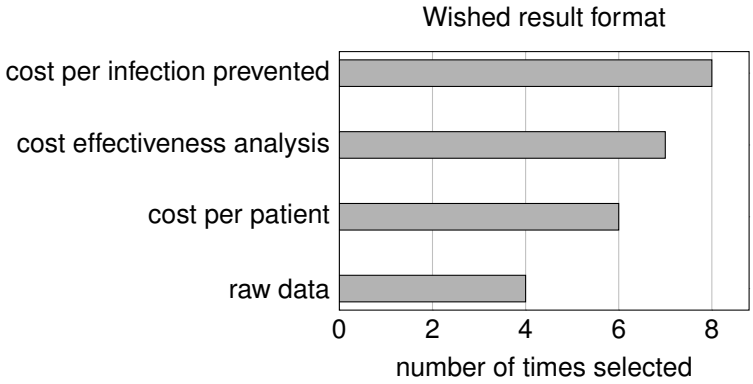


Figure 4.4: Wished result format (% of participants who voted for that option)

4.3.2 Face-To-Face Interviews

A total of five face-to-face interviews were conducted. During the interviews, the user interface drafts were continuously improved. In the last interview, no further suggestions to further improve the user interface, based on the presented wireframes were made. The wireframes are not presented in this section, as they are nearly identical with the user interfaces which were included in the software. I only present the user interfaces included in the software (see Section 4.2.4 and Appendix F).

The answers which were collected during the first part of the face-to-face interviews are presented in the following paragraphs.

Information was gathered on the professional roles of the participants. Not all commissioners had a clinical or public health background. In their jobs, they are responsible for evaluating interventions to make informed decisions. Their work is multi-faceted as they sit between different stakeholders and try to find an optimal solution for all partners. They reported that the landscape in which they have to make decisions in is influenced by many different factors, such as politics and personal experiences of stakeholders.

When asked about their experiences with disease models, all participants reported that they had used them at least once before. The experience of the participants differed greatly, as some only heard about disease models when a published paper was circulated in their department and others had participated in the development of some disease models. Tools which they used included fingertips [153] (from PHE) and other GUMCAD analysis tools.

All participants thought that disease models are potentially beneficial if they are used correctly. But not all participants said that they used disease models on a regular basis. This was mostly due to time restraints, which did not give enough room for their own research during a normal working day.

Those who used disease model regularly reported that they were not easy to use. On the other hand, models helped them to better understand the potential future impact of interventions, both planned and existing. Decision makers also said that they could imagine using decision models to simulate and illustrate "what-if" scenarios which could tell them what (not) to do.

In the interviews the participants stated that their biggest barriers to using disease models were that the results might be wrong, as the evidence basis of the model is not laid out clearly. Participants also stated that disease models are too complicated to use "so it is more trouble than it is worth using them". Participants also said that disease models tend to be too theoretical and therefore not practically applicable.

4.3.3 Implementation of the User Interfaces

The user interfaces were developed based on the input of decision makers during the interviews. All input masks are designed in a way to easily allow changes in the most relevant input parameters. The software shows the results on the user interface and allows to export results for further processing.

A more detailed description of the user interfaces and screenshots are presented in Appendix F.

4.3.4 Validation of the User Interfaces

During the validation, the Health Economics Analysis and Research Team, consisting of 5 members, reported the following issues:

- spelling mistakes,
- values that could be inputted out of the valid range,

- connected percentage values that could add up to a value above 100%.

All reported issues were resolved, and the user interfaces were improved and updated.

These user interfaces were shown to potential future users who had the opportunity to test and thereby validate the software. During this validation, the software was generally classified as "fit for purpose". One additional suggestion came up during this validation phase, which was a bigger font size. This change was implemented after the validation.

4.4 Discussion

We consulted decision makers in sexual health in a three-phase approach process, which was informed by an advisory group. During this process decision makers refined the scope of the disease models and developed user interfaces for the software.

The process was divided into two parts, starting with a questionnaire which was distributed to the target audience and followed up by interviews. Through this process decision makers as future users of the disease model influenced the disease model development and thereby also the final disease model. This increased the relevance of the disease model towards their work. It also increased the transparency of the model and thereby the trust of decision makers towards the model.

4.4.1 STI and Population Priorities

The invitation to the questionnaire was distributed to local commissioners and PHE sexual health staff. A total of nine responses was recorded. The respondents selected chlamydia, gonorrhoea, syphilis and HIV to be the most relevant STIs for their work. The majority voted to include sexual networks for young people, MSM, and BAME in the model.

Upon comparison with the selected STIs we could see that selected networks and STIs map. Chlamydia and gonorrhoea are important STIs in the young people sexual network. Gonorrhoea and HIV are relevant STIs in an MSM sexual network. Lastly, syphilis can be observed in sporadic outbreaks in BAME and MSM networks.

4.4.2 Response Rate of the Questionnaire

The questionnaire was purposely designed to be short (18 questions). It was therefore not detailed enough to capture sufficient detail in every relevant area. Nevertheless, we decided to develop the questionnaire this way to keep the response rate as high as possible as we knew that the number of eligible participants was low. We achieved a response rate of 47%, assuming that the initial invitation was not distributed any further, as we did not receive any information that the invitation was forwarded. All respondents who started to fill in the questionnaire answered all questions, and no incomplete answers were recorded.

Still, the low absolute number of responses brings the validity of the overall results into question. Consequently, multiple issues must be addressed. Firstly, it is relevant to see the breadth of professional roles which were covered by the respondents. As the number of available roles is quite limited and we saw several different job descriptions, we concluded that a reflective number of roles was represented. There was an approximately

equal amount of responses from PHE and from local commissioners.

The introduction video of the questionnaire was viewed 24 times. Considering that my supervisors, the members of the advisory group and I also watched the video, this number is in line with the number of people who got an invitation to participate in the questionnaire study via email.

4.4.3 Selection Bias of Participants of the Questionnaire

We did not capture the geographical position of the jobs in the questionnaire. Therefore, we can only estimate whether the results are biased towards a specific geographic region. As we know that the questionnaire was distributed to PHE-STI staff in Colindale, London, and approximately half of the answers were from PHE it is likely that the answers are biased towards a London-perspective.

We saw that all responses to the questionnaire came from senior members of staff. Due to their experience in the field, these answers were very valuable. Posts as local commissioners are not entry level jobs, which is why the senior staff answering the questionnaire are reflective of the target audience for the software. This was also the audience we tried to reach with this questionnaire.

4.4.4 Included Interventions and Result Presentation of the Software

The variety of interventions which were of interest to decision makers made us decide to find a flexible way of simulating sexual networks, so that all the included interventions could be simulated.

There was no clear decision on how to present the results, which is why we decided to include all suggested options in the software so that future users could decide on their own how to use the software.

4.4.5 Pre-Selection of STIs Included in Questionnaire

4.4.5.1 Number of new cases

For the initial selection, the data on new cases from 2016 was used as this was the most contemporary data available. More recent data from 2018 [152] is now available and I calculated the absolute and relative difference between the 2016 and 2018 values (see table 4.3).

Table 4.3: Number of new STI cases in 2018 as reported by PHE

STI	new cases (2016)	new cases (2018)	abs. diff to 2016	rel. diff. to 2016
chancroid/ LGV/ donovanosis	811	771	-40	-4.93%
chlamydia	204,424	218,095	+13,671	+6.69%
gonorrhoea	36,577	56,259	+19,682	+53.81%
herpes	33,041	33,867	+826	+2.5%
HIV	3,109	2371	-738	-23.74%
Molluscum contagiosum	9,374	8,909	-465	-4.96%
*Mycoplasma Mycoplasma*genitalium	205	1,794	+1,589	+775.12%
scabies	2,395	2,190	-205	-8.56%
syphilis	5,955	7,541	+1,586	+26.63%
trichomoniasis	7,209	8,730	+1,521	+21.10%
genital warts	63,459	57,318	-6,141	-9.68%
candidosis	84,284	76,040	-8,244	-9.78%
hepatitis A	100	49	-51	-51.00%
hepatitis B	1,210	990	-220	-18.18%
hepatitis C	871	546	-325	-37.31%

There was a substantial increase in new gonorrhoea cases. There has also been a rise of anti-microbial strains [40]. *Mycoplasma genitalium* infections have recently emerged as a growing issue. As for gonorrhoea, this is likely due to the rise of anti-microbial resistant strains. Under this light, the decision whether to include *Mycoplasma genitalium* might have to be revisited for the next release of the software if this trend continues. Currently, the absolute numbers are still lower than the ones of other STIs. Whether decision makers would rank STIs differently, based on the new situation could not be assessed.

Another high relative increase can be observed for syphilis, which is already included in the software, and trichomoniasis. Similarly, in a future release of the software, it could be discussed whether trichomoniasis should be included. These changes in new cases over time highlight the dynamic nature of an STI landscape. A STI which is not important at one point might be more relevant later in time. Therefore, a dynamic software such as mine is beneficial to allow users to add or remove STIs to the simulation whenever there is need to.

The largest decrease was seen in the total number of new HIV infection. Still, due to high treatment costs and the lifelong infection duration, HIV remains an important factor for sexual health care in England.

4.4.5.2 Using Costs as Proxy for the Importance of an STI

It is also valid to consider costs associated with a certain STI as an indicator for the importance of the STI. Within the next couple of paragraphs I want to show why I did not use costs to determine the importance of STIs.

The total cost caused by a certain infection is determined by multiple factors such as cost for a single treatment, treatment adherence, treatment efficacy and disease prevalence. For example, an infection with a high prevalence, but low treatment costs might have the same total cost in the population compared to an infection with a low prevalence but higher costs for each treatment. It is possible to estimate the severity of STIs based on the total costs. One option is to account for the prevalence when calculating the costs. The other option is to manually add the prices of all items and services which are needed during the average treatment of this specific STI to calculate the total cost for one treatment.

A disadvantage of the latter option is that it needs detailed information on every option in the treatment pathway, including the percentage of all patients that follow this specific pathway.

Both options need an in-depth cost data set which allows further calculations. This data set should contain nationwide data on the costs for treatments of all considered STIs. Preferably this should be in one dataset to accurately make comparisons between STIs.

A valuable dataset in this context is the sexual health tariff [154]. Unfortunately, this document is not specific enough in key aspects for this research and could therefore not be used to prioritise STIs.

4.4.5.3 Selection Process

The selection process included different perspectives on STIs, namely academic, clinical, and from a decision-making perspective, e.g. commissioners.

The respondents of the questionnaire, i.e. decision makers in health care such as commissioners had the last word in selecting the STIs, as the responses of the questionnaire determined the final set of STIs to be included in the software. This user-oriented development tried tu ensure that the selection fits their needs.

No respondent of the questionnaire added further STIs to the pre-selected list of ten STIs. Thus, I assume that this list was exhaustive.

This selection of four STIs is only valid for usage within England. Due to a different STI landscape in other countries, the selection will likely differ.

4.4.6 Selection bias of Interviewees

The interviewees were chosen from participants of the questionnaire who volunteered to be interviewed. Potential interviewees were not incentivised to participate in the interviews to avoid potential conflicts of interest of people working for public agencies. Therefore the sample of people being interviewed might already be skewed towards decision makers who tend to support decision support models. Interviewer and interviewee therefore tended to agree more with each other, and ideas and user interfaces were challenged less than they would have been in a different setting.

No invitation to the interviews was circulated other than the option to volunteer in the questionnaire. This excluded potentially interested interviewees, which did not fill in the questionnaire. Knowing that the questionnaire took five minutes to complete in comparison to the interview lasting an hour, we assumed that people who were interested in contributing would find some time to answer the questionnaire in any case.

4.4.7 Input of Decision Makers in Model Design

A mixture of PHE and local authority staff were interviewed. The process was extremely helpful and important as the resulting user interfaces looked different from what I expected in the beginning. For example, I expected that decision makers would want an opportunity to amend disease models and sexual networks. During the interviews, I learnt that they do not have enough local data to input for most of the parameters. Hence, we agreed on user interfaces which do not allow changing the disease model structure at all. The user interfaces for the sexual networks which were simpler than I expected them to be. The feedback of the interviewees at this point was that they only need to be able to change very few core parameters, such as *condom use*, and use the default values for the remaining parameters. By including decision makers in the development process the project could be tailored towards the needs of potential users and trying to make the software more user-friendly for them.

The semi-structured interview also showed that many of the barriers that were found to be hampering the use of disease models in policy-making are actually due to the software used. This makes this work very relevant and it also showed decision makers that I am working on these issues in order to provide a solution. This helped the whole development process as all participants were very cooperative and some even spontaneously agreed to have slightly longer interviews than initially planned.

The busy schedule of the interviewees was the reason for some of the interviews being shorter than the advisory group planned them to be. Due to this, not all interface drafts could be discussed with every participant. As a result, drafts which could not be discussed with one participant were prioritised in further interviews to get feedback on all drafts. This way, all user interface drafts could still be iteratively improved.

4.4.8 Transparency of Disease Model

Interviewees stated that the lack of transparency in existing disease models decreased the trust in the results of those models. To counter these doubts, in my disease model I chose a transparent modelling approach. All input can be viewed and adapted by users of the software. The most relevant input can be edited using the user interfaces, less relevant input can be edited through configuration files which are loaded upon start-up of the software. All input parameters are pre-filled with default values derived from national data sources.

All formulas which determine behaviour of the model can be viewed and edited by the user. The code of the software is completely commented and published together with the software (= open source) so that interested readers can download it together with the software.

Being part of the model development process also increased the transparency of the model for decision makers. During this process decision makers had the opportunity to understand and influence the development and thereby build trust into the disease model.

In taking these steps I achieved a higher transparency of my disease model compared to "black-box" models which do not allow user insights into how results are calculated. Nevertheless, this transparency is not for everyone as it requires some technical knowledge to understand the code of the software as well as the syntax of the formulas for the disease models.

4.4.9 Implementation of User Interfaces

I demonstrated in this chapter how user interfaces were developed and how the resulting user interfaces were included in the software. These user interfaces were developed in close cooperation with decision maker and the intention to be user-friendly. The iterative and agile development process of the user interfaces aimed to develop user interfaces fitted to the needs of future users. By including different parties from various areas of expertise, a broad bandwidth of experience could be fed into the project.

By splitting the development of the user interfaces into several steps, the aims of each step were defined clearly, so that goal-oriented working was possible.

It was beneficial to conduct a survey before starting the interview as it "primed" the first set of user interface drafts, which were presented in the first interview. Thus, the interviews could progress faster compared to a stand-alone face-to-face interview series.

Throughout the whole user interface development, it was important to understand the perspective of the future users and their expectations. By seeing the software from their point of view a result was achieved that was different from what I expected when I started this project.

4.4.10 Validation of User Interfaces

The user interfaces were validated by members of the Health Economics Analysis and Research Team at UCL, so that health economists as another potential group of future users could feedback on the usability from their perspective and suitability for potential modelling tasks of the software. The validation was performed after the advisory group checked on the results of the interviews and prepared them for further work. The validation itself did not include decision makers. This was due to several reasons.

I did not consider this as necessary, as the conceptual design of the user interfaces was done in close collaboration with decision makers. The validation on the other hand was on a much more technically detailed level, e.g. to validate input ranges of parameters or find spelling mistakes. It was not necessary to have decision makers do this kind of validation of the user interfaces.

After having contacted many decision makers for the questionnaire and the interviews, I did not find any new decision makers to speak to in terms of validation. Letting the same decision makers validate the results they helped to produce would contradict the principle of validation. Hence, I decided to ask a group of people who have previously not been in contact with the project.

Overall, the validation did further improve the user interfaces, as it showed minor issues in the software which could subsequently be resolved. No major changes of the user interfaces were made due to the validation.

4.4.11 Dissemination

During the co-operative work presented in this chapter contacts could be made which, later on, will facilitate the dissemination of the disease model. The dissemination plans for this

work are presented in Section 9.4.1. Besides introducing the work in journal papers and presenting it on national and internal conferences as posters and talks, we thought of other ways to disseminate this work, which are targeted at decision makers.

The final multi-STI software will be made available for download so that interested people can access it. Moreover, we plan to present this model in workshops, specifically targeted at the relevant audience of the software. In doing so we not only stay in touch with the users of the model, but also are able to further develop and improve the software towards the needs of the users.

4.4.12 Conclusion

In this chapter I addressed a issue, which I found was missing in most models included in my systematic review, which is the thorough inclusion of decision makers in their model development. Including decision makers in the model development process and letting them decide on the scope of the models as well as the user interfaces increased the potential relevance of the multi-STI modelling software. This might incentivise decision makers to use this model in their day-to-day work.

Using the input from stakeholders, as presented in this chapter, the next three chapters detail on the separate parts of the overall multi-STI model for simulating infections, the effect of health care on infections and the spread of infections within a population.

Chapter 5

Disease Models

5.1 Aims and Objectives

In the previous chapter I described how decision makers as future users of the software defined the scope of the software and helped to build its user interfaces.

In this and the following two chapters I look at the different model types in the software and describe how they have been developed and are integrated in the software. All three model types have been developed in close collaboration with experts of the respective areas. Chapter 5-7 should be regarded as one logical unit which have only been separated for readability and structure of the thesis.

In this chapter the models which describe the natural progress of STIs without any influence of a health system, e.g. by treatment, is described. Decision makers as future users of the multi-STI modelling software decided on the STIs to include, which were chlamydia, gonorrhoea, HIV, and syphilis. The influence of health care on the natural progress and the way STIs spread in a population of interest are described in the following two Chapters.

5.1.1 Overview

The first section describes the disease models I developed which were included in the software. As described previously (Section 4.3.1), key decision makers were consulted and chose which STIs to include within the disease models.

The second section explains how I parametrized individual model structures for each of the selected STIs. I inputted these model structures with time-to-event formulas that define the transition in the disease models, found by reviewing the literature. This chapter further shows how I attached costs and utility data to the models.

This chapter only looks at the four STIs that have been included in the software. Fur-

ther sequela models have been developed as well. These are presented in Appendix G to keep the chapter concise. Further disease models which have been developed but are not used in the software are summarised in Appendix G, too, so that future users can easily include them in the software if necessary.

5.2 Methods

In the previous Chapter decision makers decided to include chlamydia, gonorrhoea, HIV, and syphilis in the overall disease model.

The disease models presented in this chapter were developed to represent the natural progress of each infection. The natural progress is described with health states which are connected with each other by transitions.

5.2.1 Model Structure

All models were developed with the same process. A first draft of the model structure was derived from the British Association of Sexual Health and HIV (BASHH)-guidelines on chlamydia [155], gonorrhoea [156, 157], HIV [158, 159], and syphilis [160]. The BASHH-guidelines were chosen over guidelines from other organisations as the thesis adapts an English perspective and it was coherent to use UK guidelines. These guidelines, similar to guidelines from other organisations, provide a good level of detail of the infection progress to derive model drafts. Based on these guidelines I derived health states to describe an infection process and the order in which infected people go through them.

These model structure drafts were refined by comparing them to model structures of other computational disease models. Said other disease models to compare to were found through systematic searches and as false positives - as they only described one STI - from my systematic review, see Chapter 2.

The improved model structures were given to two clinical STI experts to discuss them. During this process the models were, if needed, iteratively refined until experts could successfully validate them.

Face validity of the model structure was achieved by comparing the resulting model structures to model structures of already existing disease models of the same STI and through subsequent expert discussions of the models.

5.2.2 Transitions Between Health States

The search for parameters, such as the time individuals spend in the distinct health states of the model, started by looking at the parameters of already existing models. These models were found through simplistic searches in PubMed and Embase for computational models of these diseases. The search terms were:

- `disease name`, and
- `computational model`.

No limits were applied to this search. The resulting models were the seeds for a citation tracking which was performed to find the original studies these values were taken from. During this process the value of a specific parameter which was used in this model or reported by this study was collected. The parameter value extraction was done for each parameter in the disease models.

I visualised the parameter value origin for each parameter in the disease model, which is presented in Appendix G. The resulting time-to-event formulas are also presented in Appendix G.

All values, which are presented in the following paragraphs apply in the same manner to all individuals. I do not distinguish between first and repeated infection.

5.2.3 Utilities

Jackson et al. published in 2014 a systematic review summarising the utility values of different chlamydia health states [161]. The searches of this review were carried out in 2012, which is why I looked for additional papers published after 2012 to complement their data. Subsequently, EMBASE and PubMed were searched, looking for articles about “quality of life/ quality-adjusted life years” and “chlamydia”. The results were filtered to articles more recent than 2012. In these searches I identified five additional studies [2, 162, 163, 164, 165]. Four of which did not obtain new parameters but used studies which were already included in the review by Jackson.

Sri et al. [163] assessed EQ-5D values of chlamydia positive and negative women to see whether the proportion of women with an EQ-5D value of 1.0 (= perfect health) differed. Based on the review of Jackson et al. [161] and the additional paper, I derived the utility-decrements for the health states included in my chlamydia mode, see Table 5.2 at the end of Section 5.3.1.

The same process has been used to find QoL decrements for the three remaining STI models. QoL-values for gonorrhoea, syphilis, and HIV were taken from models, which have been found during the systematic review described in Chapter 2 and from models which have been found during the parameter search described in this chapter.

5.2.4 Aggregating Outcomes From all Disease Models

This subsection shows how costs and utilities from different sub-models within the software are aggregated to calculate one cost value and one utility value which can then be used for further health economic calculations.

5.2.4.1 Aggregating Costs

Costs can be assigned to health states and to events. This means this model can use continuous costs by assigning daily costs to a health state and multiply this value by the number of days a patient was in this state to get the total costs caused by this patient in this health state. Other costs, like test and treatment costs, are assigned to events and added to the total costs of the model run at the point of time when the corresponding event is executed.

If there is a combined treatment for multiple STIs the costs only arise once to treat both. The same assumptions hold true if a test can screen an individual for multiple STIs at once.

5.2.4.2 Aggregating Utilities

QALYs are not assigned directly in the model. Utility decrements are inputted for every health state in the model. An individual without an infection has a QoL value close to 1. When being infected with one STI the decrement of being in this specific health state is subtracted from the default utility.

Aggregating utilities, on the other hand, is more challenging. There is no agreed approach on how to aggregate utilities to calculate QALYs values over multiple simultaneous diseases, which affect the same bodily functions and areas of health and well-being. If diseases affect different parts, additive methods could be used. However, this assumption does not hold true, when aggregating utility decrements of STIs in this model, as all infections affect the individual in a similar way. Adding up decrements will likely overestimate the total impact of a co-infection.

To account for the potentially smaller utility effect of a second, third, etc. infection, I used the following approach to combine several decrements, which I presented and dis-

cussed at the European Health Economics Association student supervisor conference 2017 in Lausanne. The decrements of all health states the individual is in are sorted so that the highest decrement comes first and the lowest decrement last. The highest decrement is added completely to the total decrement, the half of the second one is added, a third of the third etc., see Equation 5.1.

$$d_{total} = \sum_{i=1}^{n} \frac{d_i}{i} \tag{5.1}$$

Equation 5.1: Combination of different QoL decrements over several, not independent diseases. With d_{total} being the resulting total utility decrement, n being the number of decrements to be considered and d_i being the QoL decrements of all included diseases, sorted by their magnitude, starting with the highest.

5.2.4.3 Example for Calculating QALYs

STI_A has a decrement of 0.2 and STI_B has a decrement of 0.3. Individuals with otherwise perfect health will have a utility of 0.8 if they have STI_A, or 0.7 if they have STI_B.

Using the given formula an individual which has both infections simultaneously will have a total utility decrement of:

$$d_{total} = \sum_{i=1}^{n} \frac{d_i}{i} = \frac{0.3}{1} + \frac{0.2}{2} = 0.4 \tag{5.2}$$

This would result in an overall utility of a co-infection with STI_A and STI_B of 0.6.

5.3 Results

The tables in this section only show the default values for each parameter. The parameters have been derived from literature searches of existing values, tracing back the references to the original study. This parameter origin analysis upon which the parametrisation of all input parameters in this chapter is based can be found in Appendix G.

5.3.1 Chlamydia

The structure of the disease model for chlamydia is displayed in Figure 5.1.

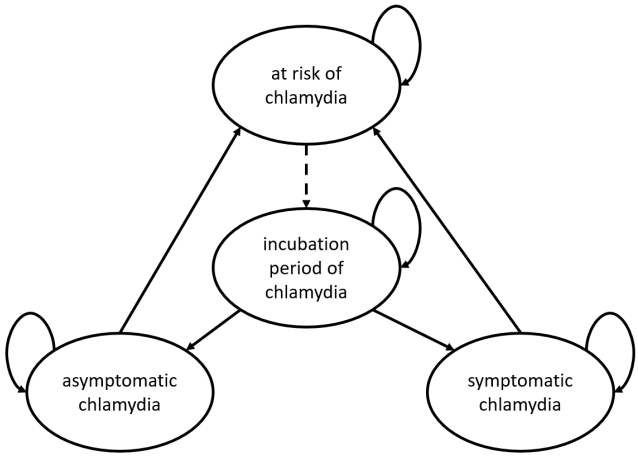


Figure 5.1: Model structure of the chlamydia model

The model consists of five health states. The uninfected state is called "no chlamydia", individuals will be in this state as long as they do not get infected. The first state to enter after an infection is "incubation period". "No chlamydia" and "incubation period of chlamydia" are not connected in this model structure as only the natural progress of the disease is displayed. An infection, on the other hand, is not part of the natural progress of the disease. The transition from "no chlamydia" to "incubation period of chlamydia" through the process of infection is simulated in the sexual network models.

After "incubation period of chlamydia", individuals can have either symptomatic or asymptomatic chlamydia. In these states, individuals, if left untreated, will proceed to "no chlamydia".

The transmission probability for unprotected sex for chlamydia is set to a default value of 33.3% [166, 167, 168] for both male-to-female and female-to-male transmission.

After the incubation period, 74% of all individuals will have an asymptomatic infection.

Table 5.1: Chlamydia values to parametrise time to event formulas

from health state	to health state	sex	value in model
incubation period	asymptomatic chlamydia	♂	10 days
incubation period	asymptomatic chlamydia	♀	12 days
incubation period	symptomatic chlamydia	♂	10 days
incubation period	symptomatic chlamydia	♀	12 days
symptomatic chlamydia	no chlamydia	♂	24 days
symptomatic chlamydia	no chlamydia	♀	238 days
asymptomatic chlamydia	no chlamydia	♂	101 days
asymptomatic chlamydia	no chlamydia	♀	258 days

Looking at the *asymptomatic proportion* which was used by different chlamydia models over time (see Figure 5.2) we can see a trend in the values for males.

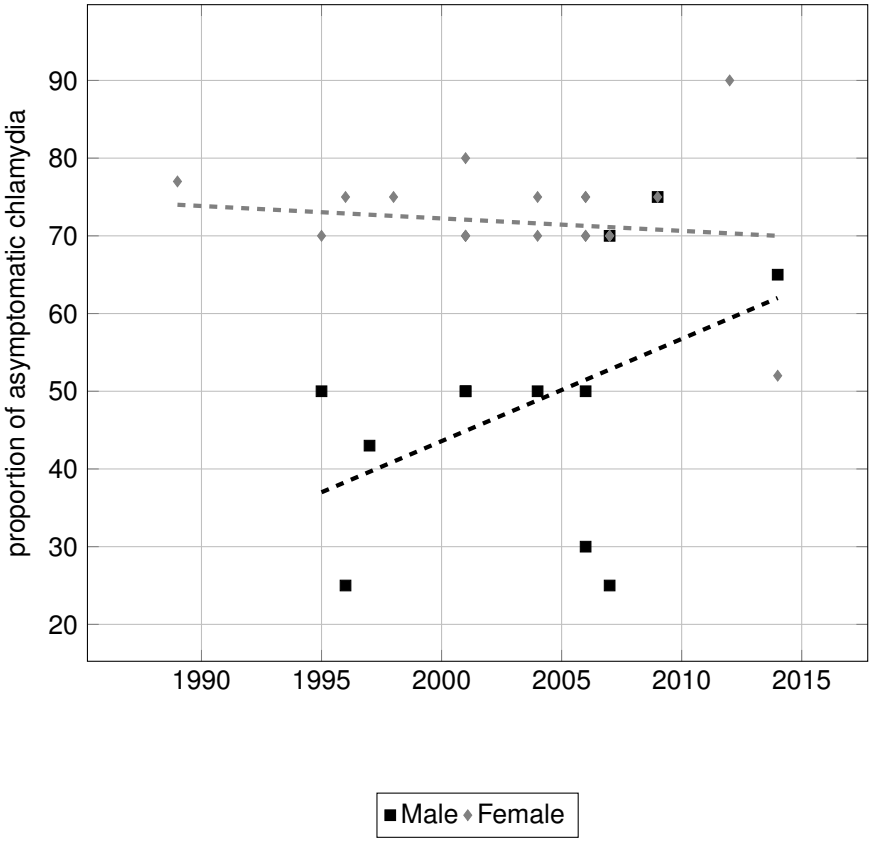


Figure 5.2: Trend of the asymptomatic proportion of chlamydia

The correlation coefficient for female data points is -0.20 showing no significant correlation between the year of the publication and the proportion being asymptomatic, whereas the correlation coefficient for the male data points is 0.44 indicating a moderate correlation between the year of the publication and the proportion being asymptomatic. The latest models are using similar proportions for male and female individuals. I set the probability

of not showing symptoms after "incubation period of chlamydia" for both sexes at a default value of 75%.

The QoL values for each health state of the chlamydia model which are used in the software are summarised in table 5.2.

The first column gives the name of the health state in question, the second and third column list the minimal and maximal QoL decrement which was found in the literature associated with this health state. The last column shows the "best estimate", which is also used in the model. This value is the mean value of all values considered [2, 161, 162, 163, 164, 165].

Table 5.2: Quality of life decrements for all chlamydia health states

Health state	Min decrement	Max decrement	Best est. for decrement
no chlamydia	0.0	0.0	0.0
incubation period	0.0	0.1	0.0
symptomatic chlamydia	0.1	0.3	0.158
asymptomatic chlamydia	0.02	0.33	0.095
chlamydia immunity	0.0	0.1	0.0

5.3.2 Gonorrhoea

The natural progress of gonorrhoea is modelled as shown in Figure 5.3

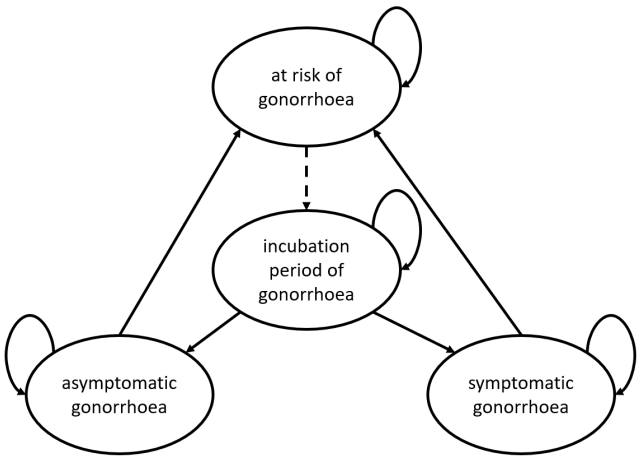


Figure 5.3: Model structure of the gonorrhoea model

The gonorrhoea model is similar to the chlamydia model. After an infection with gonorrhoea, individuals will be put in "incubation period of gonorrhoea". After that individuals can either have a symptomatic or asymptomatic infection. Even if left untreated, individuals will return to no gonorrhoea.

Infected individuals can either have an asymptomatic or symptomatic gonorrhoea in-

fection. 50% of all gonorrhoea infections of male individuals will be asymptomatic (66% for female individuals). QoL decrements were associated with each health state in the gonorrhoea model, see Table 5.4.

Table 5.3: Gonorrhoea values for to parametrise time to event formulas

from health state	to health state	sex	value in model
incubation period	asymptomatic gonorrhoea	♂	5 days
incubation period	asymptomatic gonorrhoea	♀	10 days
incubation period	symptomatic gonorrhoea	♂	5 days
incubation period	symptomatic gonorrhoea	♀	10 days
symptomatic gonorrhoea	no gonorrhoea	♂	30 days
symptomatic gonorrhoea	no gonorrhoea	♀	50 days
asymptomatic gonorrhoea	no gonorrhoea	♂	118 days
asymptomatic gonorrhoea	no gonorrhoea	♀	118 days

The gonorrhoea model was inputted with the QoL-values shown in Table 5.4.

Table 5.4: Quality of life decrements for all gonorrhoea health states

health state	QoL-decrement	reference
no gonorrhoea	0.00	n/a
incubation period of gonorrhoea	0.00	n/a
asymptomatic gonorrhoea	0.05	est. based on chlamydia and [169]
symptomatic gonorrhoea	0.1	est. based on chlamydia and [169]

5.3.3 Human Immunodeficiency Virus (HIV)

The natural progress of HIV was modelled as shown in Figure 5.4. The grey rectangles reflect the stages of an HIV infection as presented in Section 1.3.3.3. For technical purposes two of these stages are divided in further health states, depicted by white ellipses. The health state "HIV death" is not displayed in this figure due to the otherwise decreased readability as all other health states are connected with it.

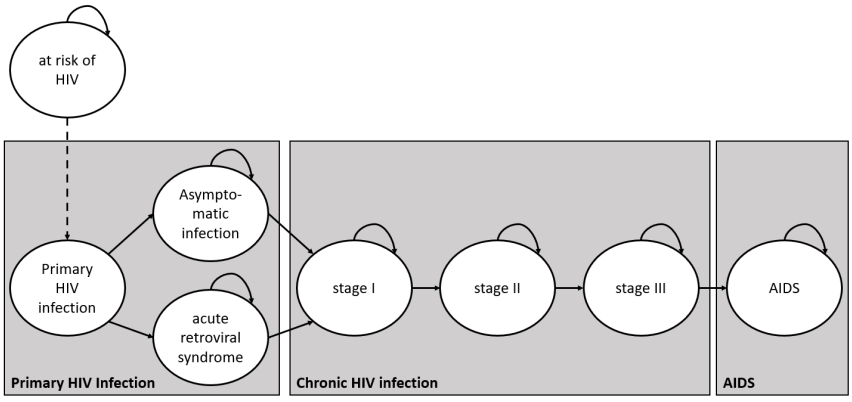


Figure 5.4: Model structure of the HIV model, "death"-state not displayed

After acquiring HIV, individuals have a "primary HIV infection" this stage is made up from three different health states in the model. First, all individuals enter the health state "primary HIV infection". This health state is technically necessary and all individuals will only stay for one day in this health state. In this health state all individuals who acquired HIV are gathered so that a random number can be drawn to determine whether a specific individual enter the health state "acute retroviral syndrome" or not. 50% of the individuals will enter the health state "acute retroviral syndrome". The other half will not show symptoms and be in the health state "asymptomatic infection".

Unless treatment is taken individuals will only be able to stay in their current health state for a certain amount of time or progress to a "worse" health state, depicted further to the right-hand side in the Figure.

After a "primary HIV infection" individuals will progress to "chronic HIV infection". To simulate the increasing severity of this stage over time, the "chronic HIV infection" is divided for technical purposes in three health states (chronic HIV I, chronic HIV II, and chronic HIV III), with increasing mortality and increasing QoL-decrement for each stage, see Tables 5.5 and 5.6. The split up of the "chronic HIV infection" into several health states has been made analogous to other HIV-models [170, 171, 172]. All health states describing the "chronic HIV infection" last together about 8 years, assuming no treatment is given to the individual.

After "chronic HIV infection" individuals progress to "AIDS" which is reflected by the health state "AIDS". Untreated individuals remain in the health state "AIDS" for about 3 years before they die.

In each of these health states individuals are also subject to HIV-related mortality. The mortality of each health state is greater than the mortality of the previous health state. If left untreated, it is not possible that individuals stay indefinitely in a health state or can return to a less severe health state.

To differentiate between death due to the underlying normal mortality and death due to HIV a health state "HIV dead" was introduced. In addition to the normal mortality, an excess mortality per year of 1.0% for all untreated individuals in the health state "chronic HIV I" is added to the normal mortality, 0.7% for individuals in "chronic HIV II", and 2.4% for individuals in "chronic HIV III". The higher excess mortality for "chronic HIV I" in comparison to "chronic HIV II" is explainable as the health state "acute retroviral syndrome" has no excess mortality. Therefore the excess mortality of "acute retroviral syndrome" is simulated in the health state "chronic HIV I". If left untreated, all patients in the health state "AIDS"

will die after 3 years.

A short summary, which shows the average duration of stay in each health state is given in table 5.5. The complete input, including all references is given in Appendix G on page 365.

Table 5.5: HIV values for to parametrise time to event formulas

from health state	to health state	value in model
primary HIV infection	acute retroviral syndrome	1 day
primary HIV infection	asymptomatic infection	1 day
acute retroviral syndrome	chronic HIV I HIV	35 days
asymptomatic infection	chronic HIV I HIV	35 days
chronic HIV I	chronic HIV II HIV	994 days
chronic HIV II	chronic HIV III HIV	898 days
chronic HIV III	AIDS	1020 days
AIDS	HIV dead	1110 days

The health states in this HIV-model are inputted with the QoL-decrements presented in Table 5.6.

Table 5.6: Quality of life decrements for all HIV health states

health state	QoL-decrement	reference
no HIV	0.0	n/a
primary HIV infection	0.05	n/a
asymptomatic infection	0.0	n/a
acute retroviral syndrome	0.10	[170, 171]
chronic HIV I	0.08	[170, 171]
chronic HIV II	0.10	[170, 171]
chronic HIV III	0.11	[170, 171, 172]
AIDS	0.16	[170, 171]

5.3.4 Syphilis

The model structure presented in Figure 5.5 was used in the syphilis model of the software.

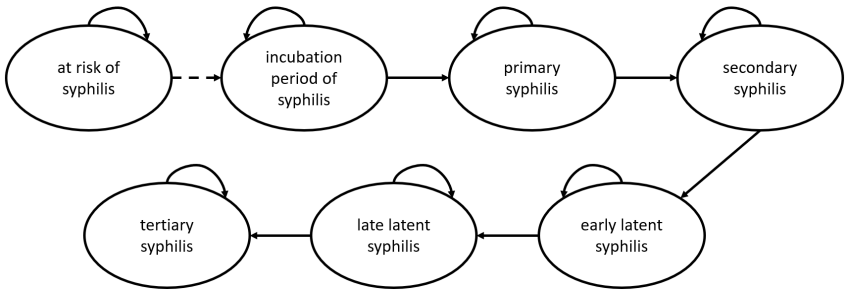


Figure 5.5: Model structure of the syphilis model

Like the HIV model, it is not possible for an individual within the natural course of the disease to reach a "healthier" state after they have already been in a worse state. It is possible for individuals to stay a long time in certain health states.

After an infection, individuals may go in this order through the following health states; "incubation period", "primary syphilis", "secondary syphilis", "early latent syphilis", "late latent syphilis", or "tertiary syphilis". They may remain indefinitely in "early latent syphilis" or "late latent syphilis". When individuals reach "tertiary syphilis" further complications such as "neurosyphilis" or "cardiovascular syphilis" are possible. Complications are regarded as sequelae and modelled in separate models.

Without treatment, the health state of an individual with syphilis will continuously get worse. Treatment is possible for all health states. 25% of all individual in "early latent syphilis" have at least one episode of recurrent syphilis. Only 40% of all individuals will transit from "late latent syphilis" to "tertiary syphilis". Individuals in the health state "tertiary syphilis" will develop further syphilis sequelae, which are "neurosyhpilis", "cardiovascular syphilis", and "gummatous syphilis". 48% of individuals having sequelae will have "gummatous syphilis", 23% will develop "cardiovascular syphilis" and the remaining 29% will have "neurosyphilis". These are modelled in SI-sequelae models. If syphilis is treated, "gummatous syphilis", "cardiovascular syphilis", and "neurosyphilis" will be treated as well.

An overview of the time individuals spend, on average, in each health state is given in Table 5.7. The model adds a random component of +/- 10% to each of the values presented in the last column.

Table 5.7: Syphilis values for to parametrise time to event formulas

from health state	to health state	value in model
incubation period of syphilis	primary syphilis	21 days
incubation period of syphilis	secondary syphilis	21 days
primary syphilis	secondary syphilis	31 days
secondary syphilis	early latent syphilis	125 days
early latent syphilis	recurrent syphilis	183 days
recurrent syphilis	early latent syphilis	90 days
early latent syphilis	late latent syphilis	183 days
late latent syphilis	tertiary syphilis	3650 days

This syphilis model was inputted with QoL-decrements as presented in Table 5.8.

Table 5.8: Quality of life decrements for all syphilis health states

health state	QoL-decrement	reference
no syphilis	0.00	n/a
incubation period of syphilis	0.00	n/a
primary syphilis	0.01	[173]
secondary syphilis	0.04	[173]
early latent syphilis	0.01	est.
recurrent syphilis	0.04	est. based on [173]
late latent syphilis	0.01	est.
tertiary syphilis	0.10	[173]

5.3.5 Initial Prevalence

The initial prevalence varies depending on the simulated population. All values which are used in the software are summarised in Table 5.9. Details on how these networks were chosen can be found in Chapter 4. For the "young people" sexual network, the first two rows are used. For the "general population" sexual network, all age bands in the table are used. For the MSM and BAME the initial prevalence was not stratified by age. The values in the table were taken from studies from Hafeez et al. [174], Coyle et al. [175], and a PHE report on HIV testing [176].

Table 5.9: Initial prevalence of chlamydia, gonorrhoea, syphilis and HIV for different age bands and risk groups

	chlamydia		gonorrhoea		syphilis		HIV	
	women	men	women	men	women	men	women	men
15 - 19	7.5%	10.0%	0.7%	1.7%	0.009%	0.5%	0.5%	0.9%
20 - 24	12.1%	19.8%	1.0%	4.5%	0.03%	1.4%		
25 - 34	6.0%	20.0%	0.7%	9.6%	0.04%	1.5%	0.4%	1.3%
35 - 44	1.1%	5.6%	0.2%	4.4%	0.01%	1.3%	0.8%	1.6%
45 - 54	0.4%	3.0%	0.1%	2.7%	0.0004%	1.2%	0.9%	1.6%
55 - 64							0.5%	0.9%
65+	0.0%	0.2%	0.0%	0.1%	0.0001%	0.1%	0.1%	0.3%
MSM	4.5%	23.1%	0.45%	24.5%	0.015%	8.4%	0.5%	1.3%
BAME	14.4%	23.2%	0.54%	5.4%	0.018%	1.42%	0.9%	0.8%

5.3.6 Validation

Face validity of all models was achieved through discussions with experts and reviewing other model structures. Experts confirmed that all model structures were reasonable. Upon comparison with other models, no relevant differences between existing models and my models could be found.

5.4 Discussion

In this chapter, I presented STI models for chlamydia, gonorrhoea, HIV, and syphilis which were included in the multi-STI modelling software. These models describe the natural progress of the disease by using health states which are connected by transitions. Each health state is associated with a utility decrement, which are aggregated to a single utility value for each individual. These are multiplied over time to calculate QALYs.

5.4.1 Approach to Developing Models

I used a threefold approach to develop the individual STI models for the software. In a first step the model structure was developed. This structure was then parametrized by transition probabilities and in a last step costs and utilities were added to the model.

This approach was chosen based on ISPOR-guidelines which recommends separating conceptualizing a model from its parametrisation. This avoids adapting the model structure to the available parameters instead of finding the best possible model structure. One might not be able to parametrize this model structure fully, which then shows the need for further research [15, 135, 140, 177, 178, 179, 180].

While developing these models I also found that there were parameters on which I could not find sufficient literature. Due to resource constraints I was not able to conduct clinical studies to obtain better values, which is why I had to use estimates. In the validation of the models I observe how much of an impact an incorrectly estimated value might have on the overall results of the model.

5.4.2 Model Structure

The four STI models consisted of a total of 23 health states (chlamydia= 4 states, gonorrhoea= 4 states, syphilis= 7 states, HIV= 8 states). If they were to be simulated in a single model this would result in a total number of (4 * 4 * 7 * 8 =) 896 health states, not considering sequelae models. This shows that splitting up the disease models into separate models drastically reduced the overall complexity of the disease models.

5.4.2.1 Chlamydia Immunity

A debatable health state in the chlamydia model structure is "(transient) chlamydia immunity". As of now, it is not clear whether immunity to chlamydia exists and therefore it is unclear whether this health state should or should not be included in the model structure of the chlamydia disease model. This question is linked to the question of whether a chlamydia vaccination exists or could be developed. Recent reviews [181, 182] conclude that there

are no vaccines so far, but there is a possibility of developing one soon. As an artificially gained immunity could be possible, we will have to consider whether natural immunity could develop after a chlamydia infection.

First, we have to acknowledge that the reinfection with chlamydia is common, a systematic review showed that 13.9% of infected women will have another infection [183]. Thus, natural immunity does not develop after every episode of chlamydia. Furthermore, there is no evidence on the length of a naturally gained immunity. After hearing experts' opinions on this topic, I understand that, if immunity exists at all, it most probably will only be a transient immunity and of short duration. Permanent immunity can most likely be excluded, because of the existence of patients who have multiple episodes [184].

Since patients can get reinfected after a successful treatment, I assume that no immunity exists after a successful chlamydia treatment. This might be due to the fact, that medication helps the immune system to overcome the infection. Therefore, the immune system does not have to cope with the bacteria on its own and will not develop immunity. Assuming transient immunity only exists after a full episode of chlamydia infection which is defeated without any treatment, we still need to answer two main questions; under which conditions a transient immunity could develop and how long does the transient immunity lasts.

Factors which define the impact of an infection on the health of an individual and their immune system could be whether the infection is symptomatic or asymptomatic as well as the duration of the infection. Symptoms are usually indicators of the body fighting the infection. This means that individuals who show symptoms tend to have a stronger immune response. But we do not know whether the intensity of the response from the immune system is linked to the development of immunity.

Asymptomatic infections last longer; the immune system is exposed to the pathogen for a longer amount of time which would give it a better opportunity to develop immunity.

As we saw there are arguments for both sides, which is why I decided that we do not definitely know whether (transient) chlamydia immunity exists. Therefore, I did not include this health state. The flexible nature of the modelling software allows the fast and easy inclusion of this potential health state to further investigate the matter using the model.

5.4.3 Transitions

Tables 5.1, 5.3, 5.5, and 5.7 only give an estimate of how long individuals stay in each health state on average. The number of days is also influenced by factors other than sex,

such as age and other infections at the same time, and by chance. The formulas which are used calculate the event time are shown in Appendix G. More information on the origins of these values, including all references which were considered, is given in Appendix G.

All time-to-event durations present in Tables 5.1, 5.3, 5.7, and 5.5 are estimated mean values for the simulation. During the simulation, a random component is added to these values. Important factors driving the time in a given health state have been presented but the actual time individuals spend in these health states varies due to this random component.

There is no good evidence for male-to-male and female-to-female transmission probability, which is why the default values for these transmissions are assumed to be the same as the male-to-female transmission and female-to-male transmission, respectively.

It was interesting to see an increase in the proportion of asymptomatic chlamydia infections in men over time, see Figure 5.2. A possible reason for this is that the detection of cases of asymptomatic chlamydia in men has become better over the years. Whereas chlamydia research in the 80s and 90s has been focussing on women, men might have been neglected. Additionally, women are assessed for chlamydia when pregnant. These could be potential reasons for not finding the same proportion of asymptomatic cases in both sexes. This is why I suggest that the trend line we can see does not reflect a real increase in the proportion of chlamydia in men but rather a decrease in the observation bias.

5.4.4 Costs

I used costs from the sexual health tariff [154] as default values in the model. These costs should be amended by every user, as costs are negotiable and the costs for the same intervention or drug can differ from one local authority to another. Therefore I decided to not present the default costs to avoid confusion.

Furthermore, costs also depend on the adopted perspective and can fluctuate heavily depending on the perspective. For this default parametrisation, a "health and social care cost perspective" was adopted. If a user wants to do a calculation with another perspective, e.g. societal perspective all costs in the model must be amended manually.

5.4.5 Utilities

Utility values for Chlamydia were taken from a systematic review by Jackson et al. and complemented by other studies on chlamydia health states which were published after the systematic review. Utility values for other STIs were found by individual literature searches.

Usually utility values which were calculated using different ways to derive preference based utility or taken from different sources should not be compared to each other. Unfortunately, I had no dataset available which included all relevant utility-decrements to completely input the model. Comparing the used utility-decrements raised no questions as the size of their relations to each other seemed to be reasonable. This face-validity check was done by STI clinicians.

Users of the model need to be aware of that utility-decrements are taken from different sources, some of which have been assessed by different methods. This issue must be discussed and considered when interpreting results of the model.

The model itself was developed in such a way that updating utility decrements is straightforward. If ever a dataset becomes available which covers all utility decrements this can be used to replace the utility values currently inputted in the model.

5.4.6 Approach of Aggregating Utilities

My arithmetic approach of aggregating utility-decrements orders all utility decrements by their size and adds the whole of the largest decrement to the overall decrement, a half of the second largest, a third of the third largest, etc.

It was inevitable to use an arithmetic approach to determine the overall utility decrement as I had no dataset available to me which showed utility decrements for all combinations of health states which could occur in the model. Probably such a dataset does not even exist.

The arithmetic approach guarantees that the overall decrement is always smaller than the sum of all individual decrements and larger than the largest individual decrement. It thereby accounts for the fact that decrements are not completely independent of each other.

The overall decrement must be larger than the largest individual decrement. This is to account for the fact that an individual which has multiple infections cannot have a better overall QoL than an individual who exclusively is in only of the infection health states the other individual is in.

On the other hand, the overall QoL should be smaller than the sum of all individual decrements, as the QoL-decrements regarded in this model are not independent of each other. All infections affect a person in a similar way. Therefore a second concurrent infection does not have as much of an additional impact on an individual as a first infection had.

5.4.7 Patients' Awareness of the Disease

A closer look at the model structure uncovers that there is no way to describe the patient's awareness of the disease. The disease models only describe the natural progress of the disease, the clinical pathway describes what happens after screening/ treatment etc., and the sexual contact network describes how sexual partnerships form and dissolve and people contract infections. None of these models has a place to describe whether the individual knows whether they are infected.

The clinical pathway model makes implicit assumptions about this parameter. A defined proportion of all individuals regardless of their health status will look for a STI test. Additionally another proportion of all symptomatic patients will also actively look for STI tests a treatment, respectively.

The real awareness of the presence of a disease is hard to access, harder than determining the proportion of symptomatic cases of a disease. Therefore, I decided to not include this attribute in the model. Though, the parameters "proportion of positively tested individuals who start treatment" and "symptomatic individuals who start treatment" might be indicators for awareness. Both parameters are included in the clinical pathway model.

5.4.8 Conclusion

In this chapter I presented STI models for chlamydia, gonorrhoea, HIV, and syphilis. The models interact with each other by referencing health states of other models in the time-to-event formulas.

The models have been inputted with default values for costs and utilities. All input can be changed, e.g. to simulate a local scenario with specific costs or to account for changes in the underlying knowledge base, e.g. to amend utility-decrements. If changes in the knowledge base occur the underlying models, including health states and time-to-event formulas can be edited as well.

The presented models can be used "out-of-the-box" with the presented default values. The option to customise input allows examining specific scenarios with the model. It also allows updating the models if changes in the knowledge base occur or specific scenarios need to be modelled. This promises to make use of the models over an extended period of time.

Chapter 6

Clinical Pathway Models

6.1 Aims and Objectives

This is the second of the three chapters describing the different models used in the overall multi-STI model. In the previous chapter I explained the models which simulate the natural progress of a disease.

Health care systems can have an impact on the natural progress, i.e. by giving treatment to infected patients. To be able to simulate these effects in the overall multi-STI model another component, describing the effect of the health care system onto the natural progression is elementary. As these models describe different clinical pathways patients can take, I call those clinical pathway models.

The development of the clinical pathway model and their parametrisation and validation is described in this chapter. Given the target users of the software are decision makers in England, this chapter specifically looks at models for English settings. The relevant pathways to simulate within health care and public health have been chosen by decision makers.

6.1.1 Overview

This chapter describes how the natural course of a disease can be influenced by interventions such as tests and treatments. I developed so called clinical pathways to simulate this.

These clinical pathways are needed to examine bits of the real world which can be influenced by decision makers, i.e. by funding a new treatment or deciding to change the scope of opportunistic screening.

6.2 Methods

Clinical pathways are one of the three model components the overall STI model of this thesis is built of. The other two are disease models, see Chapter 5, and sexual networks, see Chapter 7.

A clinical pathway is described by connected pathway elements. A pathway element can be a test or a treatment. The different pathway elements are linked to each other.

Pathway elements which are connected form a treatment pathway which is not necessarily linear. It can split up into several pathways or repeat certain pathway elements, such as retests, multiple times. Depending on the simulated reaction of individuals and test results, which are affected by specificity and sensitivity, individuals in the same health states might take different paths. Parameters to input the models were taken from other models while doing the systematic review or gathering the data presented in Appendix G. If no other model used this parameter before literature was searched to input the parameter.

A health and social care perspective (see Section 1.5) was adopted when the clinical pathway was set up and when pathway elements were inputted.

6.2.1 Tests

Clinical tests are defined by their specificity and sensitivity. A positive test result might trigger a treatment event for the tested STI. All tests, which have been included in the software are summarised in Table 6.1. Sensitivity and specificity have been inputted using values found in other modelling studies as presented in Appendix G. To calculate this value, I looked at all studies included in the reviews for the individual STIs, also see Appendix G. The mean value of all those studies which reported sensitivity and/ or specificity of a certain test was calculated and is reported in said table.

Table 6.1: STI tests included in the software

Test for	sensitivity	specificity	triggers treatment	est. based on
chlamydia	86%	97%	either azithromycin or doxycycline treatment	[168, 185, 186, 187]
gonorrhoea	86%	97%	ceftriaxone treatment	[188, 189, 190]
HIV	99%	99%	antiretroviral treatment	[191]
syphilis	84%	98%	penicillin treatment	[173, 192]

6.2.2 Treatments

Treatments are described in the software by stating their adherence and efficacy. A treatment event can be followed by other events, such as retests, or further treatment. All those

parameters are summarised in Table 6.2. Like the input of the models, the treatment parameters were also taken from miscellaneous other modelling studies presented in Appendix G. I used the mean value of all other studies as an input for my model.

Table 6.2: STI treatments included in the software

treatment name	for STI	adher.	efficacy	followed by	est. based on
ART	HIV	99%	83%	further ART, individual will be in health state "HIV stage 1"	[193]
PrEP	HIV	85%	88%	further PrEP, individual will stay in health state "no HIV"	[194]
azithromycin	chlamydia	99%	95%	chlamydia retest after 60 days, individual will be in health state "no chlamydia"	[195, 196, 197] [198, 199, 200]
doxycycline	chlamydia	79%	96%	chlamydia retest after 60 days, individual will be in health state "no chlamydia"	[195, 196, 197] [198]
ceftriaxone	gonorrhoea	99%	95%	gonorrhoea retest after 90 days, individual will be in health state "no gonorrhoea"	[166, 188, 201]
penicillin	syphilis	99%	95%	syphilis retest after 7 days, individual will be in health state "no syphilis"	[202, 167, 203]

6.2.3 Opportunistic Chlamydia Screening

All 16 to 24-year-old individuals in the software are eligible to get a chlamydia test through the NCSP. In one year 25% of all people in this age range will get a test through this program in addition to other test schemes which are also available to the young individuals as reported in NCSP reports [204, 205].

Whereas the NCSP officially only tests for chlamydia most tests which are conducted are combined chlamydia and gonorrhoea tests [206].

6.2.4 High-risk HIV Testing Recommendation

The NHS recommends people with a higher risk of acquiring HIV to get tested frequently, i.e. every three months [207]. In the model I defined high-risk individuals as MSM who are accepting concurrent partnerships. I assumed that not every-high risk individual will follow this suggestion, based on a study by Elmahdi et al. [208]. In the software 25% of all MSM who are willing to have concurrent partnerships get an HIV test within three months.

6.2.5 Face Validity

The resulting set of connected pathways was shown to two experts, one decision maker in sexual health and one sexual health physician. Those two were chosen due to their experience of working in the field of sexual health. They validated connections of the pathway elements, the efficacy of treatments, and the sensitivity and specificity of tests. The experts validated the pathway model based on their personal experience without any additional literature at this moment.

During the validation, some issues were raised and subsequently corrected:

- azithromycin is not capable of curing gonorrhoea and chlamydia simultaneously
- a pathway which allows testing of individuals without a specific reason needs to be added
- the relevant group to receive repeated HIV tests should be "MSM with multiple partners or frequent partner change" instead of "MSM"

I present the improved and validated version of the clinical pathway model in this chapter, as all issues could be addressed.

6.3 Results

The clinical pathways which are described in this next section are simplified pathways which reflect the current standard of care within the NHS. An overview of all included pathways is shown in Figure 6.1.

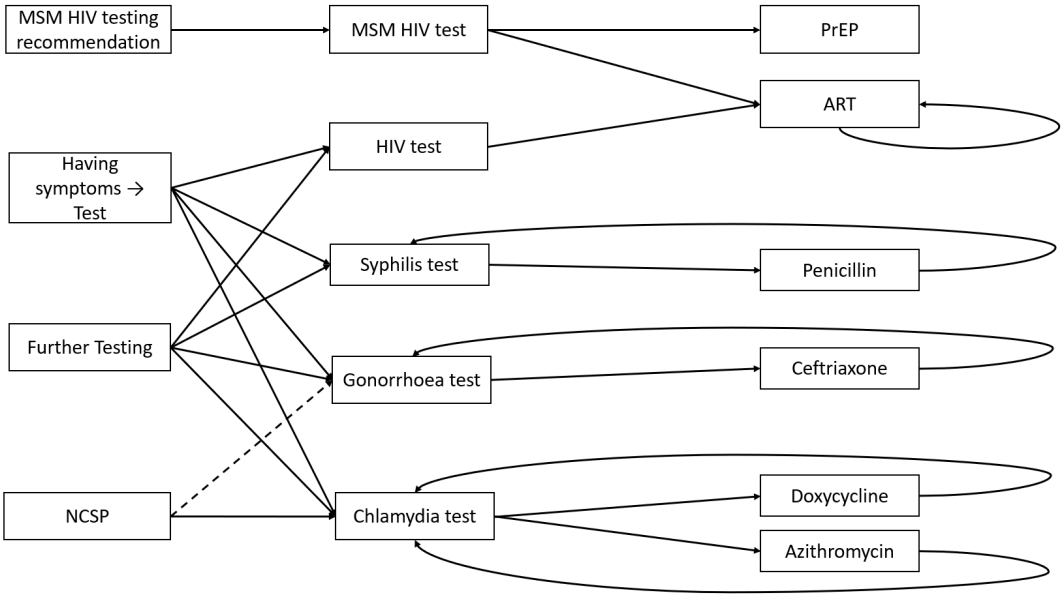


Figure 6.1: Clinical pathways simulated by the default parametrisation of the software. Individuals enter the diagram on the left hand side through inclusion in any testing scheme. After a positive test, treatment can be initiated. The treatment can be permanent or followed by a retest.

Individuals enter this figure on the left-hand side, either through systematic screening offers, such as NCSP (see Section 6.2.3), noticing symptoms (see Section 6.3.1), ordering a STI test kit without these reasons ("further testing", see Section 6.3.2), or because they should be tested regularly for HIV as they are under a higher risk of acquiring HIV, e.g. MSM with frequent partner changes. Individuals who were identified through partner notification will receive a test for the same STI(s) their partner was tested positive for.

Whereas individuals who got tested because of the NCSP will only get a test for chlamydia, individuals who go for a test without a specific reason or individuals who get a test due to symptoms will receive an STI test for all STIs included in the software. Individuals who should be routinely checked as part of the HIV high-risk screening recommendation will only receive an HIV test. If this test returns positive, they will be suggested to start ART. Only if they received the HIV test through the "HIV high-risk" testing recommendation they will be offered PrEP in case of a negative test. In any other instance, a negative HIV test

will have no effect, a positive test result will still trigger the suggestion to start antiretroviral treatment.

All other positive test results might result in a specific treatment for the tested STI, depending on the decision of the individual.

Separate from the pathways shown in Figure 6.1, there is another way individuals can get tested. This happens through partner notification when a partner has a positive STI test. In Section 6.3.3 I explain how partner notification is implemented in the software.

6.3.1 Getting STI Test After Showing Symptoms

Individuals with symptomatic infection can decide to get tested. Whether an individual will get tested after showing symptoms depends on the health states they are in at that moment. Not all individuals who enter symptomatic health states will look for treatment. This is reflected in Table 6.3 which lists all health states having a probability of an individual getting tested greater than 0%. The estimates for people looking for a test are based on the estimates of the infectivity of the infection.

Table 6.3: Probability of an individual getting a voluntary STI test based on their health status.

Health state	Probability	est. based on
symptomatic chlamydia	33%	[189, 185, 209, 210]
symptomatic gonorrhoea	50%	[167, 211, 212, 213]
primary syphilis	10%	[214, 215, 202, 216, 217]
secondary syphilis	20%	[214, 215, 217]
early latent syphilis	1.5%	[214, 215, 202, 216]
recurrent syphilis	15%	[214]
tertiary syphilis	15%	[214]
acute retroviral HIV	30%	[167, 215, 218, 219, 220, 221]
stage 1 HIV	3%	[215, 218, 219, 222, 223]
stage 2 HIV	16%	[215, 218, 219, 221, 223, 224]
stage 3 HIV	60%	[215, 218, 219, 221, 223, 224]
stage 4 HIV	70%	[215, 218, 219, 221, 223, 224]

Upon entry into this health state, a random number is drawn. Based on this value and the threshold from Table 6.3 the software decides whether this individual will search for a STI test within the next days. If individuals decide to get tested, they will always receive a test for all STIs included in the software.

6.3.2 Further Testing

Individuals might decide to get an STI test without having symptoms or through partner notification. This is reflected by a proportion of 5% of all individuals in the simulation getting

an STI test within one year. Individuals might decide to do this because of recent partner changes or seeing it as a good practice to do so [225]. As these mechanics cannot be completely reflected in the software, I assumed 5% of the modelled population looking for a test through this pathway. This value can be amended by the user of the model.

6.3.3 Partner Notification

Partner notification or contact tracing always starts with an infected person, also called the "index case". Partners, current and recent, of the index case are invited to be screened for STIs. Contact tracing is an important part of interventions to prevent the spreading of STIs [226].

During partner notification, all current and recent partners should be contacted for further testing. The look-back time for recent partnerships should be appropriate, NCSP suggests, based on BASHH guidelines, six months [204]. Due to necessary simplifications the look-back time in the model is fixed rather than dependent on the whether the infection was symptomatic or asymptomatic. In my software, the term *recent partner* refers to an individual with whom the index case has had a partnership and sexual contacts. Based on the NCSP look-back time, the look-back time in the model is set to a value of six months.

Partner notification is implemented in the model as part of the treatment pathway model. When an individual is tested positive for a certain STI their current and recent partner(s) will get a test offer for the same test. The interval of how long to look back can be adjusted by the user of the model and is set to six months (=183 days) by default based on the NCSP recommendation [204].

In the real world there is a delay between the point when a person receives a positive test result and the point when a partner (current/ recent) gets tested. I simulated this delay in the model. Within this period the positively tested individuals might already start treatment. In practice partner notification should occur in a timely fashion within four weeks after the diagnosis of the index case [227]. Based on a systematic review by Mathews et al. I estimated the default duration of partner notification to be three days, for current and recent partners [228]. Users of the model can adapt these delays separately.

Whether an individual will be tested depends on whether this individual was actually informed by their partner and whether the individual decides to get tested. Within the model, these two probabilities are summarised in one probability which should be the product of both aforementioned probabilities. Different thresholds for current and recent partners can be defined. In the NCSP audit, a partner notification rate of 0.6 per index case was

reported. This was translated in the software to a 60% likelihood of informing any partner, either recent or current. If the index case had more than one partner within the notification interval, each one will be notified with a 60% probability [204].

6.4 Discussion

The clinical pathways model can simulate a simplified reflection of the standard of care for STIs in England. Simplifications had to be made, as simulating every possible pathway was not feasible and, in fact, a model by definition is a simplification of the real world. The software still models treatments and tests and their interdependencies in more depth than other models we found in the systematic review.

Treatments and tests and their connections were defined in a flexible way. This allows future users to define more tests/ treatments or design more complex pathways.

6.4.1 Partner Notification

In the model each partner (recent and past) of an infected individual will receive a test offer for the same test with a probability of 60%. If an individual only has one partner this translates to a 60% probability of informing the partner about the disease and offering an STI test. The notified partner can decide whether to accept or decline this offer, with a 90% probability of accepting it. Combining these two probabilities leads to the actual number of STI tests conducted due to partner notification, which is $(0.6 \cdot 0.9 =)$ 0.54. This number is slightly lower than the reported value of 0.6 tests per index case, as reported by NCSP. This is countered by the fact that some individuals in the model will have more than one partner. As each of those is informed with a likelihood of 60% the overall number of tests per index case should be slightly higher than 0.6, depending on the number of individuals with concurrent partnerships in the model.

The real-world partner notification pathways have been simplified to include them in the software. I do not differentiate different ways of contacting partners, which could be by telephone or by letter. I also do not differentiate between contacting partners by the patients themselves or through the STI clinic.

6.4.2 Validation

The validation of this part was a face-validation of the model by two experts who had no additional information/ evidence to compare the parameters of the model with. This raises the question of how valid the validation process is. Based on the results from the systematic review this is one of the most complex ways to reflect tests and treatments in a model I have encountered so far. Therefore, it was not possible to achieve face validity by comparing it to similar models, as similar models, to my best knowledge, do not exist. The most important part of the validation was to confirm that all relevant connections of the real

world pathways are reflected in the model. This could be achieved by consulting experts. Uncertainty remains on whether the inputted parameters are correct. As no objective data source for these parameters could be found, expert elicitation was used. Expert elicitation has previously been used by other research teams to successfully inform decision models [229]. Whereas the elicitation process was less sophisticated as it was only applied on a qualitative and not on a quantitative level in this study, the resulting clinical pathway model could be used in this manner as a prototype.

No further validation, e.g. sensitivity analysis, was done for this part of the model.

6.4.3 Perspective and Costs

For health economic evaluation various perspectives can be used. For example, this can be a provider, such as GP, perspective, a health authority perspective or an NHS perspective or a societal care perspective [230, 231]. Depending on the perspective, the costs of items can vary.

This simulation is by default inputted with a "health and social care" perspective. This means that all direct medical costs are considered in the model. The societal perspective includes more stakeholders and is therefore often recommended [232].

As the target audience of this software are decision makers on a local level, restricting the perspective to a narrower one, such as a provider perspective, would not reflect the interest of the relevant users of the software.

NICE recommends using the "health and social care" perspective as it is not biased against the non-working population, such as teenagers or pensioners [233]. I decided to use this specific perspective for default parametrisation of the costs in the model.

As costs can vary between different local settings all costs in the model can be edited so that users can input the software to reflect the costs which are relevant to them.

6.4.4 Influence of Behavioural Factors

Many behavioural factors are likely to influence the efficacy of STI treatment. For example, the adherence to the recommendation to not have sex while waiting for a STI test result impacts the spread of STIs. A study by Llewellyn et al. [182] has found that a behavioural change due to STI tests rarely occurs. Therefore, I decided to simplify this bit of the model and not simulate behaviour change as a result of a STI test in the default parametrisation of the clinical pathway model.

Behaviour changes might also occur because of a STI infection. For example, a partner

might decide to break up due to the infection. Another potential change would be that partners in an existing partnership might decide to amend their sexual contact frequency due to an infection of one partner. I was not able to set up an overview of all potential ways a STI test or STI infection could impact existing relationships and alter behaviour. Therefore I decided to choose a conservative modelling approach and not alter behaviour of individuals.

6.4.5 Conclusions

I have presented a flexible approach to simulate testing and treatments for STIs. The most relevant treatment pathways for the four STIs which are included in the have been set up and inputted with default parameters.

The clinical pathway models are flexible in that they are designed in a way that allows users to amend any parameter, edit existing testing and treatment options or add further testing or treatment options. This enables users of the model to adapt the model to their needs, i.e. by using local prices instead of the default values and prevents the model from being obsolete as soon as new treatment options become available.

The face validity of the model was confirmed by experts, although questions remain about the validity of the parameters.

Chapter 7

Sexual Network Models

7.1 Aims and Objectives

This is the last of the three chapters describing the models in the overall multi-STI model. The previous two chapters looked at the natural progression of a STI and how health care in England interferes with this process.

To understand and properly simulate how STIs spread within a cohort of interest it is crucial to simulate the sexual contact pattern in the cohort. As the overall multi-STI model takes an individual-level approach this is done on an individual level as well.

Decision makers, as the target user group of the overall model, have decided on the relevant sexual networks to include in the software, which were sexual networks for the following populations: young people, men who have sex with men (MSM), black, Asian, and minority ethnic (BAME) communities, and an overall population sexual network.

7.1.1 Overview

This chapter consists of three individual pieces of work. In the first step I develop a generic modelling approach to simulate sexual networks. Subsequently I use this generic framework to describe the four most relevant sexual networks for decision makers in sexual health. Lastly the sexual networks described are validated. For the reasons of readability all section in this chapters are divided into these three subsections.

7.2 Modelling Framework Methods

7.2.1 Data

7.2.1.1 Natsal-3

The 3rd version of the National Survey of Sexual Attitudes and Lifestyles, short Natsal-3, examined the sexual behaviour of the British population. It was conducted between September 2010 and August 2012 and interviewed 15,162 participants who were between 16 and 74 years old [234].

I chose Natsal-3 as evidence to input the sexual networks in my software as it states to be representative of Britain. Natsal-3 has also a broad variety of outcomes to choose from for parametrisation and validation purposes and gives sufficient detail to allow stratification for age of various behavioural parameters.

Natsal-3 included people without sexual experience and sexual interest. I excluded these people and recalculated the values so that the totals added up to 100%. The recalculated values are shown in table 7.1. I summarised all rows which were not exclusively referring to one sex in the original Natsal-3 tables in the second row ("men and women"). Based on this value the sexual attraction of the "general population" sexual network and the "young people" sexual network was derived.

Table 7.1: Recalculated Natsal-3 data on sexual interest (reference table 11)

	general population		young people	
interested in	men	women	men	women
men only	1%	88%	1%	79%
men and women	7%	11%	8%	20%
women only	92%	1%	91%	1%

For the remaining parameters of the sexual network, no suitable evidence could be found within Natsal-3.

I selected further tables from the Natsal-3 for validation. I used those as comparators for the output of my software. I selected four tables, which indicate the promiscuity of a sexual network. These were:

- Number of opposite-sex partners in lifetime (Natsal-3 Table 27)
- Number of same-sex partners in lifetime (Natsal-3 Table 31)
- Number of opposite-sex partners in last year (Natsal-3 Table 29)

- Number of occasions of sex with opposite and same-sex partners in last four weeks (Natsal-3 Table 39)

These tables help to approximate the number of partner changes within a cohort, as well as the number of possible infection processes. I did not include the Natsal-3 table "number of same-sex partners in the last year", as the distribution of the "lifetime same-sex partners" table was already strongly skewed so that an even more detailed look would not yield any more insight.

7.2.1.2 Additional Evidence from the Literature

Natsal-3 did not provide any information on age preferences towards the age of a potential partner. To fill this gap in evidence I searched PubMed and Embase for literature which could close this gap. Studies from Antfolk et al. and Buunk et al. were used to parametrise the age preferences in the sexual network [235, 236]. These studies were used to input the model parameters `minPartnerAge` and `maxPartnerAge`.

As the evidence on prevalent STIs in Natsal-3 is not sufficient to input all sexual networks, this information had to be complemented by other data sources. Additional prevalence values were taken from PHE data, a study from La Montagne et al., and a study from Coyle et al. [37, 57, 175]. The values from these publications were used on their own or in combination with each other to calculate the initial prevalence of STIs in all sexual networks of the multi-STI modelling software.

7.2.2 Generic Sexual Network Framework

In Section 3.4.5.1 I explained the basic idea of having a three-fold modelling approach. The idea of using a generic sexual network framework was also already briefly introduced there, see Section 3.4.5.1. This generic framework can be used to develop several sexual networks which are comparable to each other as they have the same structure. For any new sexual network to be developed this generic framework can be used and therefore facilitates and accelerates the development process.

This software is not bound to a specific kind of research question. For different research questions, different cohorts and populations are relevant. Therefore it also is not possible to develop one sexual network which can be used for all potential research questions.

I developed the generic sexual network framework based on existing sexual networks, in particular the one by Turner et al. [237] from 2006. Whereas the sexual network from

Turner et al. had the greatest influence on the model other sexual networks were also considered [238, 239, 240, 241]. In the remaining paragraphs of this section I describe how these sexual networks influenced the development of the generic sexual network framework.

The most important commonality between all examined sexual networks was that sexual contact can only occur if a sexual partnership between two simulated individuals is present. These sexual networks ultimately describe the formation and ending of sexual partnerships. During the whole length of a partnership sexual contact occurs with a certain frequency. My generic sexual network makes the same assumption. It allows different partnership types such as short partnerships and long partnerships to occur. The number of partnership types is not limited in the generic sexual network. To describe a partnership type, it must have a name, a minimal and maximal duration, a probability of condom use, and the average frequency of sexual contact within this partnership type.

Partnerships in other sexual networks [237, 238, 239, 240, 241] are formed by selecting two random individuals from the overall cohort. If those individuals meet a set of conditions, they start a sexual partnership. This is reflected in the same way in my generic sexual network. Someone defining a specific sexual network can describe the conditions which have to be fulfilled to allow the formation of a partnership with JavaScript code snippets. These conditions can refer to the parameters of both potential partners. If all conditions are met a random number is drawn. If it is below a pre-defined threshold the partnership is started. This threshold can be adjusted by the user of the modelling software.

Upon the formation of a partnership, a partnership type is selected, based on the probabilities of each partnership to occur. Afterwards, the partnership ending event is calculated considering the time limits given in the description of the partnership type.

Based on the average frequency of sexual contact within a certain partnership type, the first sexual contact event is calculated. The contact frequency is artificially blurred creating an interval of +/- 50% around it. 50% was arbitrarily chosen to allow the number of days between two sexual contacts to vary. This is a more realistic representation than a constant rate. Sensitivity analyses have shown that this blurring has very little effect on the overall results. The mechanism was kept to underline the agent-based perspective of the model which puts individuals and their decision in the centre of the modelling process. Based on a randomly drawn value out of this artificially generated interval around the frequency of sexual contact, the time point of the first sexual contact is determined.

After a partnership ends the former partners cannot initiate new partnerships for a certain number of days. This is called partnership gap. This gap is defined separately for each partnership type. After this time has passed both individuals can start a new partnership. A certain proportion of all individuals in the cohort can have more than one simultaneous partnership. If an individual can have more than one partnership at a time, the partnership gap only affects the currently ended partnership. This individual can still start a second partnership or continue having sex with the second partner.

7.2.3 Specific Networks Included in the Multi STI Model

In Chapter 4 future users of the software identified most relevant sexual network from their point of view. Based on this selection and with the help of the generic sexual network framework, I developed the sexual networks which were included in the software.

I developed sexual networks to describe four different sexually active populations: "general population", "young people", "BAME", and "MSM".

To obtain a specific network, the attributes describing this network had to be inputted with real-life values. The first study to search within for these values was the Natsal-3 study. If attribute values could not be obtained from there suitable evidence from other literature was sought. If no satisfactory evidence could be found on the attribute in question, the attribute was backfitted.

7.2.3.1 Back-Fitting

Back-fitting was done by running the sexual network model multiple times. Each simulation had the same set of input attributes except for the attribute to be fitted. This attribute was varied after each simulation. The outcome of each simulation was compared to selected Natsal-3 results. The attribute which yielded the closest match between the outcomes of its simulation and the Natsal-3 results was selected.

The parameter `numberPartnershipTypes` in the software defines the number of different partnership types, such as one-night stands, longs partnerships etc. is an artificial attribute. This means that it needs be included in the model for technical reasons, but there is no real-world representation of it. Therefore no evidence on how to input this parameter exists. I used back-fitting to optimise the input for this parameter. In a second step, I needed to find optimal values to input the attributes describing the different parameters. Therefore `minDuration`, `maxDuration`, `frequencySexualContact`, `gapAfterPartnership` were found through back-fitting as well.

The `meetingInterval`, `meetingPercentage`, and `formationProbability` are also artificial parameters. These parameters determine the number of (successful) partnership formations in the sexual network. I had to back-fit the input for all these values.

Lastly, the parameters defining different partnership types were also backfitted.

7.2.4 Internal Validation

To prove the internal validity of the model sensitivity analyses were conducted. Sensitivity analyses observe the effect of an input parameter on a selected outcome. In this case all parameters describing the sexual networks are changed to see the effect on the total number of infections.

The first bit of the sensitivity analysis was carried out by manually changing each input value within a reasonable range. Table 7.2 shows the values which were inputted in these model runs.

Table 7.2: Input parameters for deterministic sensitivity analysis, [d = days]

	baseline	varied values
proportion of individuals accepting more than one partnership	5%	2%, 10%
the number of individuals actively looking for a new partner in the given interval	90%	10%, 50%, 100%
the time individuals spend looking for a new partner	28d	7d, 56d
probability of starting a partnership after all checks are passed	50%	10%, 25%, 66%, 75%
proportions of all partnerships being short partnerships	50%	10%, 25%, 66%, 75%
duration of a short partnership	1 / 2 d	7 / 15 d, 14 / 35 d
frequency of sex in short partnership	1/d	0.25/d, 0.5/d, 0.75/d
time individuals will not start new partnership after short partnership	14d	1d, 28d
duration of a long partnership	56/ 1825 d	28 / 365 d, 183 / 3650 d
frequency of sex in long partnership	0.25/d	0.1/d, 0.33/d, 0.5/d
time individuals will not start new partnership after long partnership	30d	14d, 60d

To counter random effects the model was run with each parameter set ten times and the mean number of infections over all ten model runs was recorded as output. The presented results are Chlamydia infections occurring in a young people sexual network.

In addition to running the sensitivity analyses with manually selected values, I varied the parameters in the following experiment by +/- 25%, where possible. In some cases, this was not possible as the calculated value would no longer be plausible. I present the tornado

plot in the same setting as before, for a young people network and its effect on the total number of chlamydia infections. This sensitivity analysis was to find the parameters which had the biggest impact on the overall outcome, in contrast to the previously mentioned simulation where I examined the validity range of each input parameter. The resulting values are summarised in Table 7.3.

Table 7.3: Input parameters for deterministic sensitivity analysis, [d = days]

	-25%	baseline	+25%
proportion of individuals accepting more than one partnership	3.75%	5%	6.25%
the number of individuals actively looking for a new partner in the given interval	75%	100%	n/a
the time individuals spend looking for a new partner	10 d	14 d	18 d
probability of starting a partnership after all checks are passed	37.5%	50%	62.5%
proportions of all partnerships being short partnerships	63.75%	85%	106.25% $\rightarrow$ 100%
duration of a short partnership	5 / 10 d	7 / 14 d	9 / 18 d
frequency of sex in short partnership	0.75 /d	1 /d	n/a
time individuals will not start new partnership after short partnership	n/a	0 d	n/a
duration of a long partnership	42 / 1368 d	56/ 1825 d	70 / 2281 d
frequency of sex in long partnership	0.1875 /d	0.25 /d	0.3125 /d
time individuals will not start new partnership after long partnership	22 d	30 d	38 d

The baseline parametrisation was simulated ten times to average out outliers. I used the same characteristics of the simulation as in the previous example, which means I modelled 1,000 individuals over a period of five years. For each value in the deterministic sensitivity analysis, I calculated the mean of the results of ten simulations.

The examined outcome was the number of chlamydia infections. The infectivity of chlamydia, symptomatic as well as asymptomatic was kept at the same level of 33% for all simulations. Condom use was deactivated for all simulated partnerships.

It was not possible to conduct a -25% change for the parameter `shortGapToNextPartnership` as it was already set to 0 days. Similarly, it was not possible to further increase the partnership building probability beyond 100%.

The resulting value of a hypothetical +25% increase of the parameter `percentageShortPartnerships` had to be limited to 100%, as the calculated value was 106% which is an impossible and implausible input value.

Furthermore, it was not possible to increase the value of the parameter `shortFrequencyContact`

as it was already set to the maximum value.

7.2.5 External Validation

The generic network was created using evidence from pre-existing sexual networks [237, 238, 239, 240, 241]. This suggests a high face validity. Direct validation was not possible, so indirect validation was conducted by attempting to simulate a real-world setting. This work is described in the next section.

The results from each simulation were compared to four Natsal-3 reference tables. More information on Natsal-3 is given at the beginning of this chapter, see Section 7.2.1.1. The data which I used for validation was not used to input the sexual networks.

- Number of opposite-sex partners in lifetime (Natsal-3 Table 27)
- Number of same-sex partners in lifetime (Natsal-3 Table 31)
- Number of opposite-sex partners in last year (Natsal-3 Table 29)
- Number of occasions of sex with opposite and same-sex partners in last four weeks (Natsal-3 Table 39)

The young people sexual network was simulated, and the outcomes of the simulation were compared to the Natsal-3 values extracted from mentioned tables.

After each simulation the distributions, calculated by the sexual network were compared to those of the Natsal-3 study. Various tests were performed to assess the quality of the simulation results.

To see whether the modelling results significantly differ from Natsal-3 data, Kolmogorov-Smirnov tests, Kuipers tests and Creamer-von-Mises tests were conducted. Chi-square tests on the distribution and on the sum of the distribution were used to see whether Natsal-3 data and the simulation results followed the same distribution. Lastly, I calculated a Pearson coefficient to see whether the results of the simulations correlate with the outcomes of Natsal-3.

7.3 Results

7.3.1 Parameters for Sexual Networks

All parameters which are used to describe a sexual network in the multi-STI modelling software are described and defined in Appendix H. The parameters have been derived from Natsal-3[234]. Whenever it was not possible to use Natsal other data sources have been used. [237, 238, 239, 240, 241]

In this subsection the four parametrisations of the generic sexual network to describe sexual networks for "general population", "young people", "MSM", and "BAME" are presented. Though all these sexual networks were developed with the same generic framework they are parametrized differently and thereby simulate different real-life settings.

An overview of all parameters is given in Table 7.4, a more detailed explanation for each attribute is given in the following subsections.

7.3.1.1 Basic Cohort Attributes

This subsection summarises basic cohort attributes, e.g. age and sex distribution. These parameters are important as partnerships are formed based on their values. Plausible input values for these attributes have been selected manually.

Age Boundaries. Three of the four sexual networks, namely "general population", "MSM", and "BAME" do not have an upper age limit for individuals which are simulated in them. The software does not simulate sexually inactive individuals so that a minimum age for individuals in the model had to be defined. The lower boundary is chosen for practical reasons as there is not much evidence on the sexual activity of young teenagers below the age of 16. The upper boundary is virtually non-existent as individuals can become older than it, though for pragmatic reasons no individuals older than 66 years will be generated upon start-up in these sexual networks. This maximum age guarantees that the age band of the cohort is not too wide, as partnership formation would otherwise become less likely.

The "young people" sexual network uses slightly different age boundaries. The boundaries are based on the target population of the NCSP [204]. As this programme is targeted at "sexually active under 25-year-olds" [242] the upper age boundary is 24. The lower age boundary of the "young people" sexual network is 16, because of the same reason as stated above.

Percentage Female Individuals. The sex split between men and women in the population is not exactly 50%. There is a slight majority of men at the point of birth. Over the course

Table 7.4: Overview of all attributes in the sexual network

	young people	MSM	BAME	general population
age of individuals	16-24	16-66		
percentage male individuals	50%			
percentage of male individuals who are interested in male individuals	8%	100%	7%	
percentage of male individuals who are interested in female individuals	99%	86%	99%	
percentage of female individuals who are interested in male individuals	99%	100%	99%	
percentage of female individuals who are interested in female individuals	19%	0%	12%	
Minimum age for a partner of a male individuals	`age - 5;`			
Maximum age for a partner of a male individuals	`age+(age/5);`			
Minimum age for a partner of a female individuals	`age-1;`			
Maximum age for a partner of a female individuals	`age+5;`			
Proportion of individuals with no concurrent partnerships	95%	75%	95%	
How often new partnerships are initialised	14 days			
How many individuals try to find a partner each time partnerships are initialised	75%			
Minimum duration of short partnerships	7 days			
Maximum duration of short partnerships	14 days			
Proportion of all partnerships being short partnerships	85%			
Frequency of sexual Contact in short partnerships	1 per day			
Probability of Condom use per sexual intercourse in short partnerships	0%			
Minimum Break between ending a short partnership and looking for new partner	0 days			
Minimum duration of long partnerships	56 days			
Maximum duration of long partnerships	1825 days			
Frequency of sexual Contact in long partnerships	1 per 4 days			
Probability of Condom use per sexual intercourse in long partnerships	0%			
Minimum Break between ending a long partnership and looking for new partner	30 days			

of the lifetime, this ratio changes so that women are in majority [243]. For simplification purposes the proportion of females in all sexual network was manually set to 50%.

In the MSM sexual network, the proportion of females was left at 50% as 86% (see 7.3.1.3) of all men in the MSM network are willing to start a relationship with a woman. To reflect this in the sexual network female individuals need to be included.

7.3.1.2 Initial Prevalence

The initial prevalence of all included STIs has already been presented in Section 5.3.5.

7.3.1.3 Contact Patterns

Sexual Attraction. One slightly amended Natsal-3 tables which describes sexual experience has been shown beforehand. The sexual attraction in the generic framework is described by three attributes, the `sex` of an individual and whether they are `attractedToFemale` and/ or `attractedToMale`. Hence, the Natsal-3 values were recalculated to fit into this scheme. The resulting values are reported in table 7.5.

The sum of all proportions in each column is greater than 100%. The overlap is equal to the proportion of individuals being attracted to both sexes or reporting having had sexual experience with both sexes in the Natsal-3 reference table.

Table 7.5: Sexual experience input for model based on Natsal-3 reference table 10

	general population		young people	
	men	women	men	women
`attractedToMale`	7%	99%	8%	99%
`attractedTofemale`	99%	12%	99%	19%

These values have been used to input the "general population", "BAME", and "young people" sexual network.

For the MSM sexual network, the proportion of males exclusively attracted to females from Natsal-3 was removed. All simulated female individuals were set to only be attracted to male individuals as well. These assumptions resulted in Table 7.6 to input the sexual attraction of the MSM sexual network.

Table 7.6: Sexual attraction of the MSM sexual network

	general population	
	men	women
`attractedToMale`	100%	100%
`attractedTofemale`	86%	0%

Age Preferences. Studies from Antfolk et al. [235] and Buunk et al. [236] were used to define preferred partner age intervals depending on their own age and sex. The resulting formula for the minimal partner age is:

```
if(male)[if(age<20)[16.0;]else[age-5.0;]]else[age-1.0;];
```

The maximal partner age is defined by the following formula:

```
if(male)[age+(age/5.0)]else[age+5.0;];
```

I did not stratify these formulas for sexual attraction. It is important that the age of the individuals is within the interval, otherwise, no same-sex partnerships could be formed.

These formulas reflect the fact that men tend to prefer slightly younger partners, whereas women prefer slightly older partners. The formula for the maximum age also reflects the fact that the preferred age range for a potential partner for a man increases with the age of the man.

These formulas have been used for all sexual networks.

Concurrent Partnerships. 95% of all individuals will be strictly monogamous. The remaining 5% will have a maximum of two concurrent partners, according to the parametrization undertaken by Turner et al. [237]. This value has been used for all sexual networks except the MSM network.

There are arguments that the concurrent partnerships in MSM communities might be higher. Based on a study by Pines et al. I assumed that 75% of all male individuals in the network will have only one partner at a time. 20% will be able to have two partners. The remaining 5% will have up to 3 concurrent partnerships [244].

Partnership Types. The attributes in the following paragraphs have been found through back-fitting.

For all sexual networks, a partnership building interval length of 14 days was found to be optimal. During these two weeks 75% of the population is looking for a partner. All potential partnerships, which passed the conditions which were stated before will result in a partnership. 85% of the partnerships started will be short partnerships, the other will be long partnerships.

A short partnership is defined by a partnership length of 7 to 14 days, with a frequency of sexual contact of 1 per day. There is no partnership gap after the end of a short partnership.

A long partnership will last between 56 days and 1825 days. The upper limit is in this

case equal to the used time horizon. The frequency of sexual contact in a long partnership is once in four days, and the gap is 30 days.

These partnership type definitions have been used for all sexual networks.

7.3.2 Internal Validation

The results of the sensitivity analysis with manually selected values are only summarised here and presented in detail in Appendix I. The results confirmed that a higher number of unprotected sexual contacts lead to higher number of new infections. The only exception to this rule is a sexual network in which all individuals are strictly monogamous and live in long-term partnerships as in this network the prevalence of the modelled STI decreases to 0%.

In this section, the validation results for the "young people" sexual network are shown. These validation calculations have been performed for the three other sexual networks as well. The mean number of new chlamydia cases over ten simulations were used as a baseline value to calculate deterministic sensitivity analyses. The results of the deterministic sensitivity analyses are presented in a so-called tornado plot in Figure 7.1 the data which was used to generate this graph is shown in Table 7.7.

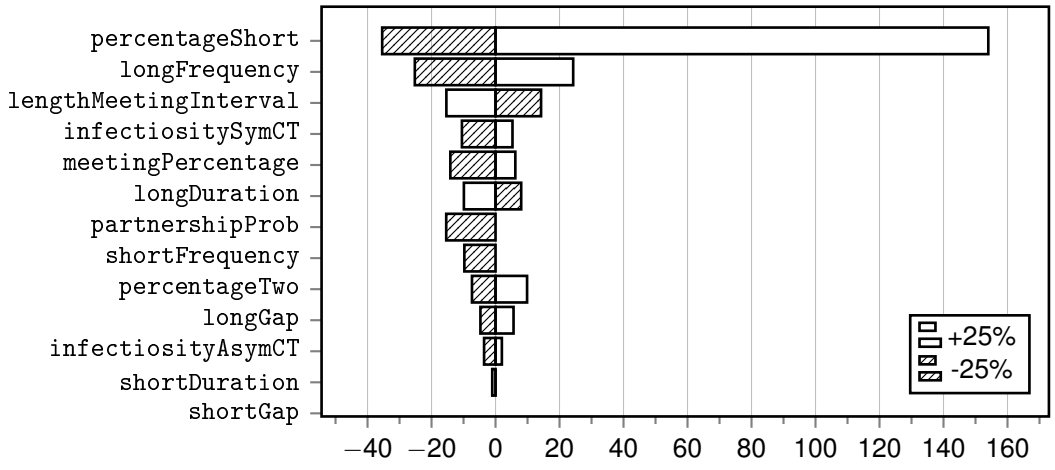


Figure 7.1: A sensitivity analysis of major input parameters of the model has been performed. The results are shown in this tornado plot. White bars indicate that the value of interest has been increased by a quarter, striped bars indicate that it has been lowered. If the bar ends to the right-hand side (positive) the total number of infections has been increased by this change and vice-versa.

Table 7.7: Data of tornado plot

parameter name	-25%	+25%
percentageShort	154.12	-35.42
longFrequency	24.27	-25.22
lengthMeetingInterval	-15.36	14.23
infectiositySymCT	5.3	-10.5
meetingPercentage	6.19	-14.12
longDuration	-9.89	8.02
partnershipProb	0	-15.41
shortFrequency	0	-9.74
percentageTwo	9.86	-7.36
longGap	5.63	-4.72
infectiosityAsymCT	1.98	-3.58
shortDuration	-1.03	0
shortGap	0	0

7.3.3 External Validation

To understand these results better all Natsal-3 results are shown together with the corresponding modelled outcomes in the following figures.

Figure 7.2 shows the number of opposite-sex partner over the whole lifetime. The Pearson tests have shown that the results are not highly correlated. The face validity confirms this result showing that in the modelled outcomes individuals tend to have more partners.

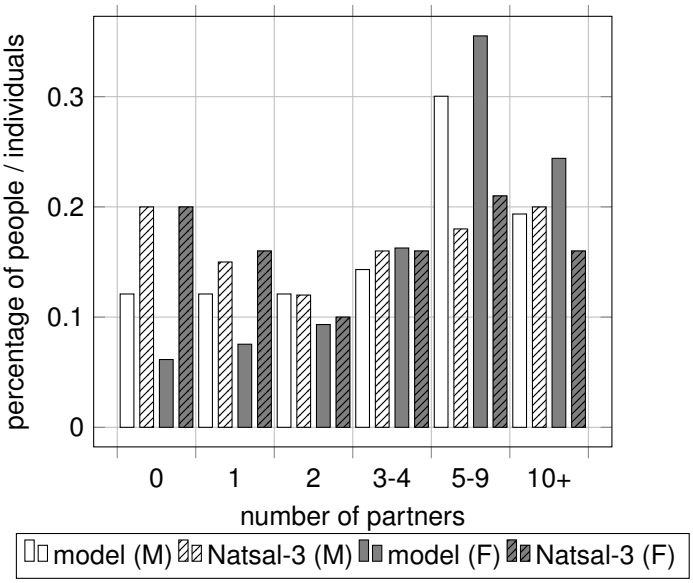


Figure 7.2: Natsal-3 vs simulation: Opposite-sex partners over lifetime

For the spread of an STI within a population of interest, the total number of partners over the whole lifetime, is not as relevant as the number of partners within the last year. Therefore, I tried to match the outcomes of the sexual network to the Natsal-3 data of this

dimension. Figure 7.3 shows the comparison of these distributions.

Natsal-3 did not list a “4” category, which is why there is a gap in the figure. This gap made it impossible to conduct a Chi-square test. Thus, I artificially added a small margin to this field so that the Chi-square test could be conducted. Overall, all distributions follow a similar, slightly right-skewed distribution.

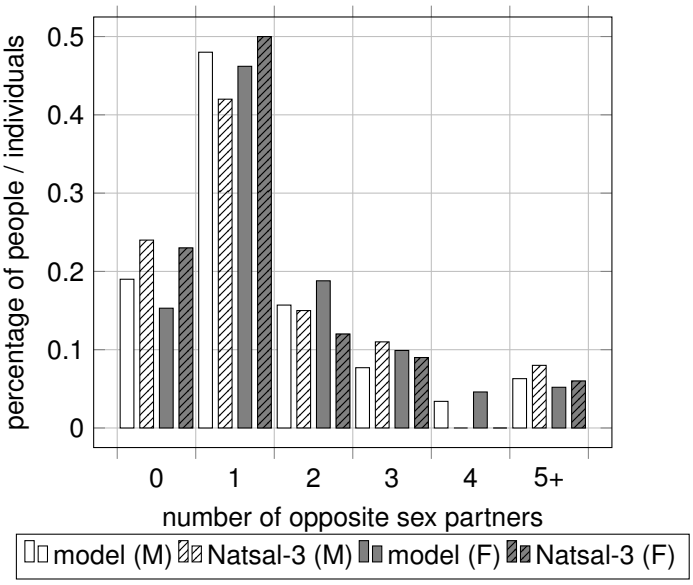


Figure 7.3: Natsal-3 vs simulation: Opposite-sex sex partners over last year

Figure 7.4 shows the number of sexual contacts within the last month. It does not differentiate between homosexual or heterosexual contact. The modelled outcomes follow a bimodal distribution, which is also seen in Natsal-3 data.

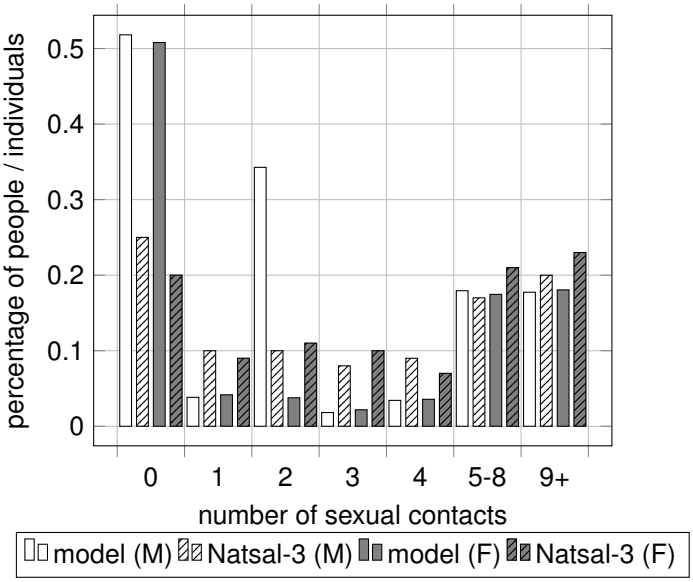


Figure 7.4: Natsal-3 vs simulation: Sexual Contact within the last month

In Figure 7.5 the lifetime same-sex partners are shown. Most individuals within the sexual network have not had any same-sex partners, which is also reflected by Natsal-3. The shape of this distribution also lead to the decision to not include the number of same-sex partners within the last year.

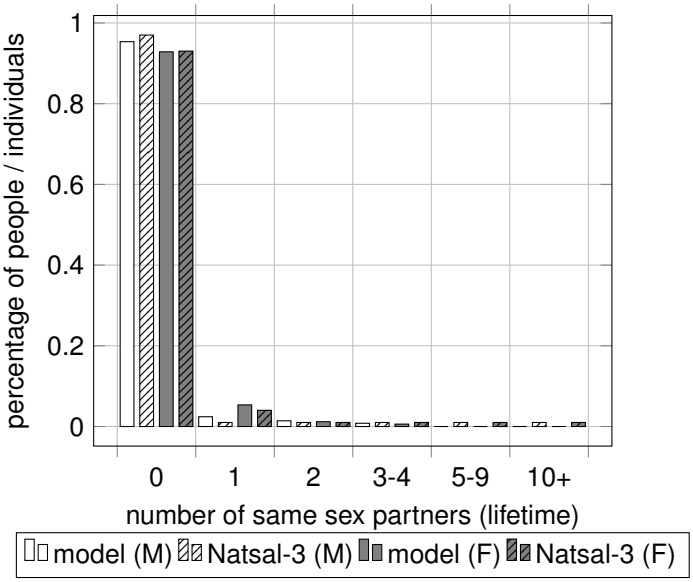


Figure 7.5: Natsal-3 vs simulation: Lifetime same-sex partners

Table 7.8 shows the test results for all test. Asterisks indicate that the test value is significant to a 5% significance level.

All Kolmogorov-Smirnov tests, Kuiper's tests and Cramer-von-Mises tests showed no

Table 7.8: Test results of software vs. Natsal-3. Asterisks indicate significance to a 5% level.

	Kolmogorov -Smirnov	Kuiper's test	Chi-Square (dist)	Chi Square dist. sum	Cramer von Mises	Pearson's dist.	Pearsons' (dist sum)
# of contacts last month (male)	0.268	0.258	0.998*	0.998*	0.179	0.931	0.967*
# of contacts last month (female)	0.308	0.318	0.996*	0.991*	0.301*	0.692	0.978*
# opposite sex partners lifetime (male)	0.124	0.120	0.999*	0.999*	0.0417	0.378	0.994*
# opposite sex partners lifetime (female)	0.2301	0.232	0.998*	0.994*	0.125	0.432	0.982*
# opposite sex partners last year (male)	0.050	0.068	0.999*	0.999*	0.0417	0.970*	0.998*
# opposite sex partners last year (female)	0.115	0.123	0.999*	0.999*	0.042	0.960*	0.993*
# same sex partners lifetime (male)	0.016	0.026	0.999*	1*	0.125	0.999*	0.930
# same sex partners lifetime (female)	0.014	0.015	0.999*	1*	0.152	0.999*	0.975*

significant difference to a 5% level. On the other hand, all Chi-square tests showed to a 5% significance level that the distributions are similar. Most of the Pearson tests showed a significant correlation.

7.4 Discussion

7.4.1 Key Findings

It was possible to develop a generic framework, which I used to develop sexual networks to simulate the following populations "general population", "young people", MSM populations and BAME communities. The sexual networks could be validated and included in the multi-STI modelling software.

7.4.1.1 Challenges

During the development of the framework, it was demanding not to not make any assumptions and thus keep the generic framework as flexible as possible, whilst at the same time giving enough and detailed options to enable simulating vastly different sexual networks. This was also limited by the availability of information in English scenarios.

Developing sexual networks largely depends on the availability of evidence to input them. Although back-fitting could be used to input some attributes, I tried to avoid it where possible as I considered the evidence generated from back-fitting to be not as trustworthy as evidence from the literature.

7.4.1.2 Strengths

The sexual networks are validated and have shown to be able to reproduce real-life outcomes reliably.

The way which was chosen to develop the sexual networks tries to adopt the perspective of an individual and is thereby easy to communicate to potential users because no advanced mathematical knowledge is necessary.

The simple way of describing the sexual networks makes it easy to amend them, if necessary, quickly and without advanced modelling knowledge.

7.4.1.3 Weaknesses

Back-fitting was necessary to find parameter values for nine attributes. These attributes are more likely to be amended as they are not based on credible sources, such as published clinical trials or observational data. Due to the artificial feature of these attributes, it was not possible to find any real-world evidence for them.

7.4.2 Natsal-3 Data

Natsal-3 was used as a key study for parametrising and validating the sexual networks, which is why it is worth to have a closer look at it.

The study was conducted nearly 10 years ago. The social structure and behavioural data which was captured back then could have changed vastly in the meantime. For example, the rise of dating apps like Tinder, which were published after Natsal-3 was conducted, might have an impact on the partnership building patterns and sexual risk behaviour [245, 246]. The next Natsal study, Natsal-4, is planned to be conducted in 2021-2022 [247]. The attributes of this sexual network certainly will have to be compared to the outcomes of the Natsal-4 to keep the model up to date.

Natsal-3 reported national averages in their outcomes. This is good to understand overall trends in the population, but it does not match the needs of decision makers. They want localized, very specific, data which describes the situation in their area of interest. This need cannot be satisfied by the software yet, as - to my best knowledge - no registry data on the sexual behaviour and partnership building patterns of localized communities is available. However, I assume that regional variance in sexual behaviour exists.

Looking at the Natsal-3 cohort we could see that the selected sample of participants was not fully representative for the whole population. Looking at a skewed sex distribution - more women than men were interviewed in Natsal-3 - the question remains on how reliable and representative Natsal-3 really is.

Natsal-3 is the biggest study on sexual behaviour and attitudes in Great Britain which makes it also the best possible data source for developing sexual networks. Unfortunately, there are not many other sources which is why I had to use it for parametrisation and validation. Whereas I did not use the same data to input the model as for validation it would have been beneficial to use completely different data sources for these two tasks.

7.4.3 Generic Sexual Network Framework

The progress of STIs are described in the software in a rather deterministic and precise way. In contrast sexual networks are modelled in a more random fashion. This is partly due to the contrasting nature of both underlying research questions of those model parts. We know much about disease progression, for example we know which sequelae follow to which diseases, how long the incubation period of certain STIs lasts, and how many infected individuals will show symptoms, it is much harder to formally describe human behaviour. Human behaviour is not as deterministic. More factors than the sexual networks could ever include influence the duration of a partnership and the frequency of sex in partnerships. There are many mechanisms which could influence all behavioural attributes in the sexual network. For example, the frequency of sex could decrease over time in a

long-term partnership. It is not certain whether including various rules and exceptions to the rules actually improves the quality of the sexual network. A review has also shown that more complex sexual networks do not seem to be more accurate [248]. This is why I decided to find a consensus between existing sexual networks and I manually selected factors which were used in multiple sexual networks as they have proven their importance by the overlap in usage over several sexual networks.

The same sexual network will be used to simulate all STIs within a single simulation. This means that is not possible to examine different sexual networks in one simulation.

It is possible to include the STI status of individuals into the conditions which must be fulfilled to form a partnership. This approach might be used to reflect the fact that people might not want to start a partnership with a currently infected individual.

7.4.4 Validation

Overall, the external validation showed that key outcomes of the sexual network closely match with real-world evidence.

Deterministic sensitivity analyses showed expected behaviour when relevant input parameters were altered.

7.4.4.1 Tornado Plot

By far the most influential parameter was `percentageShortPartnership`. A 25% increase in the number of short partnerships, translated to an increase in chlamydia infections of 150%. Furthermore, a decrease of 25% meant that the number of infections shrunk to 65% of its baseline value. An increased proportion of short partnerships yields to an overall higher partnership change rate in the sexual network. This means that more individuals can potentially be infected. This effect is reversed if the individuals in the sexual network tend to form longer partnerships and therefore change their partners less often.

The parameter `lengthMeetingInterval` played another vital role, being in a reciprocal relation to the number of infections. If said interval becomes shorter, more potential partnerships are formed. This means that infectious people are more likely to get into a partnership and infect another, previously uninfected individual. On the other hand, if the meeting interval lasts longer it means that fewer partnerships are formed and therefore fewer infections can occur.

In line with the previous paragraph is the observation that a higher percentage of individuals looking for partners within the partnership building interval leads to more partner-

ships and ultimately to more infections and vice versa.

With a decreasing length of long partnerships, the number of infections increases. This is since individuals who will end a long partnership will be available to a new partner sooner. This puts these individuals under risk of catching further infections sooner, or increases the risk of them infecting somebody else earlier, depending on their health state.

The next two entries in the tornado plot are at this position as the entries are sorted by the sum of the absolute values of the relative changes. Both values could only be varied in one direction, which is why their calculated sums tended to be smaller. Nevertheless, we can observe a significant decrease of the total number of infections of 15%, for a decreased `partnershipBuildingProbability` and a decrease of 10% for a decreased "frequency of sexual contact in short partnerships".

If the frequency of sexual contact within short partnerships is decreased from 1.0 times/ day to 0.75 times/day the number of chlamydial infections drops by 10%. This underlines the fact that not every partnership with an infected individual will automatically lead to an infection, even with unsafe sex practices. The likelihood of getting infected by a partner depends on the length of the partnership, the usage of condoms, the infectivity, and the frequency of sexual contact during the partnership, see Formula 1:

$$p_{partnership} = p_{contact} \cdot f_{contact} \cdot duration \cdot p_{CondomUse}$$

With

$p_{partnership}$	The probability of getting infected in this particular partnership.
$p_{contact}$	The infectivity of the STI of interest.
$f_{contact}$	The frequency of sex in this particular partnership.
$duration$	The duration of this partnership.
$p_{condomUse}$	The probability of condom use in this partnership.

This formula only applies if one of the partners is infected and the other one is susceptible.

With a decreasing frequency of sexual contact, the probability of infection drops.

The last relevant effect in the software was that a 25% decrease of `percentageTwoPartnerships` leads to a 5% decrease in the number of infections, as the overall number of concurrent partnerships decreases.

All other effects, as well as the effect of an increased concurrency, did not show impact the outcome to a notable extent. The last row in the tornado plot is empty as the value of `shortGapToNextPartnership` could not be altered.

In line with the results from the deterministic sensitivity analysis (DSA), we can see

that the `partnershipBuildingProbability` does not have any effect on the number of infections. Also, the frequency of sex within long partnerships does not seem to matter, as an infection will occur within these partnerships anyway, if one of the partners is infected, due to the length of the partnership.

7.4.5 Pregnancy

Another important issue to address is the question of why pregnancies are not included in the sexual network by default. As pregnancies are not relevant for all research questions, I decided to not include them by default but to offer the option to include them manually, if needed.

Pregnancy-related sequelae, like neonatal death or neonatal pneumonia, can be included in the software as normal "sequela" model without explicitly modelling pregnancies. For some studies, especially in younger populations, research questions might address issues around pregnancies, especially unplanned pregnancies [249, 250]. In these cases it is possible to include pregnancies in the sexual network. In this case, an additional disease model must be added which simulates pregnancies, which is not intuitive as pregnancies are not diseases.

7.4.6 Travel and Migration

Modelling infectious diseases becomes an even more complex topic if issues like travel and migration are considered. Depending on how the software is used, these issues are addressed differently. In a closed cohort model it is not possible for new individuals to enter the modelled cohort. This means that no new individuals can migrate into the cohort. In an open cohort, new individuals can enter the cohort. These new individuals can have pre-existing infections. Whenever a new individual enters the cohort its starting parameters are drawn based from the boundaries which are given in the input files. This means that the prevalence of STIs within all new individuals is the same as the initial prevalence in the population.

The effects of travelling are handled the same way for open and closed cohort models. In both instances, relationships with individuals who are not explicitly modelled are possible. Infections in these relationships can occur, based on the initial prevalence of the STI. Therefore, it is possible for an individual to get infected by an individual which is not explicitly modelled. These individuals outside the modelled cohort are always "average" individuals as derived from the input parameter boundaries of the cohort. No partner notification can

occur with those individuals either.

Whereas the effects of migration and travelling are in fact more complex than the way they are simulated in this software, this approach accounts for the existence of effects, which can be approximated by the existing mechanisms.

7.4.7 Parametrisation

Parts of the sexual network were fitted manually, which introduces the risk of only finding a locally good fit but not the globally best fit of the sexual network with real-world evidence. The sexual network also seems to put much weight on long partnerships, which might result in the overestimation of this partnership type. Although the sexual network has shown to match closely with Natsal-3 data it is important not to generalise these results too much. This sexual network also depends on parameters outside of the social network for proper simulations.

I have seen that it is possible to set up a sexual network which can be validated using Natsal-3 data. If set up incorrectly other sexual networks could be generated which are very similar to the reported Natsal-3 outcomes but at the same time do not allow the spread of diseases within this sexual network as they are largely based on long partnerships in a mainly monogamous population. Only the second part of the validation, looking at the number of new chlamydia cases, uncovered that this network was not able to simulate a stable STI prevalence over time. This example shows that face validity is inevitable in developing sexual networks. Even after a good match is retrieved, I questioned the results to find an explaining mechanism behind the observed effects. Especially with regard to using the same network to validate the clinical pathways it was crucial to use a parametrisation which mirrors real-world sexual networks.

The split between males and females is an important underlying factor. As the Natsal-3 population was mostly heterosexual, the number of sexual contacts within the last months would reduce if the sex distribution in the simulated cohort was strongly skewed. It is therefore not possible to blindly take this sexual network and use it for any young population of interest.

This sexual network has been optimised for a time horizon of five years. If another time horizon is needed some parameters of the sexual network might have to be adjusted to account for this change. For example, the maximum duration of a long partnership is currently set to the time horizon of the simulation and should be amended in this case.

7.4.8 Gender vs. Sex

I made a simplification in terms of the sexual identity of the simulated individuals. We know that sexual orientation and gender cannot be reflected adequately in a binary attribute. This is also the reason why I only used the word "sex" in this chapter, meaning the assigned sex, instead of the more precise term "gender". Non-binary people cannot be assigned to being either male or female. Non-binary people experience social stigmatisation and are often discriminated against. They are also more likely to encounter problems while accessing health care, while at the same time being more likely to get infected with STIs [174, 251, 252].

The data on non-binary and transgender people and their sexual behaviour is still scarce. To correctly reflect them it would also have to be further divided to adequately approximate various characteristics in this group. The national lesbian, gay, bisexual and transgender (LGBT) survey [253] found in a sample of non-heterosexual young people 6.9% of the participants identified themselves as non-binary. Combined with a total of 6.8% of all adults not identifying as heterosexual [254] the overall proportion of non-binary people is approximately 0.5%. This low number made it not feasible or practical to include them into the general population sexual network now.

As I stated earlier, studies indicate the increased risk for non-binary people of getting infected, therefore further research should aim to develop another sexual network specifically targeting a non-binary population. This is especially relevant as the proportion of non-binary people is increasing. Further studies should be conducted to understand this population better. These studies could be enhanced by my software, equipped with a new non-binary sexual network, in order to develop or STI interventions for this population.

7.4.9 Conclusions

Four different sexual networks have been described using a generic sexual network template I developed specifically for the multi STI-model presented in this thesis. These networks have been chosen by decision makers and reflect the networks which are most relevant to them in terms of their work. If other sexual networks are to be modelled, those can be set up and integrated in the overall model in a straightforward manner. The existing sexual networks can be fitted to local networks by amending parameters.

The sexual networks have calculated results which are similar to observations reported by Natsal-3 data. This result must be regarded very carefully as the sexual network have

taken a simplified view on human behaviour. Assumptions had to be made, which exclude certain options of individual behaviour in the model which are possible in the real world.

Chapter 8

Using the Multi-STI Modelling Software

8.1 Aims and Objective

In the previous chapters, I described the different parts of the model and how they interacted with each other. This chapter will look at the whole multi-STI modelling software and how the previously presented different parts of model interact with each other. It demonstrates the capabilities of the model in terms of simulating and enhancing outcomes of a real-world clinical trial.

8.1.1 Overview

This chapter showcases the capabilities of the software by simulating a clinical study and subsequently using the results of the trial in another (hypothetical) cohort.

The simulation is two-fold; In the first part I replicate a real-world clinical study. This is also used to validate the results of the software with real-world data. I simulated the study outcome with the software by using publicly available baseline data of the MenSS-trial.

In a second step, I enhance the examined real-world scenario by a hypothetical scenario, not covered by the MenSS. As MenSS only recruited men who have sex with women, I added women to the modelled population and increased the size of the modelled population to generate a population which is reflective of a random sample from the population. In this analysis, I also prolonged the time horizon of the study to observe long-term effects and sequelae. These adaptions demonstrate the options the disease modelling software provides which go beyond the limits of a clinical trial.

8.2 Background

8.2.1 Men's Safer Sex Trial (MenSS)

To showcase the capabilities of the disease modelling software I used data from the MenSS trial [7].

MenSS was conducted in 2014 and 2015 to examine the feasibility of a behaviour change therapy for men who have sex with women to promote safer sexual behaviour. The study recruited a total of 159 male attendees of a GUM clinic who were at least 16 years old and at a high risk of acquiring an STI. This was defined as having at least two partners in the last year and did not use a condom in at least one occasion within the last 3 months. The intervention was delivered via a website with which the participants could interact in the waiting room of the clinic. During this interaction, they chose a username which they could use later to log on to the website after their clinic visit.

Follow-up data was collected three, six, nine and twelve months after the collection of baseline data. These questionnaires collected HR-QoL using the EQ-5D-3L, the sexual Quality of Life (sQoL), self-reported STIs, number of partners and estimators for condom use. The questionnaires also had a qualitative component which I do not introduce further in this summary. If participants consented beforehand, the medical records of the clinic, where they were recruited, were linked to their follow-up questionnaire data. The control group reported the same follow-up data, but they did not have the option to access the website.

37% of the participants in the intervention arm did not visit the website at all, even in the clinic. The median number of website visits was two, with a maximum of eight visits. The feasibility trial found no significant difference in the usage of condoms between intervention and control at three months. Seven (8.8%) new STI diagnoses were found in the intervention arm and nine (13%) in the control arm.

The authors concluded that behaviour change is feasible but further research, like implementation studies is needed to maximise the engagement of the participants with the website and to improve data collection.

Based on the data from this feasibility trial an economic evaluation was conducted. The previously mentioned HR-QoL and sQoL were used. Unit costs were estimated based on published sources, e.g. from NICE or DoH. The costs of developing the website were reported to be £101,515. As these are fixed costs, the costs per QALY gained will decrease with each new person using the website.

In the trial, no significant QALY difference between the intervention and control arm was found. No significant difference in resource use was found either, but small cost differences were observed. This difference was only observed when pregnancies were included in the HE evaluation. This conclusion stayed the same independent of whether questionnaire data or data obtained from the clinical records was used.

The authors concluded that - with a 61% to 88% probability - the examined intervention is cost-effective, using a cost-effectiveness threshold of £20,000 per QALY gained.

8.3 Methods

8.3.1 Simulating MenSS

Two different cohorts have been set up to simulate the MenSS trial. One cohort simulated the control arm and one simulated the intervention arm. The cohort size was taken from MenSS and was 84 for the intervention and 75 for the control. Drop-outs were not simulated so that the cohort size stayed at the same level throughout the whole simulation.

The mean age for the intervention group was 29.3 (standard derivation (SD) = 8.8) and 29.5 (SD = 8.4) for the control. The "general population" sexual network, see Section 7.3.1, was used. The homosexual parts of this sexual network have been removed to fit the inclusion criteria of MenSS.

The study only recruited men who have sex with women. Therefore, the main mechanism of simulating partnerships with the sexual network model did not work as it assumes that there are individuals in the simulated cohort with whom partnership formation is possible. One of the criteria for partnership formation is that the sexual orientation of an individual must match with the sex of a potential partner. This condition can only be true if two bisexual male individuals are randomly drawn. Considering the low total number of individuals in the simulation and taking the low proportion of bisexual male individuals into account, this will rarely happen.

Therefore, the other included mechanism of simulating partnerships was more important in this case. This mechanism simulates sexual contacts of individuals in the simulated cohort with individuals from outside the simulated cohort. This mechanism is normally used to acknowledge the fact that sexual networks are never fully closed, e.g. to simulate the effects of travelling.

By default, the proportion of individuals in the model having sex with somebody from outside the modelled cohort is quite low, as I assume that the core sexual network is simulated in the software. MenSS only included men who have sex with women in a men-only cohort. Therefore, all episodes of sex of simulated individuals occur with individuals who are not explicitly simulated. To allow the spread of STIs in this specific modelling situation, the parameter for sexual episodes with individuals outside the model was fitted to the reported MenSS-data. To do so the reported number of unprotected sexual episodes from MenSS were transformed in a rate, telling the number of episodes of sex per individuals per year. This rate was then used to input the proportion of sexual episodes of simulated individuals with individuals from outside the model.

The condom use likelihood was set to 0% as MenSS only reported on occasions of condom-less sex so that the software could be fitted to these values.

Table 8.1 shows the parameters which have been used to parametrise the sexual network model, which differed from the default parametrisation.

Table 8.1: Clinical Pathway parameters for the comparison with MenSS

parameter name	default value	value used in simulation
`proportion male`	50%	100%
`condom use`	34%	0%
`sex episodes (outside)`	3%	18%

MenSS reported a small difference in the types of service use in the control and in the intervention was found. Participants in the intervention arm were more likely to have an STI home test kit in contrast to getting tested in a clinic. The default clinical pathway model does not differentiate between those two ways of getting tested. As a result, an adapted version of the clinical pathway model was used which is shown in Figure 8.1. This Figure depicts a simplified view on the clinical pathways as a home test in reality usually not qualifies for treatment. Instead, in reality, a test at a clinic has to be done. Based on the result of this second test, treatment might be initiated. In the simulated clinical pathway, a positive home test is followed directly by treatment. To account for the necessity of a second test at a clinic, its costs are added to the total costs in case of a positive self-test result. This assumes that the second test at the clinic would be positive. Afterwards treatment is initiated.

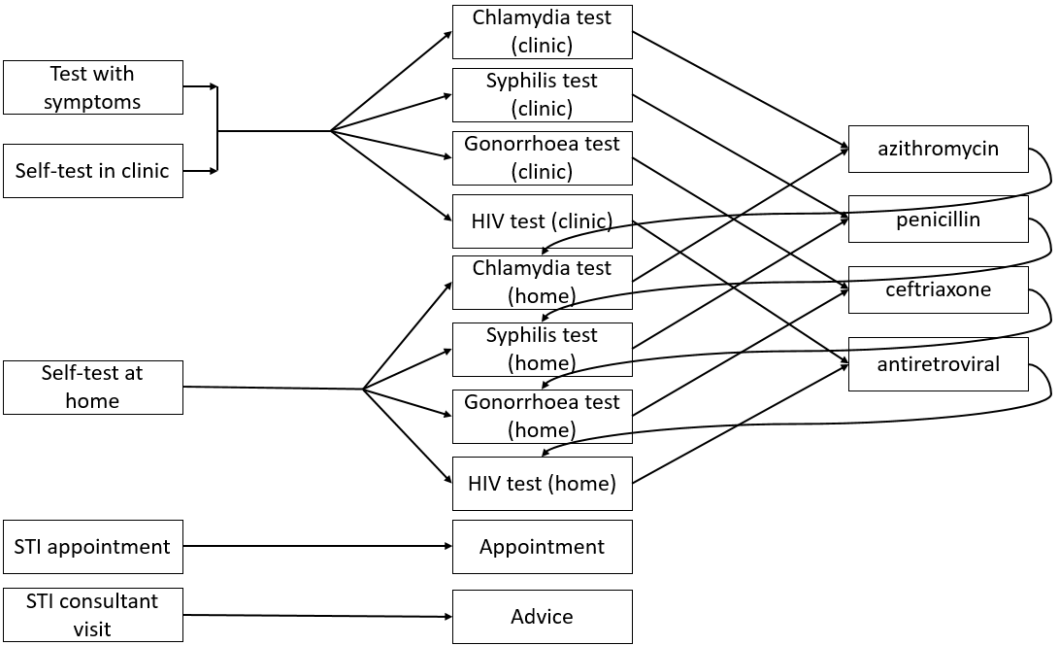


Figure 8.1: Clinical pathways of the MenSS feasibility trial, as simulated by the software

As depicted in this Figure NCSP is not included in the clinical pathway model of this simulation as most of the simulated cohort is already too old to qualify for a test from this scheme. The proportion of individuals taking STI tests in the software were amended so that they matched the reported numbers from the MenSS-study.

The pathway for individuals with a higher risk of acquiring HIV is not included in this pathway model. I made this adaption as only MSM with frequent partner changes or concurrent partnerships can receive a test through this scheme in the software. As no MSM were modelled this simulation, nobody could possibly be eligible for it.

Prevalent HIV or hepatitis type C (HCV) infection were part of the exclusion criteria of the study. To account for this criterion, I have set the initial HIV prevalence to 0%. All other STI prevalence values were kept at the default values. Still, HIV infections from outside the modelled cohort could still occur.

Two other pathways have been added to allow for the STI consultations and STI advice sessions, both of which are associated with - compared to a single test - high costs. These consultations are assumed to be given to randomly selected individuals at a constant rate. MenSS Table 9 was used to input the data costs and QALY data for the simulation. Table 8.2 shows the cost data which has been used in the simulation and was different from the default values.

Table 8.2: Costs as derived from MenSS and inputted in the software

name of costs	value
syphilis treatment	£116.00
gonorrhoea treatment	£116.00
gonorrhoea treatment	£116.00
appointment	£105.00
STI advice	£20.00
STI test (home)	£18.52
STI test (clinic)	£72.00

I included four main STI models in this simulation. These were chlamydia, syphilis, gonorrhoea, and HIV. One sequela, urethritis, was included as well. Due to the short follow-up of the study no general mortality was considered in the simulations. The default parameters of the included disease models have not been altered for this simulation.

To compare the intervention with the control arm of the study in the simulation, the parameters describing the infection from the outside of the cohort were varied accordingly so that more individuals from the simulated intervention arm were using STI-home test kits, and less were using test kits in STI clinics.

Table 8.3 lists the parameters which were different from the standard parametrisation of the model and not already listed in the previous table.

Table 8.3: Remaining parameters of the models for the comparison with MenSS

parameter name	default value	value used in simulation
all NCSP parameters	see section 6.2.3	removed
all HIV screening parameters	see section 6.2.4	removed
STI appointment	n/a	12% per year
STI self-test (clinic)	5% per year	16% (control)/ 9% (intervention)
STI self-test (home)	5% per year	1% (control)/ 7% (intervention)
STI consultation	n/a	18%

For this simulation I used a time horizon of 12 months. The main outcome of this simulation was the cost per QALY gained, calculated as the difference between simulated intervention and simulated control arm. The simulated result was compared to the MenSS trial result.

The results of the simulation were compared to the outcomes of the MenSS economic evaluation as reported in tables 14 and 15 [7].

8.3.2 Using Parametrisation in New Context

After fitting parameters during the MenSS-simulation process, the software was used to simulate scenarios which were derived from the MenSS trial but could not be examined

with the study data.

As the previous results showed that the simulation results were similar to the MenSS results, I continued with the used parametrisation. In this second part of the analysis the same parameters to describe the male cohort are used, but additionally female individuals are also included in the modelled cohort. The included female individuals make up half of the new cohort and have the same age variation. As decision makers have to think about the effect of an intervention in a larger cohort, the modelled cohort size was increased to a total number of 10,000 individuals.

The comparator of the following scenarios is a mixed-sex cohort where no intervention is being rolled out. Two different implementation strategies are regarded. In both interventions the reported numbers of condom use are inputted in the model:

1. The intervention is only delivered to male individuals. Only male individuals will change their behaviour towards a more frequent use of STI home test kits. I will refer to this strategy as "male only".

2. Female individuals will also change their behaviour and start using more STI home test kits instead of going to a clinic to get tested. I will refer to this strategy as "mixed-sex".

Both strategies are simulated over a time horizon of five years, instead of one year, to observe more long-term effects of the potential roll-out of this behaviour change intervention.

I used the same set of disease models for these simulations as in simulating MenSS. Additionally, the PID-model model, presented in Appendix G was included.

Most of the parameters I used were equal to the ones described in tables 8.1 and 8.3. All parameters which have been changed are listed in Table 8.4. These changes were necessary to include female individuals in the simulation.

Table 8.4: Parametrisation differences between a male-only cohort and a mixed-sex cohort

parameter name	intervention "mixed-sex"	intervention "male only"
`partnership formation interval`	21 days	14 days
`partnership formation proportion`	100%	75%
`duration short partnership`	1-14 days	7-14 days
`duration long partnership`	28-365 days	56-1095 days
`short frequency sex`	0.75 per day	1.0 per day

8.4 Results

8.4.1 Simulating MenSS

The objective of this first part of the simulation was to validate the model using MenSS data. Therefore, I compared the results calculated by the software to the MenSS outcome.

With the previously described parameters, a simulation of the MenSS trial was performed with the software. The time horizon was set to one year. Table 8.5 shows the reported outcomes of MenSS side-by-side with the results of the simulation.

Table 8.5: Results of the simulation in comparison with MenSS-outcomes

	intervention		comparator	
	MenSS	software	MenSS	software
# of individuals	84	84	75	75
# of male individuals	84	84	75	75
cost per patient	£189	£150	£214	£185
avg. QALY	0.905	0.9137	0.862	0.9156
avg. condom-less sex acts per male	10	n/a	12	n/a

Due to the simplifications which had to be made in the sexual network, it was not feasible to count the sexual contacts of the individuals included in this simulation

Alongside the economic data, it is relevant to compare the number of STI infections as reported by MenSS and calculated by the software. These numbers are shown side by side in table 8.6.

Table 8.6: Infections in the simulation in comparison with MenSS-outcomes

	MenSS	software comparator	software intervention
urethritis	7	4	5
chlamydia	7	7	8
gonorrhoea	3	5	6
epididymitis	2	n/a	n/a
molluscum contagiosum	2	n/a	n/a
syphilis	n/a	2	2
HIV	n/a	1	1

In MenSS, the number of infections was reported aggregated for the intervention and control group, which is why the results are presented in one column only. MenSS did not report on syphilis and HIV whereas in my software no disease models for epididymitis or *Molluscum Contagiosum* infection were included.

8.4.2 Using Parametrisation in New Context

Similar to the table, which was used to validate the software, key information from all three simulations are summarised in table 8.7.

Table 8.7: Comparison of the simulated control arm and two hypothetical interventions

value	control	intervention "mixed-sex"	intervention "male only"
# of individuals	10,000	10,000	10,000
# of male individuals	5,066	4,973	5,034
cost per patient	£135.43	£155.21	£128.57
avg. qaly	0.911	0.914	0.905
cost per QALY	£148.66	£169.81	£142.07
cost per QALY gained	n/a	£6593.33	£1643.33
avg. condom-less sex acts per male	10.56	9.98	11.54

The number of male individuals fluctuated between the three arms, as the simulated cohorts were generated randomly. The proportion of male individuals was set to 50% so that the difference is due to random effects. As the difference was only one individual, we decided to not run the simulation again.

The cost per QALY gained is for both interventions positive, but the results must be interpreted with caution. The intervention "mixed-sex" is both more expensive and more effective than the control whereas the intervention "Male-only" is cheaper but also less effective than the control group by a small margin.

In these model runs sexual networks were enabled. Therefore, the number of condom-less sex act per male were compared to the values which were reported by MenSS. MenSS reported in control and intervention on average 13.8 episodes per 100 participants of unprotected sex. The simulations calculated a total of 11.9 - 16.0 episodes of unprotected sex per 100 individuals.

Table 8.8 shows number of infections of each STI simulated and calculated the cost per infection prevented for each row individually.

Table 8.8: Comparison of number of infections in the control arm and two hypothetical interventions

	control	intervention "mixed-sex"	intervention "male only"
urethritis	244	190	246
chlamydia	1250	1369	1952
gonorrhoea	1547	849	1227
pid	244	61	125
syphilis	179	182	183
hiv	119	125	116
total	3583	2776	3849

The cost per infection prevented, looking at the total number of infections is for the "mixed-sex" intervention £245.11 whereas for the "male-only" intervention it sits at £257.89. The "mixed-sex" intervention has higher costs and a lower number of total infections compared to control, whereas the "male-only" has lower costs and higher number of infections.

8.5 Discussion

8.5.1 Validation with MenSS Data

It was possible to use the software to simulate the trial and the control arm of the MenSS trial. The validation has shown that results of MenSS are similar to the results from the model. The number of infections and QALY results of the simulations were similar to the outcomes as reported by MenSS, whereas the model tends to underestimate the total costs. The costs difference between intervention and control was similar for MenSS and the software.

I did not have patient-level data of the trial to follow up these cost differences. Looking at the cost types and their usage from the model and MenSS (Table 15), I conclude that most of the difference is caused by a difference in the types of services which were used. This means that the clinical pathway model, which had to be set up for this validation was not optimal.

Considering the differences in service use, it is worthwhile discussing how suitable MenSS was to validate the model. Especially, when looking at the adaptions which had to be made before the validation could be started, the question might arise whether the actual software or a different version of the software has been validated. The central point of this validation was to show the capabilities of the software, e.g. to simulate a situation for which it has not been programmed. During the preparation of the validation, I could see that it was possible and easy, at least from my perception, to fit the model to a completely new scenario. This is the most valuable lesson from this validation, as it showed that it is possible to simulate a setting for which the model has not been set up.

MenSS was used for this validation, as it posed some challenges which were not considered during the model development, such as a sexually active single-sex, but mostly heterosexual cohort. During the validation, the software gave the user enough options to simulate this scenario.

A component of the software, which was not used in this validation was the sexual network model. It was replaced by a simpler approach, as no females were included in the validation. This approach assumed a constant sexual contact rate with individuals from outside of the model. The sexual networks had to be validated with MenSS data before running the example calculations shown in the next section.

The simulation has shown to not be very QALY sensitive. This result is in line with the observation from the study where a barely observable QALY effect was documented. We

also know that standard QoL instruments are not very sensitive towards sexual health, but this was countered in the study by assessing sQoL.

Therefore, it remains to be proven that the software can simulate significant QALY changes. The given scenario was not optimal for this, as individuals with HIV were excluded from the trial. With HIV having the biggest and longest lasting effect on QoL a major driver was eliminated.

The small impact of a curable STI on the QALY is demonstrated in an example calculation in this paragraph. Symptomatic chlamydia is assumed to have a utility decrement of 0.3. Without treatment, symptomatic chlamydia will relapse within 14 to 35 days. For this calculation, we will assume that an otherwise healthy individual has an average utility of 0.9. This means that the QALY for a healthy individual after one year would be $\frac{0.9 \cdot 365}{365} = 0.9$. If we now have a look at the individual with one episode of chlamydia in one year, we get a minimal QALY (for the maximum duration of the episode) of $\frac{(0.6 \cdot 35)+(0.9 \cdot 330)}{365} = 0.87$ and a maximal QALY (for the minimum duration of the episode) of $\frac{(0.6 \cdot 14)+(0.9 \cdot 351)}{365} = 0.89$. This shows that for a low-risk population without any long-lasting STIs we do not expect a great QALY-impact. This small QALY effect is further diminished by the fact that not everybody in the cohort will get infected, not all infections are symptomatic, and infected individuals will receive treatments which shortens the time living with a decreased utility.

In MenSS, 21 infections in a total of 15 distinct people were observed in one year. These numbers are also reflected in the simulation with 18 infections in the control (22 in intervention) in 16 individuals (17 in intervention) in one year. This shows that the overall results, whereas the observed QALY-decrease was small, were not unexpected.

8.5.1.1 Drop-Outs

I decided to not include drop-outs in the software. MenSS had to work with high rates of missing data and wide uncertainty ranges. The advantage of a simulation approach, on the other hand, is that these drop-outs can be avoided. Therefore, the software could be used to enrich studies with a high drop-out rate and make their results more meaningful.

The software does not include a drop-out mechanism. It would have been possible to include such a mechanism to the software. For example, an additional disease model could be defined. This model would have to states `ACTIVE` and `DROPOUT_DEAD`. Due to the ending `_DEAD` every individual which dropped out, will not be simulated further. It is also easy to distinguish the drop-outs and the individuals who died during the simulation, as their final health state is different.

Not looking at the drop-out assumes that the drop-outs occurred randomly and the missing data is "missing at random" [255]. The authors did not indicate that the drop-outs of MenSS were not missing at random. If I knew that certain people were more likely to drop out, e.g. those who were less responsive to the intervention I needed to amend the assumption to account for it. Currently, I estimate that the observed effects are indicators for the real average effects on a population level. A biased drop out would also mean that the observed effects cannot be extrapolated and simulated that easily. In that case, the model must be parametrised differently, but I would lack a sufficient data source to do this.

8.5.2 Showcase of Capabilities of Software

The software was inputted to simulate the effect of the MenSS intervention on the partners of the included men. These women were not surveyed in MenSS which is why the software calculates important output to enrich the data which was assessed in the trial. Additionally, another hypothetical treatment option was simulated to see the health economic effect which would occur if the behaviour change intervention would also be rolled out to women as well.

It was more costly but also more effective give the intervention to both sexes. At the same time giving the intervention only to men it was less costly but also less effective. The ICER was in both cases well below the willingness to pay (WTP) threshold, so that, solely based on this data a suggestion to implement the intervention for both sexes would be likely.

The presented simulations allow a more detailed view on its results than the analysis of the MenSS results. For example, it is possible to examine the prevalence over time with a granularity of only one day compared to a snapshot view every three months. The detail of the results combined with the fact that there is no missing data in the simulation results can make this modelling software a valuable resource for decision makers and researchers conducting clinical trials as well.

8.5.2.1 Behaviour Change

While simulating the mixed-sex cohort I assumed that the behaviour change in terms of service use would be the same for women as for men. But we also know that women and men tend to differ in their behaviour. For better input parameters further research results are needed. As no data source was found at the point of modelling, I simulated it with the assumption of female and male individuals showing similar behaviour.

In the simulations with a mixed-sex cohort, the overall cohort does not really reflect one core sexual network. This is because women (and therefore female individuals) tend to choose slightly younger male partners and vice-versa. The age range for both sexes was the same in these simulations. This means that the model had some young male individuals and old female individuals who were less likely to find a partner due to their age preferences towards a potential partner.

8.5.3 Conclusions

In this chapter I showed an example on how the software could be used. The disease modelling software calculated similar results to the outcome of the MenSS-study when inputted with MenSS data. The software was able to simulate a larger cohort inputted with parameters derived from MenSS. This demonstrated how the software could be used in practice by decision makers, i.e. to see the potential effect of an intervention on a different population, not covered by the original trial, they are interested in.

Chapter 9

Conclusions

9.1 Rationale

This thesis examined the feasibility of developing a user-friendly multi-STI modelling software as a decision support tool for decision makers in sexual health. This concluding chapter brings together the individual parts of the thesis and shows how it improved the state of research in the field of STI-modelling. It reflects on key challenges I encountered during this research project and discusses the software in general. It also reflects the methods which were used in this thesis and discusses the impact of the thesis and potential future research which might follow this thesis.

9.1.1 Overview

This chapter starts by recapitulating the state of the literature at the beginning of this research project, which leads into a summary of my thesis.

In the following subsections, the results of the different chapters are brought together and synthesised to show how this thesis influenced the state of research. This then leads to a general discussion about potential future application of the software resulting from this PhD project. I outline how the software was disseminated and I plan to disseminate this further to be used within the English health care system.

In Appendix J I reflect explicitly on each research question, aim and objective of the thesis as stated in the beginning and summarise what I did to fulfil each of those goals.

9.2 State of Literature At the Beginning of the Thesis

The inspiration for this thesis originated from my Master's thesis on chlamydia modelling. The conclusion of this Master's thesis was that due to biological and social interaction of

STIs, individual modelling was insufficient. This finding led me to develop my PhD idea to model multiple STIs simultaneously.

In this thesis I have presented the development process of a multi-STI modelling software. This process started with a systematic review of disease models which are capable of modelling more than one STI simultaneously.

My systematic review has shown that 44 disease models exist which are capable of simulating multiple STIs simultaneously. These models have been developed to reflect geographical settings from around the world with a focus on the USA and sub-Saharan Africa. Most of these models simulated HIV in combination with other STIs. The key issues found during the literature review (see Chapter 2) were confirmed by discussions with experts (see Chapter 4) and are summarised in the following list:

- In my systematic review I could identify 44 multi-STI models. Whereas single STI models do play a role in decision making and can be used to examine a STI in more depth they are not capable of simulating the interactions between STIs. STIs do not operate in isolation therefore multi-STI models are needed to simulate and examine those interactions and their effects.

- The majority (70.5%) of the multi-STI models which were included in the systematic review are not capable of running health economics evaluations and can therefore only be used to a very limited extent to inform decision making. These disease models are developed for research purposes only to answer one specific research question and then discarded.

- Only two models were developed for a UK context, none of which contained more than two STIs. Though, the actual STIs which were simulated in both disease models differed from each other.

- Policy makers reported that many disease models lack usability, which hampers them from including these models in their processes at work.

- Policy makers commented that they often are not directly involved in the development of models whereas the results of the models are relevant for their work and could have a direct impact on their decisions and policy changes.

- A general problem, which goes beyond the limits of STI modelling is the lack of adequate communication between researchers and policy makers and timely translation

from state-of-the-art research into policy.

The last two points result in a translational problem between decision makers and disease modellers. Decision makers need to contact disease modellers to use the disease models. Disease modellers must communicate the results back to the decision makers. During this communication, information might get lost. Furthermore, this process takes time, so that the decision-making process is delayed [256].

9.3 Strength and Limitations

9.3.1 Summary of the Development of Modelling Software

I focused on developing a multi-STI disease modelling software trying to address the aforementioned flaws. The development process was in close cooperation with decision makers in sexual health so that the software would be more likely to be useful for them.

Decision makers defined the scope of the software. This included selecting relevant input parameters, output values and the way the output is presented, the included STIs and included sexual networks. Decision makers were also an integral part of the development of the user interfaces for the software. In using a collaborative approach with decision makers I developed software which was tailored to their needs, to fit into their existing processes.

The modelling approach I chose was an individual-based discrete event simulation. Individual-based modelling has, especially in the context of STI-modelling several advantages. It is possible to simulate the spread of the infection on a detailed level instead of assuming or deriving an infection rate. When looking at behaviour change interventions which target a specific component of the infection chain this can be examined in detail. In individual-based models it is also possible to perform contact tracing or give individuals based on their attributes personalised treatments. This opinion is in line with the finding of a systematic review by Roberts et al. [142] who found that individual-based models are better suited to simulate chlamydia infections.

The software consists of three mostly independent modules, each of which is responsible for a separate task. These modules can communicate with each other by putting events in the main event queue. One of these modules describes the natural progress of STIs and sequelae included in the software by state transition disease models. The sexual network module describes how partnerships form and dissolve and thereby how often sexual contact between individuals occurs. The clinical pathway module describes how sexual health care alters the course of the disease, e.g. by treating infected individuals.

All modules were developed and validated separately. In the next step, the parts were connected to each other so that they could communicate. The resulting prototype was equipped with user interfaces. I developed user interfaces together with decision makers with the aim to make create an accessible and easy-to-use software.

The software and its contained models were validated by comparing its simulated results to the outcome of a sexual behaviour change trial. The same trial data was then also used to simulate a different cohort than the one which was looked at in the original trial and

looking at the HE outcomes of this hypothetical change.

9.3.2 Flexibility of the Software

During the development of the software, I expected changes in the STI landscape to occur which is why the model was flexibly designed so that it can be used even though the initial scope changed. For example, as of now the software can simulate ART for HIV, see Section 6.2.1. But with the second patient being cured of HIV [257, 258] there might be a chance of finding an HIV treatment which might be administered to more people living with HIV at some point in the future. Right now, we do not know enough about treatment parameters to start the modelling, but the software will be able to simulate these new treatments at some point as well. This example shows that changes will always occur, and that the software is able to reflect them.

We know that changes in the STI landscape, treatment, etc. occur. We cannot and do not want to prevent these changes but the software has to be prepared to simulate them. The flexible design of the software allows making these changes so that the software does not have to be thrown away. This means that the software might probably be used for a longer time and potential users might be more willing to learn how to use the software, as it is not bound to a specific setting.

9.3.3 Validation of the Disease Models Used

The model has been validated using deterministic sensitivity analysis. This has been done twice. One time by manually selecting parameter values to test values just inside the plausibility interval. Another time by adding or subtracting a pre-defined percentage of the original value.

Following ISPOR-guidelines the model was calibrated to estimate parameters for which no evidence could be found. A deterministic sensitivity analysis was performed to validate the calibration [140].

Probabilistic sensitivity analysis has not been performed. This was due to the large number of computational runs and the computational time needed for running the probabilistic sensitivity analysis. Methods to decrease the necessary number of calculations for a probabilistic sensitivity analysis in a patient level simulation have been developed but have not be used in this project [259].

9.3.4 Default Values Facilitating Usage of Software

In the software, every parameter is inputted with a default value. These default values are evidence-based and clearly defined so that users of the model can understand where it was derived from. This helps to build trust in the model, as the origin of the input is clear and can be verified.

This also means that the software can be used out of the box to calculate trustworthily. At the same time, it allows decision makers to input other parameters if they have a better dataset available or localized data for this parameter to reflect the situation in their area of interest. This is especially relevant for costs as they can fluctuate from one region to another.

It is important to acknowledge that each parameter describing the initial cohort in the model has a plausibility interval around it. To generate an individual in the model a random value out of the plausibility range is drawn. This means that all generated individuals in the model are different, although they are generated from the same input.

9.3.5 General Limits of Disease Modelling

A general restriction of all models is that they are simplifications of the real world. These simplifications are not necessarily a limit to the model, as often simpler models have shown to produce more reliable results [248, 260]. On the other hand, some interactions could not be observed if the model was kept too simplistic.

Due to the complexity of the real world, it is not possible to reflect all relevant influencing factors in our models. This means that during the model development a selection has to occur. E.g., during this thesis, a set of STIs had to be selected as well as input parameters.

All the selected parameters are in some form or another incorporated in time-to-event formulas. This means that upon validation we will always see an effect of these parameters towards the modelling outcome. This is not surprising as the models were set up so that they react to changes in these parameter values.

I did not include any parameter in the model without having evidence on why this parameter should be included and which effect it has. This approach does not allow the discovery of new correlations and interaction, as relevant factors for those interactions are not included.

Therefore, disease modelling in the form I have used it in this thesis can only be used to examine already existing hypotheses, but it is not able to derive new hypotheses without

any further knowledge, only based on disease models. Hence, this model "behaves" in a way we expect it to behave, which is like a self-fulfilling prophecy, or in other words a technical Pygmalion effect [261].

This might change in the future as big data methods, such as machine learning, can be used in combination with large data set to discover connections which were hidden beforehand. Methods of data mining could be used on big data to discover dependencies and connections which were hidden beforehand.

9.3.6 Selection of Included STIs

The selection of STIs was done at one point in time and might therefore be subject to an urgency bias at that point. If we repeated the same procedure at a later point of time a slightly different selection might have been the result. For example, due to the rising number of new cases of *Mycoplasma genitalium* infection in combination with antimicrobial resistant strains of this pathogen, it is possible that this infection might now be relevant enough to include it in the software. For users of the model who want to have a look at STIs which are not included in the default version of the software as described in this thesis, other STI disease models have also been developed. These models are shortly summarised in Appendix G.

9.3.7 Requirements Towards Users

The user interface provides users of the model with a frictionless option to input data into the software. Nevertheless, advanced users can directly input and run the model without this user interface, e.g. if they want to examine scenarios which cannot be inputted using the standard user interface. Therefore, the input *.txt and *.js files must be edited directly. In doing so they might accidentally implement infinite loops and therefore lead to a crash of the program. At this stage, there is not much which can be done to prevent this, other than to sensitize users not to work on these files unless they know exactly what they are doing.

9.3.8 Challenges

9.3.8.1 Background Knowledge

Coming from a different background, the first roadblock I had to overcome was to understand the clinical aspects of STIs and the English health care system. Before starting my work, basically no knowledge in both areas was possessed by me. Whereas I have studied medical informatics and did study the structure of the German health care system I did not know much about the English health care system.

It was inevitable to build this knowledge about those topics to be able to effectively communicate with decision makers and clinicians. Reviewing the literature and discussions with experts helped my understanding of the area.

9.3.8.2 Development of Disease Models

Based on my background search to learn about STIs, I started to develop STI models which were finally not included in the software. If I had prioritised my work differently, I could have saved some time, as these models are currently not being used in the software.

Nevertheless, I think it was worthwhile developing these models, as they helped me to understand how STIs can affect the human body and this was an important part of my initial reading. Furthermore, these models can be used when the users of the software want to include other STIs as well.

9.3.8.3 Choice of modelling approach

When I started this PhD project, I was convinced that individual-based Markov models were the best modelling approach to use in such a simulation software. I also built the prototypes with the expectations that the Markov model prototype would be superior to the discrete event simulation prototype. I was surprised to see that the actual results turned out to be the other way around.

This showed me that I have to hold back my own opinion when objectively evaluating distinct options as my subjective impression can be biased towards a certain alternative. In this specific case I assume that I was biased towards Markov models, as I had already worked with them in different projects before, such as my Masters' thesis.

Overcoming this bias and finding the objective, best suited approach was necessary for the successful progression of the project.

9.3.8.4 Expectations Towards the project

I started the PhD project with my own expectation how the software should look. I had ideas of which functions could be included, what the software could look like and how it could be incorporated into working processes. For example, I wanted to develop a disease model editor tool where the structure of disease models could be edited in a drag-and-drop like fashion.

But this was neither needed nor wanted by decision makers. Over the course of the first few months, it became obvious that I have to overcome those expectations so that the final product of the thesis will have maximum use for the user of the software and thereby

also maximise the impact of my work.

At the same time I was overwhelmed by the amount of potential features the software could include, when initially pitching the idea to stakeholders. I had to manage these expectations and reject ideas which could not be implemented by one person in a period of three years, such as a data connection to the GUMCAD database. Especially the start of the PhD project was therefore driven by finding the right scope to maximise the relevance of the output towards future use and impact in the field.

9.3.8.5 Evidence

Some parameters were inputted with values from old studies. This was mainly because I could not find any newer studies which estimated these values. From my point of view two main reasons contribute to this. The first is that there was a large agreement on a certain value so that new studies are not financed as they are not likely to bring new data.

Another reason is, and this was relevant when I tried to describe the natural progress of a disease, that similar studies could not be conducted any more for ethical reasons, e.g. studies which assess the time of an untreated symptomatic chlamydia infection.

Due to this lack of more current literature, some of the evidence used to parametrise the model is older than I would like it to be.

9.3.8.6 Parametrisation

Some specific parameters were needed to input the model. In some instances, I could not find evidence for these parameters, which is why I tried to estimate those, e.g. the frequency of individuals looking for new partners as well as the success rate of this process.

Upon validation I could see that the estimation of the parameters was most likely wrong. To avoid parametrisation problems, I had to go one step back in some models and work with a more simplistic version than I initially intended to in order to be able to have sufficient evidence for each parameter. For example, I removed more complex partnership building criteria from the model. In the final version only the sex and the age of the individual in comparison with the other individual's sexual orientation and age are relevant.

9.3.8.7 Communication with Future Users of the Software

Working with decision makers is a challenging task as their schedules tend to be very packed. As a result, they are only willing to invest time into projects in which they can see clear benefits, which also impacts the participation in studies as described in Chapter 4. Recruitment for any study or trial is known to be challenging, with recruitment of deci-

sion makers being no exception. This particular target audience were receptive to being contacted but this did not always translate into engagement in the study.

In Chapter 4 I showed that it is beneficial for both modellers and decision makers to be included in the development process. Decision makers also demand to be included in the modelling process to make the models useful for them. Having had the experience of recruiting decision makers to participate in a project I saw how complex it is to get decision makers' input. This ties in with many other models included in my review which did not receive input from decision makers.

I tried to communicate with decision makers in the most concise and clearest way possible. This was necessary so that the purpose of the project as well as their potential benefit was laid out clearly.

During meetings with decision makers it was necessary to make the most use of the limited time. Having a clear structure in these meetings and communicating the rationale of each meeting helped them to identify with the project and not give up on it.

This challenge was not unique to this research project as other researchers have encountered similar challenges before as well [262].

9.3.8.8 Communication

Whereas all meetings were held in English, the involved parties sometimes spoke different professional languages as their backgrounds were different. An interesting example of this is the word "to implement", which has a clinical definition in the context of clinical trials and a technical definition in software development. This created communication barriers and included the potential to confuse the involved parties. This issue was especially relevant as English is not my mother tongue and I am therefore not as sensitive as others towards small linguistic differences.

Especially the communication between researchers and policymakers can be difficult as the scope of their work is vastly different. Whereas researchers try to find general applicable statements to describe a majority of the population, decision makers are often interested in very detailed statements for very specific populations [263]. Therefore the intrinsic interest of the involved parties differs, and it might be difficult to find common ground in this discussion. In other research projects this issue during collaborative research has also been observed [264, 265].

To avoid this problem, I had to learn to see the problem from the perspective of the other parties so that I could anticipate potential areas of conflict. This also involved "sacri-

ficing" time at the beginning of meetings to harmonise the understanding of key concepts. In doing so most of the communication issues could be avoided.

9.4 Use and Potential Future Use

9.4.1 Dissemination

During the development of this software, I was constantly in touch with decision makers, e.g. commissioners on a local level or PHE staff. They had influenced the development of the software. I also used the time during my PhD to present and disseminate my work.

The work has so far been presented at various conferences as poster or talks. A paper on my systematic review has already been published and we plan to publish further papers covering the rest of the thesis.

Closer to the end of this PhD project I presented the software at PHE and got the invitation to present at the STI commissioners' forum. During these presentations, we also discussed options of how this software can be used in practice. We will continue to have this discussion to find a way that my work can influence and support their work.

Besides displaying my ideas to an academic audience, it was also important to introduce my tool to future users. In some way this was already done by itself, as the development of the model included people from the target audience. During the development process I made decision makers and potential users aware about the existence of this software. Those who stated that they were interested in my work and would like to keep updated, received regular information about the status of the PhD project.

9.4.1.1 Further Planned Dissemination

To disseminate the software further, I plan to make it available for everybody on a website. Before this step can be taken, an exhaustive user manual has to be written to avoid the software being used wrongly. Whereas I put effort in making the user interfaces intuitive and easy-to-use, documentation will further facilitate the usage of the software. I plan to do this in written form as well as video tutorials on how to use the software. To enable users to correctly input the model, the information in Appendix D will be made available alongside the other documentation.

After this step is taken, I plan to hold workshops on the software to showcase their usage and motivate attendees to use the multi-STI modelling software in their working life. Thereby I hope to get users to use the software, gather further feedback on it and being able to further improve the software by adapting it to the potentially evolving needs of its users.

When the multi-STI model is actively used it would be worthwhile for us and for other

researchers to summarise our process and our lessons learned in a journal paper. At the same time the support for the software should still continue to encourage users to continue using the software and thereby benefiting from its decision support functionalities.

9.4.2 Potential Future Applications of the Software in Decision Making

In Chapter 8 one potential use case of the software was demonstrated, which showed that the software itself is valid and can be also be used to examine hypothetical interventions to enhance real-world study results. Many other research questions can be answered with this software. A short overview of possible use cases is given in this section.

All presented scenarios are derived from discussions with clinical experts, health economists or decision makers on how the software can be used to support their current work. Seeing the difference in how research is perceived by policy makers and the researchers who conducted it, it is good to see that the collaboration during the conduct of the study already enables further cooperation in the project [266].

As explained in Section 3.4.5.1 the software is designed in a flexible way. This makes all presented scenarios easy to examine with the software in its current state without the need of further development. Most scenarios do not require changes of the current models. Wherever changes are needed it is clearly laid out what kind of changes are necessary. The changes which need to be made are only changes to the input files (*.txt files). These can be changed by any user of the model and do not require a programmer to alter the program code. Given the limited time and disease modelling capabilities of decision makers it might be advisable to let health economists do these changes.

9.4.2.1 STI Vaccination

During recent years significant progress has been made in terms of vaccinations for STIs. For some STIs, vaccination is already available, such as HPV [267]. For other STIs research for vaccination is ongoing, such as chlamydia [181, 182], gonorrhoea [268], and syphilis [269]. In all cases, the software can be used to evaluate the impact of a potential vaccination or a change in the scope of the current vaccination strategy.

There are multiple ways of realising STI vaccination in the software. One option, which provides transient immunity to the disease is the approach which was already taken to simulate PrEP for HIV in the software, see Section 6.2.2. In this approach, individuals are immune to a disease as long as they continuously receive the drug.

Another slightly more complex way of simulating a permanent vaccination effect would be to introduce an additional health state "immunity through vaccination". Individuals will be put in this health state after a successful vaccination. Individuals in this health state cannot leave it which makes an infection is impossible. using the second option to simulate STI vaccination places the need for the current model to be enhanced.

This is relevant for future use as new vaccinations might be developed, and vaccination strategies are an important public health measure.

9.4.2.2 Antimicrobial Resistance

Regarding gonorrhoea and *Mycoplasma Genitalium*, antimicrobial resistance (AMR) is already a crucial topic [40]. Different strains of gonorrhoea are immune to different antibiotics. Already resistant strains can develop further AMR if treated people do not adhere to their medication plan. It is therefore relevant to understand the impact of non-adherence to the recommended first-line therapy for gonorrhoea on AMR [270].

The software could also be used to evaluate antimicrobial resistant gonorrhoea. To do this another gonorrhoea disease model would have to be set up, which has the same health states and transitions as the current gonorrhoea model, with the exception that the new model is not linked to any treatments in the clinical pathway model and can therefore not be treated. As it would still be linked to test events it would still be detectable. A similar approach would also work to model the effect of a recently observed chlamydia strain in Finland [271], which cannot be found through a certain standard test or *Mycoplasma genitalum* infection with an antimicrobial-resistant strain of the pathogen.

To understand the impact of non-adherence on AMR, the software would need to include the two versions of the gonorrhoea model, as mentioned in the previous paragraph. To model the rise in AMR after non-adherence, individuals would then switch from the gonorrhoea model without AMR they are currently in, to the gonorrhoea model with AMR. If these individuals now infect somebody the next individual will get infected with the AMR gonorrhoea pathogens.

9.4.2.3 Examining the Behavioural Interaction of STIs

Most of the presented use cases of the software focus on the additional effect a change in a single intervention will have on several STIs, e.g. as an additional outcome to enrich the results of a study or a trial. In this section I want to present an example of how the software could be used to examine the interactions of STIs.

With PrEP currently being of high relevance, its effects on other STIs such as gonorrhoea, chlamydia, and syphilis, especially in MSM are still not clear. In these scenarios, we can think of mechanisms by which individuals stop using condoms as they can no longer get HIV, but they are still susceptible to other STIs. These behavioural mechanisms are not yet reflected in the sexual network model. To simulate this in the model, scarce behavioural data would need to be translated into parameters. A large proportion of this sexual network model input process would be based on assumptions as evidence on relevant parameters does not exist, e.g. how much lower the condom use percentage is within in PrEP users compared to non-PrEP users.

Until further evidence is published, this scenario is probably the most complicated one to simulate due to the evidence base, or the lack thereof, which could be used to input relevant models it.

9.4.2.4 Examining the Effect of Screening Programs on other STIs

The software can be used to understand the effect of existing screening programs, such as for HIV, on STIs which are not covered by the screening. A potential mechanism which could be relevant in this context is that positively tested people will receive a test offer for other STIs. Thereby further potentially asymptomatic infections can be found.

This scenario can be examined with the current version of the software, as I included a way to simulate the quarterly HIV screening of high-risk individuals. If a positive test returns the individual will receive test offers for all other STIs included in the software. To examine the effect of the quarterly HIV screening of high-risk individuals on prevalence and incidence of the other STIs in the software, the software has to run two calculations, one which includes test offers for other tests after a positive HIV test and one without.

9.4.2.5 Chlamydia Immunity

As already discussed, while introducing the chlamydia model (see Section 5.3.1), the software can simulate the effects of newly discovered health states, such as a potential transient chlamydia immunity.

To evaluate these changes in medical knowledge, two different disease models would have to be set up, one including the new health state and one without it. This can be done by every user of the software. To add a health state to a disease model a user must amend the corresponding .txt-file and .js-files to describe the new transitions, see Appendix D for a more detailed description. The model could then simulate both scenarios and compare the

outcomes to a real-world data set to see which of both approaches is closer to this data. Thereby the software could help to understand disease progression better and support hypotheses building. Arguably this first scenario is not a decision-making use case but more useful in terms of epidemiology and research.

9.4.2.6 Health Economic Evaluations

The software can also be used to help health economists while running clinical trials or economic evaluations of new technologies or policies. There are multiple options where this software could be useful in this context. It could be used to simulate the expected outcome at the start of the study, e.g. to inform the trial design process. At the end, the model could be used, as shown in Chapter 8, to enrich the results of the trial by extrapolating the results. This could be done in different ways, either to transfer observed effect of the intervention to another cohort, or to extend the duration of the intervention or the observation period after the end of the trial to capture sequelae which can occur a long time after the end of the original study. It would also be possible to examine effects of the intervention examined in the trial on outcomes which have not been captured such as STI incidence of STIs not covered by the trial. Chapter 8 is a detailed description of how a health economic evaluation supported and enhanced by this model could look like.

9.4.2.7 Evaluating Dual Testing of NCSP

The NCSP currently tests for chlamydia and gonorrhoea in a combined test. It might be relevant to examine the effect of only testing for chlamydia instead of for both STIs, to validate PHEs position on dual testing [272]. This can easily be tested in the model by adapting the treatment pathway of the NCSP, which is currently connected to a chlamydia test and a gonorrhoea test. After the connection with the gonorrhoea test is removed, the software will not evaluate it any further. The probable decrease in the gonorrhoea detection rate can then be observed by comparing the outcomes of simulations with and without this pathway.

9.4.2.8 Examining change of test strategy of NCSP

It is another interesting research question to examine the effect on chlamydia infection rates if opportunistic chlamydia testing in males was stopped if at the same time opportunistic screening in females was increased. With the current version of the clinical pathway, this can be done easily. As of now, NCSP is modelled as an opportunistic offer for all individuals in a certain age range (16-25 years). To account for the suggested changes this

opportunistic offer would be split up into two opportunistic offers, one for male individuals and one for female individuals. The difference in those would be that the male version has lower coverage than the current non-stratified version, whereas the female offer would have increased coverage.

9.4.2.9 Hypothetical Increase in Re-Test Rate of NCSP

Another relevant question is to understand the impact on chlamydia detection rates of increased re-testing rates at three months past treatment and increased numbers of partners that proceed to have a chlamydia test. These are parameters which are already included in the clinical pathway model of the software to describe the clinical care pathway. To examine this a modelling study could be performed to evaluate the impact of changes in these parameters, by increasing their value and comparing relevant outcomes.

9.5 Potential Impact

9.5.1 Relevance of the Model to Decision Makers

In 2004 Drummond challenged health economists in a journal article with the question about whether economic evaluations in health care were useful or "whether health economist were just kidding themselves". Drummond concluded that there was potential for better use of health economics in decision-making, but it is overall worthwhile to conduct health economic studies and analyses [273].

From my perspective, Drummond's conclusion that health economics is useful and needed still holds true today. Consequently, this thesis discussed how the usefulness of health economics can be maximised for decision makers. In a today's context, in which decision makers are faced with a limited budget and numerous potential treatment options, decision models can provide a way to present cost and outcome information to help decision makers. Grutters et al. showed that a decision-analytic model can be a valuable tool nowadays for decision makers and provide valuable input for them to decide on policy questions [274].

There is limited evidence of health economic evaluations and decision models being used in practice particularly by local decision makers in contrast to the general agreement that both can be useful, if implemented correctly. This is mostly due to barriers, such as accessibility and terminology, towards using these methodologies. Furthermore, health economics and decision modelling are just one of many factors considered in the decision of decision makers. Especially on a local level, decision making is influenced to a lesser extent by health economics and decision-support modelling [275, 276, 277]. My decision support software helps decision makers on a local level to run individualised decision models with locally relevant parameters. Hence the software can enrich their decision-making process by modelling outputs which were not accessible to them beforehand.

The general problem of translational issues between research and policy making is not limited to decision modelling. In a systematic review Oliver et al. [278] found that the most relevant barriers to using research in policy were timely access to good quality results. On the other hand, the transition of research to policy was found to be facilitated by collaboration between researchers and policy makers, as done during the development of the multi-STI model presented in this thesis.

One key feature of a health economic model being used in policy making is the usability of the decision model. Cheung et al. found that their model profited from the collaborative

developing approach of the software [279]. This goes hand-in-hand with the development process used in this thesis to optimise the software towards its potential users. Cheung et al. suggest taking such an approach even though it takes more time upfront, as this pays back on the long run because the thereby optimized usability will enhance the impact of the research to policy making.

Engaging with decision makers presents a way to improve the use of decision models as a tool to help with resource allocation decisions. In this study I ensured that end users, people responsible for making local resource allocation decisions, were involved throughout the development of the model. Other authors regard this as a best practice to facilitate the transition of research into policy making. It was my aim that if a decision maker was presented with, for example, a decision about increasing STI testing, the ability use the model as a decision support is not hampered by lack of usability or avoidable technical barriers. The decision support software is supposed to be a straightforward way to find the most efficient patient group to implement said STI testing and its financial implications. Examples on how this software might help policy makers in their decision making were given in Section 9.4.1.

9.6 Future Research and Development

9.6.1 Potential Technical Improvements of the Software

A major flaw of the current software is that it runs on the computer of the person who has the code. This means that new versions can only be distributed to potential users by circulating another version to all potential users.

A neater solution would run the code on a server and people who want to use the software can access it through an internet browser. I planned to migrate the software to a website, but unfortunately, I could not get any webspace to do so.

Making the software accessible through a website instead of forcing potential users to download it has further advantages. Some users might be restricted by the data security policies of their workplace so that they are not allowed to download software or to install software on their own. If the multi-STI software was available through a website these problems would not occur.

Having the software available online brings further advantages with it; If an update of the software has to be distributed it will be available for all users immediately, compared to the need of downloading a new version by each user on their own after the version has been made available for downloading.

9.6.2 Model Development and Model Updating

Whereas the model itself is structured flexibly and equipped with graphical user interfaces it is still necessary to develop new model structures by hand. This requires users to manually input data. A solution to this problem would be to automatically generate models from descriptive, e.g. epidemiological, data sets. A typical use case would then look like this, for example:

A decision maker has a specific research question on a disease for which he has no model available yet. They have access to a descriptive dataset of cases. This dataset is fed into a model generator, which automatically generates a model out of this data set. In the next step, they use this model in my software to answer certain research questions around this disease. Some promising steps in this direction have already been made in other disease areas [280].

9.6.3 Localized Parametrisation of the Models

A pre-requirement of this is making the dataset available which contain relevant data. A good trend is that a lot of publishers actively ask their authors to submit data alongside

studies. But further initiative is needed so that researchers can use the available datasets for their own research. This poses many new questions, especially when we consider General Data Protection Regulation (GDPR) so that the rights of the people described in the data sets are not violated.

9.6.4 More Detailed Models

An interesting area of research with potential impact on the modelling software is genome sequencing and personalized medicine. Whereas already genome sequencing and personalized medicine is used in clinical practice, only a few models have been developed to successfully show this in silico. These models are mostly in-host models, which examine the interaction of the host with a pathogen on a very detailed level. It will be interesting to see, whether the in-host modelling could be brought together with population-wide models. A combination of those models could use genome data and examine the individual effects in much more detail than current models could do.

9.6.5 Usage of Software in Other Countries

Every parameter used in the software is adjustable. The current parametrisation is done in a way to reflect an average English setting. These parameters can be modified if more localized data is available to input a simulation for a more specific geographical area of interest.

The modelling software could also be used to simulate STIs in countries other than England. Therefore, the list of simulated STIs might need to be changed or the description of the sexual network needs to be amended. All those changes do not require any change in the software, but only in the inputted models and can hence be done by sophisticated users of the model who could program new software code.

9.7 Concluding Thoughts

In this thesis, I have presented an approach to simulate multiple STIs simultaneously in one disease model. The default models and parameters which are included in the software reflect the English STI landscape with a special focus on decision makers in sexual health care. All aspects of the model are designed flexibly to allow users of the model to amend parameters. This can be used to examine various kinds of research questions or to fit the model to changes in medical knowledge. It is also possible to use this model in a non-English context if the parametrisation is done accordingly. In contrast to many other models, as shown in Chapter 2, this model is able to calculate health economic results such as CUA, based on inputted costs and utility decrements. These inputted values, especially the costs, can also be adapted by users to fit it to their local prices or to use a different perspective than the one which was used by default in this software.

I have shown that it is possible to develop a multi-STI software which can directly assist decision makers in cooperation with decision makers. Other recent research has shown that this approach can be beneficial for both the researchers and decision makers. For example Maluka et al. concluded in their work with Tanzanian decision makers that collaboration between researchers and decision makers is advantageous for both parties, but it also brings new challenges into the work [281]. Gagliardi et al. agree that the communication between researchers and decision makers can be difficult and examined how this communication can become more effective. They concluded that exchange is facilitated by involvement of sufficient number of decision makers in the process, sharing of background knowledge and incentivising decision makers to participate [282]. The last of these suggestions was not done in my study to avoid potential conflict of interests on their side.

This thesis has also shown that it is possible to develop a disease model in a flexible way to allow for changes in the model in future. The model itself was designed in a way so that it can be reused to examine various questions, which will hopefully be an example of how to avoid research software being thrown away after one usage. This development was possible thanks to close cooperation with decision makers.

It is in line with other research showing that close cooperation of decision makers and researchers is beneficial for both parties, as decision makers can get software which facilitate their daily decisions and researchers can see a direct impact of their work on real-life policy decisions.

9.7.1 Final Statement

In this thesis I have presented a piece of work which showed the beneficial results of a close cooperation between decision makers and researchers during research. The software which was developed during this thesis can be used in research and policymaking without further amendments.

I have shown that it is possible to develop a multi-STI modelling software which is able to calculate health economic results to support decision making in sexual health care whilst providing an intuitive user interface to keep the technological usage barrier of the software as low as possible.

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Appendix A

Systematic Review

A.1 Search Strategy

I used the same search strategy for all databases, which were included in the systematic review. As the syntax of those databases, as well as the offered functionality, slightly varies the strategy was amended for each database.

The search strategy for Medline and Embase has already been presented in the thesis, see section 2.3.3.1. In this section, I only present the adaptions for other databases which have not been mentioned yet.

A.1.1 Cochrane

Cochrane uses the same thesaurus as Medline and Embase. The syntax is slightly different. Cochrane does not support the limited suffix syntax, e.g. “*2”, which is why these were replaced by unlimited suffix searches. The adjacent operator uses another syntax in Cochrane, therefore all “adj” instances have been replaced by “near”.

1. interact*.mp
2. coinfect*.mp
3. parallel.mp
4. simultaneous*.mp
5. coexist*.mp
6. multi*.mp
7. "more than".mp
8. #1 or #2 or #3 or #4 or #5 or #6 or #7

9. (compart* near model*).mp
10. (mathematic* near model*).mp
11. (comput* near model*).mp
12. *decision support techniques/
13. *models, theoretical/
14. *models, statistical/
15. exp models, economic/
16. exp nonlinear dynamics/
17. "agent based model*".mp
18. (decision* near support*).mp
19. (quant* near model*).mp
20. "discrete event".mp
21. "markov* model*".mp
22. STDSIM.mp
23. "micro simul*".mp
24. "agentbased model*".mp
25. "theoretical model*".mp
26. "statistical model*".mp
27. "economic model*".mp
28. "nonlinear dynamics".mp
29. microsimul*.mp
30. "individual based model*".mp
31. #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30

32. exp Sexually Transmitted Diseases/
33. "sexual* transmit* infect*".mp
34. "sexual* transmit* disease*".mp
35. STD*.mp
36. STI*.mp
37. HIV.mp
38. "human immunodeficiency virus".mp
39. Hepatitis.mp
40. "Genital Herpes".mp
41. HSV.mp
42. HSV-1.mp
43. HSV-2.mp
44. "acquired immune deficiency syndrome".mp
45. mycoplasma.mp
46. gonorrhoea.mp
47. syphilis.mp
48. Chlamydia.mp
49. "Lymphogranuloma Venereum".mp
50. Chancroid.mp
51. "Treponema Pallidum".mp
52. Trichomon*.mp
53. "Human Papillomavirus".mp
54. "Genital Warts".mp
55. "Pelvic Inflammatory Disease".mp

56. PID.mp
57. "Condylomata Acuminata".mp
58. Cervicitis.mp
59. Epididymitis.mp
60. Urethritis.mp
61. Infertility.mp
62. "venereal disease*".mp
63. "venereal infect*".mp
64. #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63
65. #8 and #31 and #64

A.1.2 Dart Europe

Dart Europe is, compared with Embase and Medline, a small database. The search interface is therefore not as sophisticated and does not allow thesaurus searches. The search strategy was therefore held as simple as possible to not accidentally exclude any relevant PhD theses.

1. “sexually transmitted”
2. “model”
3. #1 and #2

A.1.3 OpenGrey

Preliminary searches found, that OpenGrey only contains very few articles which could possibly be relevant for the Systematic Review. Considering the simple search user interface this resulted in a very simple search strategy.

1. “sexually transmitted”

A.1.4 PLOS and ProQuest

The Public Library of Science (PLOS) does not have any underlying thesaurus to support the search. Furthermore, the syntax does not support the adjacent operator. PLOS allows searching the title, abstract or full text, I decided to search for all terms in the title and abstract only.

ProQuest does not support thesaurus search or advanced syntax, which is why I had to simplify the search strategy as well. I decided to search anywhere but in the full text. I searched for scholarly articles, dissertations, theses, working papers, reports, conference papers, and conference proceedings. I did not search for wire feeds, newspapers, trade journals, magazines, blogs, podcasts, and websites.

Due to the similar requirements, I developed one search strategy which was used with PLOS and ProQuest.

1. interact*
2. coinfect*
3. parallel
4. simultaneous*
5. coexist*
6. multi*
7. "more than"
8. #1 or #2 or #3 or #4 or #5 or #6 or #7
9. compart* model*
10. mathematic* model*
11. comput* model*
12. "agent based model*"
13. decision support
14. quant* model*
15. "discrete event"

16. "markov* model*"
17. STDSIM
18. "micro simul*"
19. "agentbased model*"
20. "theoretical model*"
21. "statistical model*"
22. "economic model*"
23. "nonlinear dynamics"
24. microsimul*
25. "individual based model*"
26. #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25
27. "sexual* transmit* infect*"
28. "sexual* transmit* disease*"
29. STD*
30. STI*
31. HIV
32. "human immunodeficiency virus"
33. Hepatitis
34. "Genital Herpes"
35. HSV
36. HSV-1
37. HSV-2
38. "acquired immune deficiency syndrome"

39. mycoplasma
40. gonorrhoea
41. syphilis
42. chlamydia
43. "Lymphogranuloma Venereum"
44. Chancroid
45. "Treponema Pallidum"
46. Trichomon*
47. "Human Papillomavirus"
48. "Genital Warts"
49. "Pelvic Inflammatory Disease"
50. PID
51. #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50
52. #8 and #26 and #51

A.1.5 Web of Science

Web of Science does not have a thesaurus. The database also does not have a limited suffix search, which is why I replaced those with unlimited suffix searches. The adjacent operator is the same as the one of the Cochrane interface. As Web of Science also accesses non-medicinal journals, I decided to not use any abbreviations to decrease the possibility of finding completely unrelated articles.

1. interact*
2. coinfect*
3. parallel
4. simultaneous*
5. coexist*

6. multi*
7. "more than"
8. #1 or #2 or #3 or #4 or #5 or #6 or #7
9. (compart* near model*)
10. (mathematic* near model*)
11. (comput* near model*)
12. "agent based model*"
13. (decision* near support*)
14. (quant* near model*)
15. "discrete event"
16. "markov* model*"
17. STDSIM
18. "micro simul*"
19. "agentbased model*"
20. "theoretical model*"
21. "statistical model*"
22. "economic model*"
23. "nonlinear dynamics"
24. microsimul*
25. "individual based model*"
26. #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25
27. "sexual* transmit* infect*"
28. "sexual* transmit* disease*"

29. "human immunodeficiency virus"
30. hepatitis
31. "genital herpes"
32. "acquired immune deficiency syndrome"
33. mycoplasma
34. gonorrhoea
35. syphilis
36. chlamydia
37. "Lymphogranuloma Venereum"
38. Chancroid
39. "Treponema Pallidum"
40. Trichomon*
41. "Human Papillomavirus"
42. "Genital Warts"
43. "Pelvic Inflammatory Disease"
44. "Condylomata Acuminata"
45. Cervicitis
46. Epididymitis
47. Urethritis
48. Infertility
49. "venereal disease"
50. "venereal infect*"
51. #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50
52. #8 and #26 and #51

A.2 Data Items

The following paragraphs detail each data item which was collected during the systematic review. They summarise why these items have been selected to be extracted and what I hoped to gain by gathering information on these items.

A.2.1 Modelling Approach

I extracted the general approach the modellers used. This can be for example “Discrete Event Simulation” or “Markov Microsimulation”. This approach is described in more detailed by the following items.

A.2.1.1 Entity Level

This item was used to describe whether an individual-based or a compartment-based approach was used, which means whether the model simulates each simulated patient individually or whether they were put into subgroups of the population, for example, infected and non-infected.

A.2.1.2 Open Cohort vs Closed Cohort

I extracted information on whether new individual can enter the cohort (open cohort) so that the simulated cohort stay at the same size or whether simulated patients who leave the cohort are not going to be replaced (closed cohort).

A.2.1.3 Interacting vs. Non-Interacting Population

I extracted information on whether the individuals in a model can interact in some form with each other or whether they are mostly independent of each other.

If they can interact with each other I looked at whether a sexual contact network is used to describe this model and how this network is described.

A.2.2 Time Handling

I looked at how time is simulated in a model. For example, does it proceed in slices of fixed length or does the model jump from one event to the next? Another option is that time is handled continuously as an unrestricted input parameter.

A.2.3 Data Origin

I looked at the inputted cohort of the model. Whether it is based on a real-life cohort or whether hypothetical data is used. If hypothetical data is used, I looked at the origin for the authors’ assumptions.

A.2.4 Cohort Size

I looked at which part of the population is simulated in the model. Whether the model looks at the whole population or whether only a sub-group is regarded.

A.2.5 Time Horizon

I extracted data on the time horizon of the model which can be useful to understand the purpose of the model.

A.2.6 Modelling Software

I extracted the modelling software which was used to develop and run the model. This could be either specialised modelling software or more general tools like spreadsheet tools.

Several software packages exist which are readily available to model diseases. Most of these have not been specifically developed to simulate STIs. Most software is developed for disease modelling in general or for other, e.g. statistical, purposes.

The most important examples of this kind of software are WinBUGS [1] and TreeAge [2].

Other software is sometimes free to use, like R or LibreOffice, or requires licenses such as Statistics and Data (STATA)[3], Statistical Analysis System (SAS)[4], or Microsoft Excel [5].

A.2.7 List of Included STIs

I summarised all STIs which were examined in this model.

A.2.7.1 Interaction

I extracted whether the simulated STIs are modelled in parallel or whether they interact in some form. If possible, I described how the interaction affects the STIs.

A.2.7.2 List of Sequelae of STIs

I extracted sequelae, long-term and short-term, which are included in the model.

A.2.8 Interventions

I looked at the interventions which were simulated by the model and whether the model recommends the implementation of this intervention.

[1] https://www.mrc-bsu.cam.ac.uk/software/bugs/the-bugs-project-winbugs/
[2] https://www.treeage.com/
[3] https://www.stata-uk.com
[4] https://www.sas.com/
[5] https://www.microsoft.com/Microsoft/Excel

A.2.9 Economic component

I extracted information on the economic component of the model if there was any. I extracted the type (or types) of analysis this model is able to perform.

A.2.10 Year in Which the Study Has Been Conducted

As there might be some time difference between conducting a study and publishing it, it is relevant to know the year in which the study has been conducted. If this year was not reported in the article, I assumed that the study has been conducted in the year of the publication.

A.2.11 Input

I collected all relevant parameters which can be inputted by a user.

A.2.12 Country

I extracted information on the country (or countries) of the modelling study. The region was mapped to the high-, lower middle-, upper middle-, or low-income region based on the World Bank definition of July 2017 [283], see also table A.1.

Table A.1: Mapping of average gross national income per capita to income group by World Bank definition

Average gross national income per capita	Group
<=$1005	Low income
<=$3995 and >$1006	Lower middle income
<=$12235 and >$3956	Upper middle income
<=$12236	High income

A.2.13 Output

I collected all relevant output parameters which can be calculated by a model.

A.2.14 Customisability

Based on the possibility to generalise a model I tried to extract information on the generalisability. More specifically whether the model can be used by other researchers for other research questions.

A.3 Database Scheme

The database scheme of the database, which I have set up in Microsoft Access to document and conduct the systematic review is shown in Figure A.1.

A.4 Databases

The UCL library offers a list of all databases, which can be assessed as a member of UCL [6]. This list does not contain all databases, but it contains the most important databases for academic articles. Within this list, I searched for databases which might contain relevant articles for my field of research. This included all databases which include journals about medicine, economics, and computational modelling. The resulting databases are introduced shortly within the following paragraphs in alphabetical order.

A.4.1 ASSIA

Applied Social Sciences Index and Abstracts (ASSIA) is part of the ProQuest network and links to more than 500 journals. The scope of this database covers articles on health, social services, psychology, sociology, economics, politics, race relations and education. Although this database looked promising at first glance it was not used for literature reviews, as the "umbrella" database of ProQuest contains all ASSIA articles. Therefore, every article which was be found in this database was also found using ProQuest [284, 285].

A.4.2 Cochrane Library

The Cochrane Library[7] is a service offered by Cochrane. Cochrane is an organization which tries to deliver high-quality information for making health-related decisions. Cochrane is an international network of people working in health care and healthcare research. Therefore Cochrane conducts trials and systematic reviews to generate credible and accessible information. Cochrane offers a web interface, Cochrane Library, to search within all articles they have published. The database is small than other databases included in this review, but the quality of the included articles is high.

A.4.3 Embase

The Excerpta Medica Database (EMBASE)[8] contains mainly biomedical and pharmacological articles and is produced by Elsevier. It indexes over 8500 Journals, with the earliest records dating back to 1974. Overall more than 30 million articles are in the EMBASE database. It contains more than 6 million articles from 2900 Journals, which are not Medline-indexed. The usage of EMBASE is charged, but free for members of UCL.

[6] https://www.ucl.ac.uk/library/electronic-resources/databases.
[7] http://www.cochranelibrary.com/
[8] http://www.ovid.com/site/catalog/databases/903.jsp

A.4.4 PloS

The PLOS[9] is an open-access database. The usage of this database is free. It contains articles from all PLOS Journals. These journals mainly focus on medical and biomedical topics.

A.4.5 ProQuest

ProQuest[10] is a network of 36 databases from various fields. To conduct a more specific search a user can decide which databases should be included in his search.

A.4.6 PubMed

PubMed[11] is an American meta-library consisting of Medline, old Medline, and PubMed Central. Accessing the database is free. The database is governed by the US National Library of Medicine. It contains more than 26 million articles from more than 5500 journals.

A.4.7 Web of Science

Web of Science[12] is managed by Thomson Reuters. The usage of Web of Science is not free, but UCL members have full access to Web of Science. It contains articles from more than 500 journals. Web of Science offers the possibility of displaying the citation network around an article to see which articles are cited and which articles cite a specific article.

[9] https://www.plos.org/
[10] http://search.proquest.com/
[11] https://www.ncbi.nlm.nih.gov/
[12] https://www.ncbi.nlm.nih.gov/

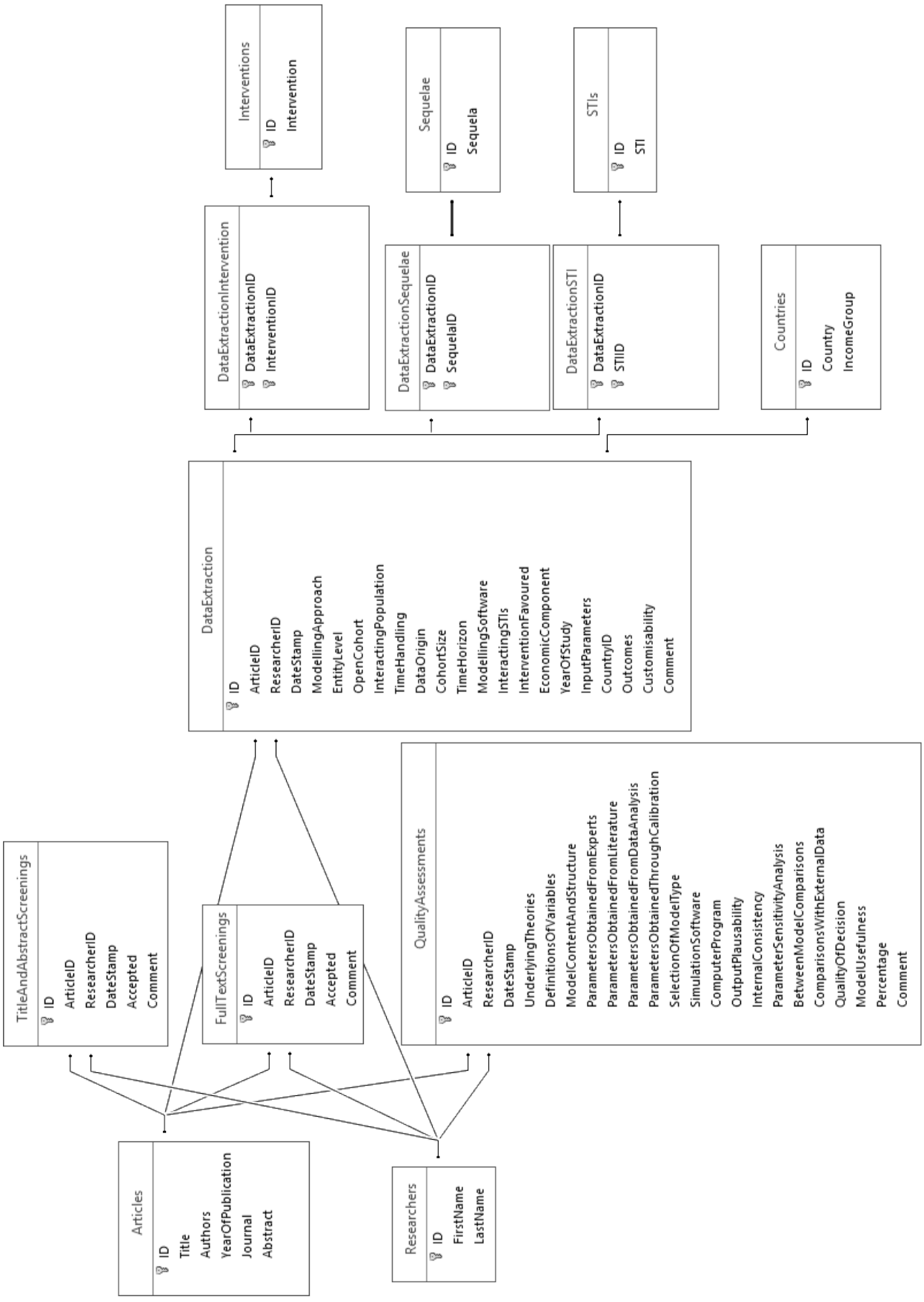

Figure A.1: Database Scheme of the Microsoft access database

Appendix B

Prototyping to Compare Markov Microsimulation and Discrete Event Simulation for Simulation STIs

To be able to compare both modelling approaches, they should simulate the same scenario. Therefore a fictional STI was modelled. This STI was connected with hypothetical sequelae. The model structure of this disease model is described in more depth in the next section, see Section B.1.2.

The main difference between MMS and DES is the way they handle time as described earlier, see Sections 3.2.1.3 and 3.2.1.2. An MMS will move forward in cycles of a fixed length, e.g. one day. DES jumps on the time axis from one event to the next. This means that the model can, for example, calculate an event on day 5 and then jump to day 47 if there are no events in-between. These jumps do not have a certain length, the next one might only be one day long. They only depend on the next event in the event queue.

B.1 Methods and Aims

The main aim of this prototype was to compare the suitability of a DES and an MMS modelling approach when modelling STIs on an individual level in a multi STI model. Therefore I compared the complexity of setting up a disease model in both approaches. After both models have been developed, I compared whether both models produce similar outcomes. This was necessary to understand whether they are comparable in terms of outcome quality. Furthermore, I compared key performance indicators of the model runs to see which approach simulates faster and can cope better with the expected complexity of a big dis-

ease model.

The prototype was modelling a hypothetical STI, which might lead to hypothetical sequelae. In order to allow infections, a simple sexual network was set up. The sexual network is described in the next two paragraphs. After that, the STI model and the sequelae model is described. No treatments have been included in this prototype.

B.1.1 Sexual Network

The sexual network in this prototype randomly draws two random individuals. This happened each day one time for every 20 individuals in the model. These individuals thereafter had unprotected sexual intercourse which might lead to the infection. An infection can only occur if one individual is infectious and the other one is healthy. If both individuals are healthy or both individuals are infected with the STI nothing will happen. Individuals who are in the incubation period will be treated as if they are not infected for this comparison. But these individuals cannot be infected and are not able to infect others.

Condom use is not modelled in this simple sexual network. The behaviour of an individual will not change due to their infectious status. The same sexual network has been used for both modelling approaches to prevent any influences from the network. The disease models communicated with the sexual network using a previously defined interface so that no disease model had an advantage over the other. The same random seed for the model has been chosen, so that the same pseudo-random individuals were picked in both prototypes. A separate random number generator was used for random numbers which were drawn within the disease models.

Figure B.1 shows a simplified class diagram to showcase the connection between the sexual network and the STI models as explained above.

B.1.2 STI Model

The model does not consider immunity again the hypothetical STI and therefore consists of three stages: susceptible, pre-infected, and infected. Susceptible individuals can get the disease by being infected. Pre-infected individuals already caught the disease, but they are not contagious at this point. This time is also called "incubation period", in this example it lasts between one and two days.

Individuals who are in the "infected" state can infect others. An infection will last at least five days. 60% of all infected people will cure within 10 days after first showing symptoms. An infection will not last longer than 30 days.

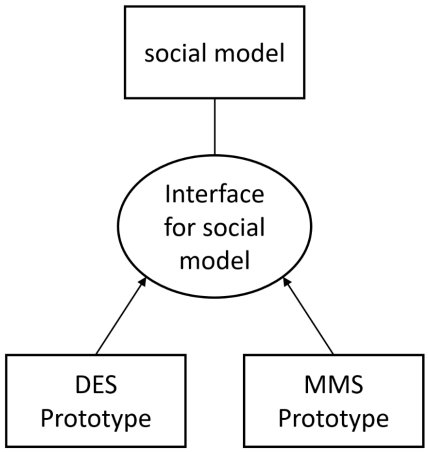

Figure B.1: A simplified schematic class diagram of the prototype

As no treatment is included in the model, the only way to get back into the "uninfected" state is to recover on their own.

The resulting model structure for this prototype is the same for both disease model, as the medical evidence does not change with the modelling approach. The model structure is displayed in Figure 3.1 in Section 3.3.

B.1.3 Sequelae Model

The sequelae model has the three health states as well: "uninfected", "incubation period", and "infected".

As long as an individual is in health state “infected” of the STI-model the individual is under risk to develop the hypothetical sequelae. Two per cent of all infected individuals will get this sequela. The incubation period of the sequela is 10 days. The sequela will not occur in healthy individuals. Individuals with the sequela will recover after at least one day and no more than 28 days of being in the health state "infected"

No treatment option for the sequelae has been included.

B.1.4 Markov-Based Microsimulation

In MMS time proceeds in fixed time steps, called cycles. The shortest time interval in the model is one day. For example, the incubation period in the STI-model is one day, such as the minimum duration of the sequela. To guarantee that no transition is "lost" or postponed due to the granularity of the time scale the cycle length of the model must be one day.

State transition probabilities have been calculated based on the parameters which have been described above. All transition probabilities in the model are fixed and will not change over time. The only exception to this assumption is the transition from “no sequela”

to “sequela”, which can only occur as long the individual is “infected”.

The parameters in Table B.1 have been used to parametrize the MMS model. The probabilities are all daily probabilities, which have been calculated by using formula B.1.

$$p_2 = 1 - (1 - p_1)^{\frac{t_2}{t_1}} \tag{B.1}$$

With the following parameters:

p_1 the old transition probability,

p_2 the new transition probability,

t_1 the old interval length, and

t_2 the new interval length.

Whereas t_1 was set to the average duration in a health state and p_1 to 50%.

Table B.1: Parameters of the MMS prototype model

from state	to state	probability	comment
no STI	no STI	100%	All individuals stay in this state until they are infected (via social model).
no STI	incubation (STI)	n/a	Simulated in social model.
incubation (STI)	incubation (STI)	0%	Tunnel state transit, no individual must stay longer than one day in this health state.
incubation (STI)	STI	100%	Stay one cycle in “incubation (STI)” then proceed top “STI”.
STI	no STI	7.41%	Average duration is 9 days, therefore after 9 days 50% should leave this health state, see formula B.1.
STI	STI	92.48%	Individuals who do not transit to "no STI" stay in "STI": 100% - 7.41% =92.48%.
No sequela	No sequela	100% or 99.78%	If STI is not present, individual will stay in this health state, otherwise: everyone who does not transit to "sequela" will stay in "no sequela": 100% - 0.22% = 99.78%
No sequela	sequela	0% or 0.22%	no STI is present, this transition is disabled, otherwise: Within 9 days 2% should develop the sequela, see formula B.1.
sequela	sequela	95.17%	Everyone who does not leave "sequela", stays in "sequela": 100% - 4.83% =95.17%
sequela	no sequela	4.83%	Average Duration is 14 days, therefore after 14 days 50% should leave this health state, see formula B.1

B.1.5 Discrete Event Simulation

In this approach, all state transitions are transcribed into so-called events. All events for all people are stored in the same event queue. This queue is sorted chronologically so that the earliest event will be processed first. Each event describes a time point when something will happen and what happens at this time point, e.g. a transition from "uninfected" to "incubation period".

If a person is infected with the hypothetical STI (= getting into the "infected" health state of the STI-model) two events for this person will be added to the event queue. One is for the cure of the STI-infection (= "cure event"). The other one is for the sequela becoming

present (= "sequela-event"). The time-to-event for both events are calculated at the same time and both have a random component. This means that for some people the cure-event will happen first and for other the sequela-event. If the "cure-event" happens first the "sequela-event" will be deleted from the event queue without taking effect. If the "sequela-event" occurs first, the "cure-event" is not affected.

The time to event calculation in the first version of the DES-model prototype used Kaplan-Meier curves. Therefore, a random number is drawn (between 0% and 100%). This value will be used as y-value for a Kaplan-Meier curve. The corresponding x-value is looked up, by drawing a horizontal line until it crosses the Kaplan Meier curve. The x value from the intersection is then the event time. This process is equivalent to solving the describing function of the Kaplan Meyer Curve. This x-value is then added to the current day, to calculate the point of time when the event will occur. This event will be added to the event queue. If multiple transitions are possible the "Kaplan Meier lookup" is processed individually, with individual random numbers, for each transition.

The model was parametrised in a way which exactly fitted the description above. The parameters and time to event formulas are listed in Table B.2. Some probabilities were recalculated to adjust for the duration of a person being in a certain health state. A sequela event will be created in 5%-threshold of all cases instead of 2%, to account for the fact that some events will not be processed. Because individuals might recover before they develop the sequela. We know that the incubation period of the sequela is 10 days and there is the possibility of curing the STI infection within these 10 days. Only 40 per cent of all people will still be infected after 10 days. Therefore this probability has to be adjusted as follows: of 100% get 2% infected, to keep the same absolute amount infected of 40% of all 5% need to be infected).

Table B.2: Initial parameters of the DES prototype model

from state	to state	formula	comment
no STI	no STI	n/a	no event needed
no STI	incubation (STI)	n/a	modelled in social model
incubation (STI)	incubation (STI)	n/a	no event needed
incubation (STI)	STI	1	after 1 day the person transits into health state "STI"
STI	no STI	if(random $>$ 0.4) $\{\frac{1.72-random}{0.12}\}$ else $\{\frac{0.63-random}{0.02}\}$	A random value is only drawn once and then used to calculate the event time. These formulas describe the shape of the Kaplan-Meier curve, which was derived from the aforementioned information.
STI	STI	n/a	no event needed
No sequela	No sequela	n/a	no event needed
No sequela	sequela	if(random $<$ 0.05) { 9 }	In 5% of all cases a sequela will occur
sequela	sequela	n/a	no event needed
sequela	no sequela	14 +/- random component	duration of 14 days.

Upon comparison with the MMS-model, I saw that both models produced significantly different output. Therefore the model parametrisation was revisited to fit the parametrisation of the MMS-model as closely as possible. This was necessary as the minimum and maximum duration in a health state could not be defined in the MMS-model. The explanation for this is in detailed in Section B.2.1. This resulted in a different set of time-to-event formulas, see Table B.3 being used by the DES-model:

Table B.3: Optimised parameters of the DES prototype model

from state	to state	formula	comment
no STI	no STI	n/a	no event needed
no STI	incubation (STI)	n/a	modelled in social model
incubation (STI)	incubation (STI)	n/a	no event needed
incubation (STI)	STI	1	after 1 day the person transits into health state "STI"
STI	no STI	$\frac{1.0-random}{0.033}\}$	Simplified Kaplan Meier curve, not taking the differences in incidence over time into account
STI	STI	n/a	no event needed
No sequela	No sequela	n/a	no event needed
No sequela	sequela	if(random $<$ 0.05) { 9 }	In 5% of all cases a sequela will occur
sequela	sequela	n/a	no event needed
sequela	no sequela	14	duration of 14 days.

B.1.6 Comparisons

To evaluate the performance of both prototypes I varied the size of the cohort from 1000 individuals to 10000 individuals (in steps of 1000). I increased the duration of the simulation from one year to ten years (in one-year steps). Therefore, 100 different input combinations were tested. For each of those model runs I assumed, that the number of initially infected people was 1% of the total cohort. I assumed that each day for every 20 people in the model one contact, which might lead to an infection as explained above, occurred.

B.2 Results

B.2.1 Comparison Parametrisation

The used transition probabilities (and their derivation) in the MMS-model are hard to explain to non-modelling experts. This is since they are not intuitive to read, as they have to be recalculated to daily probabilities. In this prototype, the daily probabilities were still high. If we would start looking at long-lasting diseases, e.g. HIV the daily probabilities would be very low which would make them barely readable. been recalculated to daily. The readability of these probabilities depends on the cycle length, with longer cycles resulting in probabilities which are easier to read. To capture various health states, including transient health states are likely to be short in a general STI-model and therefore the probabilities would be harder to read and understand. A way to avoid this issue would be to allow the users of the model to only see monthly or yearly probabilities and transform them into daily probabilities without displaying these probabilities to the user of the model.

It was not possible to set a minimum length of stay in this version of the prototype. As I used fixed probabilities for each health state transition, the probability could not vary by the length of a person being in a certain health state. There are options to avoid this problem, e.g. so-called tunnel states [83]. These states have a 100% transition probability to the next state and thereby allow people to stay in them for only one day. Using this mechanism, a minimum number of days can be counted until the normal transition probability takes over. Tunnel states, on the other hand, are not able to determine a maximum length in a certain health state. To solve this problem another mechanism, which contradicts the memoryless feature of Markov models could be used, which are n^{th} order Markov models.[83] These deduct a transition probability not only from the current health state a person is in but also on their previous health states.

By deciding to use fixed transition probabilities and not developing a 2^{nd} order (or higher) Markov model people entered and left the health states too early or too late. Looking at the example of people leaving the "infected" state of the hypothetical STI-model. We can see that 32.35% (=$1-(0.9248^5)$) will leave the “infected” state before the minimum infection length of 5 days. 8.86% (=0.9248^{31}) will stay in the “infected” state for at least 31 days. These sum up to an overall error of 41.21%. Similar numbers can be observed for the sequela model: 23.79% (=0.9517^{29}) will stay longer than 28 days in “infected”. There was no minimum stay in the sequela model, therefore we could not observe a left-sided error.

B.2.2 Comparison Outcome

The orange lines show the prevalence calculated by the MMS-model, whereas the blue line shows the prevalence calculated by the DES-model. The models were not calibrated with real-world values and especially the social model does not retrieve any reliable results. These prevalence values are only good to show, whether the results of both prototypes are comparable.

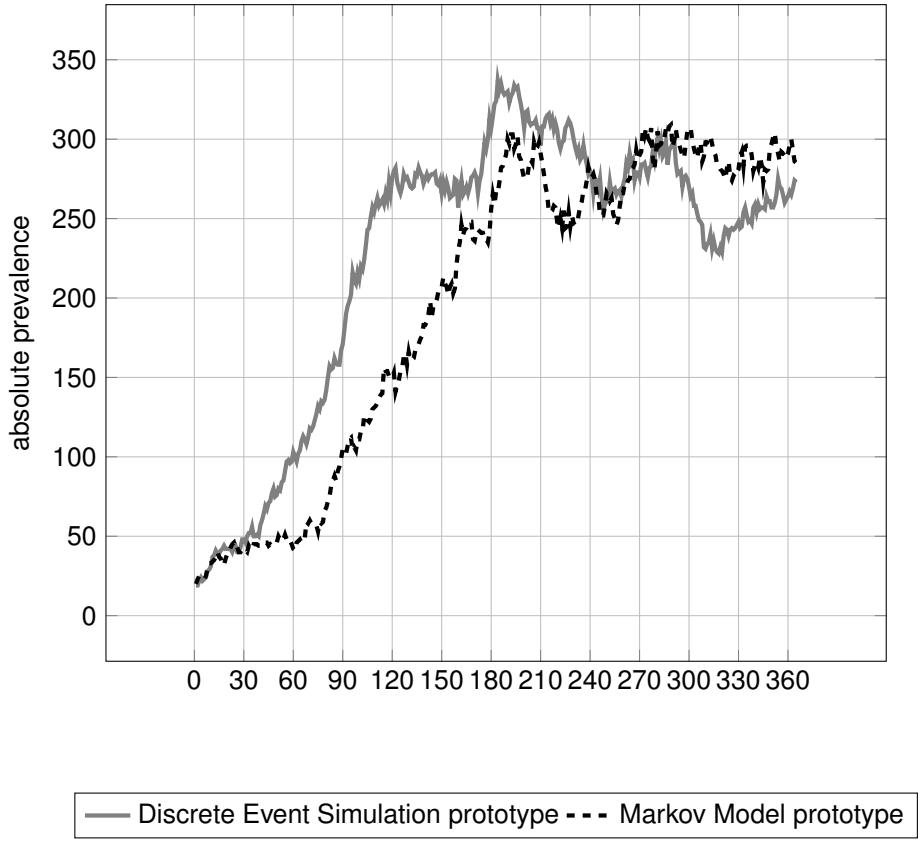

Figure B.2: Comparison prevalence of STI

The model was run with 1000 individuals over one year and 20 initially infected individuals. Both models needed a warm-up period before the prevalence stabilized. The warm-up period for the DES-model lasted approximately 120 days whereas the Markov model needed 165 days. After these 165 “warm-up” cycles both models output values, which fluctuate on a stable level. Regarding only the last 200 values (day 165 until day 365) I performed a t-Test to see whether the output differs significantly. The t-test resulted in a p-value of 0.5220, therefore the difference is considered to not be statistically significant. The mean difference in-between both curves from day 165 on was 30 individuals, which was 3% of the cohort.

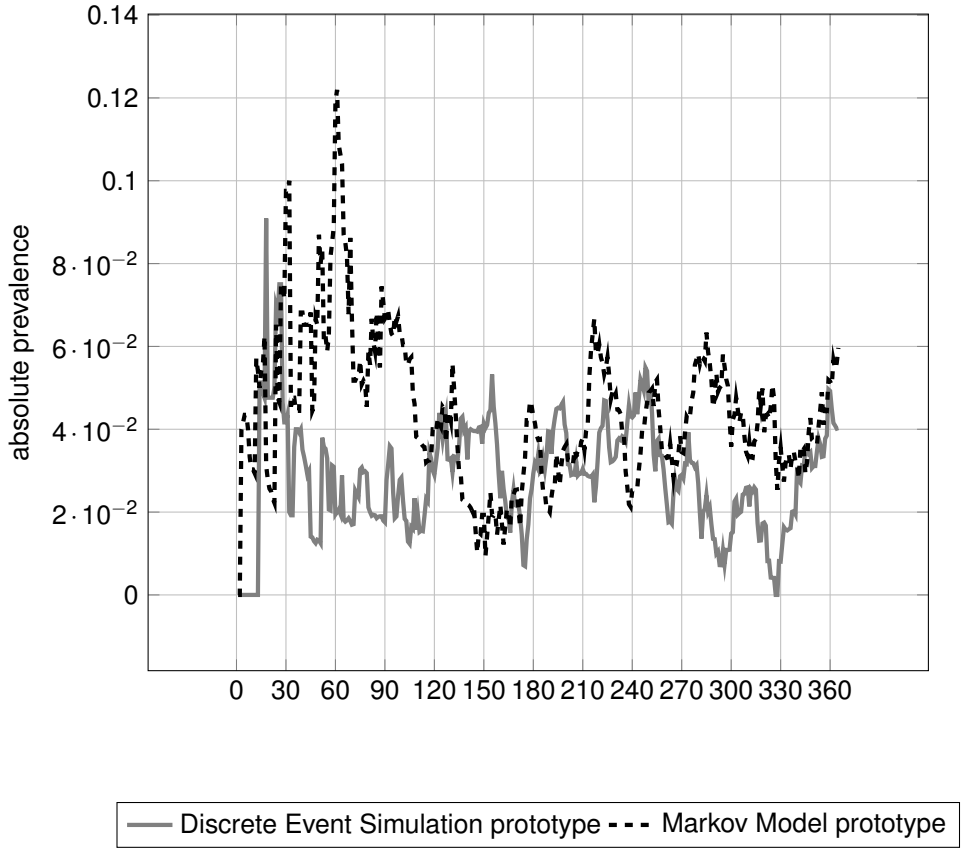

Figure B.3: Comparison prevalence of sequela

This graph shows the prevalence of sequela within the infected individuals. Both curves are above the 2% line, which we would expect. The Mean value for the last 200 days (regarding the warm-up period) for the DES-model is 2.83%, whereas for the MMS-model it is 4.01%. Again, both curves look very similar. The p-value of the t-Test is below 0.0001, therefore the difference is significant. But the output of the DES-model model is much closer to what I expected, than the output of the Markov microsimulation. Several parametrisations to lower the sequela prevalence of the MMS-model failed.

In conclusion, the output of both models is comparable. Both models need time to warm-up and reach a stable level and fluctuate at the same height afterwards. It was easier to input the DES-model to match the expectation based on the hypothetical input data we have got.

B.2.3 Comparison Calculation Time

Table B.4 shows the relative difference in the calculation time of both models for all input combinations. Negative numbers indicate that the DES-prototype was faster, positive

numbers indicate that the MMS-prototype was faster.

On average the DES-model was 73.97% faster. The DES-model was better to cope with an increasing number of individuals whereas the MMS-model dealt slightly better with increments in modelling time. Overall DES is in this aspect and context superior to MMS as it was at least 65% faster.

Table B.4: Comparison of calculation times. Each column increases the number of individuals in the model by 1000 individuals. Each row increases the modelling time by one year.

	1k	2k	3k	4k	5k	6k	7k	8k	9k	10k
1y	-66.67%	-69.23%	-71.43%	-70.37%	-77.14%	-74.42%	-76.00%	-75.86%	-77.27%	-78.48%
2y	-69.23%	-74.07%	-73.81%	-75.86%	-76.71%	-77.27%	-78.30%	-77.31%	-77.61%	-77.33%
3y	-65.00%	-74.42%	-76.12%	-76.14%	-75.89%	-77.21%	-76.88%	-75.14%	-77.78%	-77.29%
4y	-68.00%	-73.68%	-74.71%	-75.42%	-76.67%	-75.84%	-76.08%	-75.93%	-76.19%	-74.83%
5y	-68.75%	-72.86%	-76.11%	-74.32%	-74.33%	-75.33%	-75.09%	-74.84%	-75.65%	-75.52%
6y	-68.42%	-72.09%	-73.88%	-74.87%	-75.64%	-74.46%	-74.30%	-74.53%	-75.18%	-75.11%
7y	-68.09%	-71.84%	-73.58%	-73.02%	-74.26%	-74.70%	-74.67%	-75.57%	-74.65%	-74.50%
8y	-67.92%	-71.79%	-73.08%	-73.88%	-73.40%	-73.68%	-74.38%	-73.96%	-73.90%	-73.90%
9y	-67.21%	-72.18%	-73.81%	-73.76%	-73.52%	-73.54%	-73.76%	-73.95%	-74.03%	-74.41%
10y	-68.18%	-71.43%	-72.73%	-72.61%	-73.67%	-72.90%	-73.43%	-73.99%	-73.85%	-73.92%

B.3 Discussion

MMS performs a high number of unnecessary calculations. This is because MMS draws for each individual in each cycle a random number. Afterwards, this number is compared to state change thresholds and state changes might occur or not. For small cycle numbers, transition probabilities tend to become very small. This means that transitions become rare, which leads to a bunch of unnecessary drawing of random numbers and comparisons. If the cycle length is prolonged to avoid those unnecessary calculations the precision of the result decreases, as some transitions might be lost due to the granularity of the model.

DES-modelling only calculates new event times when an event happened, in between events there are no calculations necessary. Therefore less processing time is needed for these. But it is time-consuming to keep the data in the correct order and form, e.g. to maintain the correct order in the event queue as constantly events are deleted or added. Overall this still advantaged DES as we saw in the previous section.

From a subjective point of view, it was easier to parametrise a DES model. If something is wrong with the inputted values debugging is easier in the DES-model than in the MMS-model. This reflects, to a certain extent, my personal view on this topic. But as I have to develop the models, I can select a modelling approach which suits me best if comes to personal preference.

I think that more Markov models than DES-models are being developed and therefore are more common. People not used to modelling might be more familiar with Markov models and it might need more time to explain the concept of a DES to them. But from my point of view, this is worth doing as it is easier to explain the time-to-event formulas to non-experts that daily transition probabilities.

Besides all mentioned points a DES-model is able to handle more sub-models in a far easier way. As described in Section 3.4.1, diseases have to be modelled with a model for each STI. This will lead to several separate models. In a DES approach different disease models, the sexual network, and treatment models will add their events into a central event queue. All sub-models observe this event queue and wait for events which might affect them. If we would split up the overall model into several sub-models, which is necessary to avoid a health state explosion it would be necessary to connect each of the MMS-sub-models to each other. This would result in $\frac{n^2+n}{2+n}$) communication pathways.

It is easier to look at incidence in a DES model as this is equal to counting processed events, whereas in MMS state changes have to be observed. DES also enables an easy

way of modelling complex transition probabilities, including minimum and maximum duration of illness. As described above these are not trivial to realise in MMS. As a lookup from a Kaplan Meier curve is performed, the exact shape of the Kaplan Meier curve does not matter. Using nth-order Markov chains can solve this problem. But it would yield model structure with long chains which are complicated, less intuitive, and hard to maintain.

It is complicated to update the event queue in a DES approach so that obsolete events get deleted. Especially with many individuals, it becomes inefficient to go through the whole event queue to delete events which have not been affected in some way by the previous event. I describe a solution to this problem in Section 3.4.3.

Both modelling approaches are equally able to handle costs and utility input. Costs can be inputted as daily costs per health state. They can also be connected with transitions to simulate one-time costs. Utility decrements can be attached to each health state. These decrements then have to be combined to one quality of life value. I present an approach to do this in Section 5.

B.3.1 Conclusion

Considering these arguments I decided to use DES as a modelling approach for the overall STI-model. Especially the fact that it helps to simulate health progress more precisely and is easier to understand at the same time is a big benefit of DES in this specific field. It also keeps the complexity low which is an important point when the model has to be explained to non-modelling experts. As a nice side effect, it will also be faster.

Appendix C

Technical Description of The Backend Structure of the Disease Model

This section describes how the backend of the model is structured. The backend is the part of software which is hidden from the user behind user interfaces. The backend is responsible for performing all calculations, whereas the frontend enables the communication with the user.

To allow flexible model design, the *backend* of this STI modelling software should give the user as much freedom as possible. Every attribute value, formula and even the model structures have to be editable to allow a multitude of scenarios in which the software can be used.

At the point of programming, the only constraint regarding the model structure is that discrete event simulation will be used to simulate STIs. Every other aspect of the model should be able to be edited by future model creators. This means that models must not have restrictions on

- the number of states,
- the number of transitions between those states,
- the formulas used to calculate these transitions,
- the number of modelled individuals,
- the time horizon of the model,
- the possible interactions a model might have with another model,
- the number of included STIs,

- the number of included tests and treatments,
- the effect of treatment, and
- the costs and disutilities of all included aspects of the model.

I decided to use the programming language Java to develop the backend of the disease model. Often a computer program is divided into three parts. One part is responsible for the representation and user interaction, which is called view later. The view is the part of the program users interact with and is therefore sometimes also referred to as frontend. Another part is the “brain” of the program, this is the part where all calculations are performed, it is called controller. The third and last part stores the data, either temporarily or permanently. The last part is also called model. A program which is made up of those three parts has a model - view - controller (MVC) architecture. I used an MVC architecture to implement the disease model. This section will describe the model and controller part of the program.

C.1 Model

This part of the backend is called model as it models real-world entities by describing them in a way a computer can process them. Whereas the overall software also is a disease model is is not to be confused with the (data) model of the software which I describe in this section. The description of the model includes information about:

- the connection between different parts of the data,
- which formats (eg. Integer values, String values) are used to describe the data and
- is responsible to store data permanently.

As mentioned earlier all parts of the software have to be adaptable. Therefore I developed a flexible structure to describe necessary elements of the software. On overview of this structure is given in Figure C.1 which has been created with StarUML[1].

This figure is a so-called unified modelling language (UML) class diagram [286]. Class diagrams are used to show which objects are included in the software and how these objects are defined. Each rectangle represents one class. A class is a "type of similar things" from the real world. Each class can have many entities during the runtime of the software and thereby represent different entities of the same type. For example, the class

[1] http://staruml.io/

`DiseaseModel` describes how I define a disease model in the software, this includes its name and a set of health states. During the runtime, I create for each disease which has been defined (see appendix D on how to do that) an entity of the class. These entities vary in their manifestations of the parameters so that they describe different diseases, like `chlamydia` and `gonorrhoea`.

We will now go through the UML class diagram step by step and explain the function of each class. Whenever the number of entities during the runtime is mentioned, this refers to the number of entities per model run. This means that during a multi-threaded model run multiple entities of some classes will be created, e.g. of the class `PartnerNotification`, one per thread.

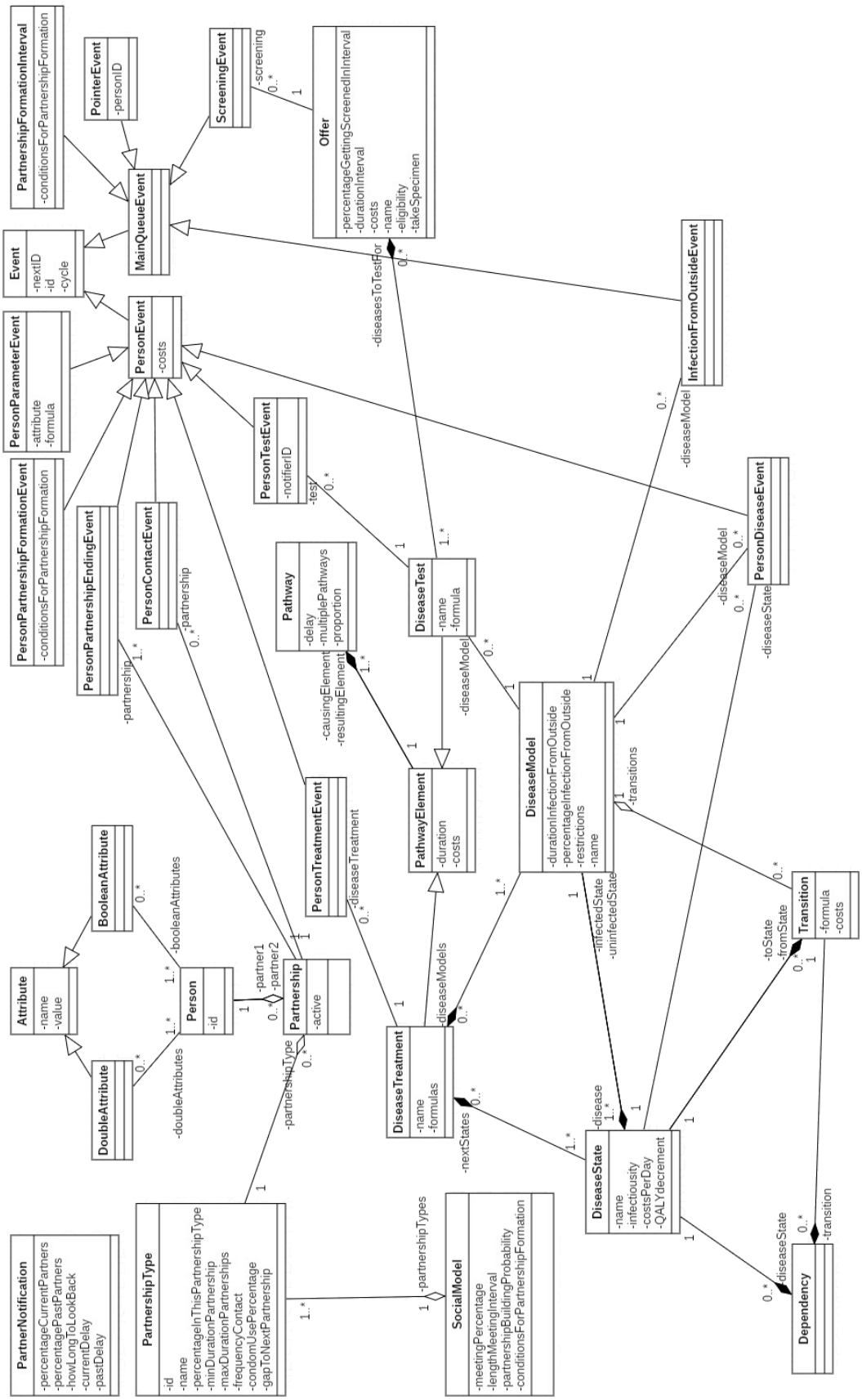

Figure C.1: Simplified UML class diagram of the software

C.1.1 PartnerNotification

The class `PartnerNotification` contains all information which has been defined in the *partnerNotification.txt*,see SectionD.3.5. It is used during the runtime of the program to determine whether a positive test result of an individual will lead to this individual informing their current partner(s) or past partner(s) about the infection. This could then lead to a test of the partner. Whether a current or past partner is informed is a random process and will be decided for each partner individually.

During the runtime, there is only one entity of this class. The class contains the following parameters:

`percentageCurrent`	The likelihood of informing a current partner.
`percentagePast`	The likelihood of informing a past partner.
`howLongLookBack`	Maximum number of days of partner notification after partnership end.
`currentDelay`	How many days the notification of a current partner will be delayed after a positive test result.
`pastDelay`	How many days the notification of a past partner will be delayed after a positive test result.

C.1.2 PartnershipType

During the runtime, one entity per partnership type defined in the *socialmmodel.txt*, see Section D.4.2, is created. Each of those partnership types is defined by the following parameters:

`id`	A unique identification number, generated by the software.
`name`	The name of this partnership type which is displayed alongside results, e.g. active partnerships over time, or sexual contacts over time per partnership type.
`proportion`	Percentage of all newly created partnership being of this type. Percentages of all partnership types have to add up to 100%.
`minDuration`	Minimum duration of a partnership of this type.
`maxDuration`	Maximum duration of a partnership of this type. The duration of a partnership is a randomly drawn and uniformly distributed value between the minimum and maximum duration.
`frequencyContact`	The frequency of sexual contact per day.
`condomUsePercentage`	In how many per cent of all sexual contacts within this partnership type a condom is being used.
`gapToNext`	How long the individuals in a partnership of this type will not look for a new partner after their partnership ends.

C.1.3 SocialModel

The class `SocialModel` contains all information which is written in the *socialmmodel.txt*, see Section D.4.2, except the partnership types. These are:

`proportion`	How many per cent of the total population will be picked to start looking for a partner within the given interval.
`lengthInterval`	Tells the time (in days) which has to pass, before a new fraction of potential partnership seeking individuals is randomly selected. All partnership initiation events are distributed randomly over the whole length of the meeting interval.
`probability`	The probability which is used to determine which proportion of potential partners who fulfil all conditions will start a partnership.
`conditions`	A set of formulas which have to be `true` so that a partnership can be started.

During the runtime, one entity of this class is created.

C.1.4 Attribute

The class `Attribute` is an abstract construct which defined the attribute as a named value. As this class is abstract no entities can be created during runtime.

C.1.4.1 DoubleAttribute

This class inherits its parameters from the class `Attribute`. The names and initial values of all double attributes are defined in the files *doubleAttributes.txt* and the folder *attributes/init*. For each individual and each double attribute an entity of this class is created, which hold the following information:

`name`	The name which can be used to address this parameter, e.g. in time-to-event formulas.
`value`	A numeric value. This can value change during the runtime of the model.

C.1.4.2 BooleanAttribute

This class inherits its parameters from the class `Attribute`. The names and initial values of all boolean attributes are defined in the files *booleanAttributes.txt* and the folder *attributes/init*. For each individual and each double attribute an entity of this class is created, which hold the following information:

`name`	The name which can be used to address this parameter, e.g. in time-to-event formulas.
`value`	A dichotomous `true/false` value. This value can change during the runtime of the model.

C.1.5 Person

The class `Person` represents an individual in the model, for each individual in the model one instance of this class is created. An individual is defined by the following parameters:

id	identification number generated by the software.
doubleAttributes	A list of double attributes describing this individual.
booleanAttributes	A list of boolean attributes describing this individual.

C.1.6 Partnership

The class Partnership describes the sexual partnership of two individuals in the model. It is therefore defined by:

partner1	The first individual in this partnership.
partner2	The second individual in this partnership.
partnershipType	The partnership type of this partnership.
active	Tells whether this partnership is still active. If a partnership is active, sexual contact between the partners can occur. When the partnership is not active any longer no sexual contact will occur, but the previously engaged individuals will not start looking for a new partner A partnership is inactive for the number of days given in the gapToNextPartnership-parameter of the partnershipType. After that time has passed the partnership will be deleted completely.

The number of instances of this class constantly changes during the runtime, as new partnerships form and some older partnerships dissolve.

C.1.7 PathwayElement

This class is an abstract representation of anything which can be part of a pathway, e.g. a test or a treatment. The following parameters are associated with each PathwayElement:

duration	How long it takes to perform the action described by this PathwayElement.
costs	How much it costs (in pennies) to perform the action described by this PathwayElement.

C.1.7.1 DiseaseTreatment

The specific realisation of the class PathwayElement which represents a disease treatment. In addition to the parameters which have been defined in PathwayElement, it uses the following parameters:

name	The name of this treatment which will be used to display the results of a model run.
nextStates	The states in which an individual will be put after a successful treatment.
diseaseModels	The diseases which can be cured by this treatment. They are associated and in the same order as nextStates.
formulas	The formulas which tell how successful the treatment for a specific disease is. The formulas are associated with and in the same order as nextStates and diseaseModels.

For each treatment listed in the folder *pathway/treatment* one instance of this class is created.

C.1.7.2 DiseaseTest

The specific realisation of the class `PathwayElement` which represents a disease test. In addition to the parameters which have been defined in `PathwayElement` it uses the following parameters:

`name`	The name of this treatment which will be used to display the results of a model run.
`diseaseModel`	The disease which can be tested for with this test.
`formulas`	A formula which returns `true/false` to indicate whether the test will be positive or not. This formula should take sensitivity and specificity into account.

For each test listed in the folder *pathway/tests* one instance of this class is created.

C.1.8 Offer

This class contains the information which is given in the files of the *pathway/offers* folder. One instance of this class per file in the folder is created. These files are defined by the following parameters (see D.3.3):

`percentage`	the fraction of all eligible individuals which will get tested during a single interval.
`duration`	The length (in days) of a period in which eligible individuals will get tested. The conduct of a test will happen on a uniformly chosen random value in the interval.
`costs`	How much it costs to do this screening offer.
`name`	The name of this screening offer, which will be displayed alongside at the result presentation of the model.
`eligibility`	A formula which defines the eligibility for this test offer. The formula must return `true/ false`.
`takeSpecimen`	How many of the eligible individuals who got a test offer will actually take the test.
`diseases`	Which tests are included in this offer.

C.1.9 Pathway

A pathway connects two `PathwayElements` with each other, one of which being the `causingElement` which then might lead to the execution of the `resultingElement`. For each pathway defined in the *pathway.txt* file (see D.3.4) an object of this class is created. Besides the before-mentioned two parameters (`causingElement`, `resultingElement`) it is described by these parameters:

delay	How much time (in days) passes between the causingElement is finished and the start of the execution of the resultingElement.
multiplePathways	Tells whether this pathway should be considered every time or whether it is one of multiple pathways which start from the same causingElement and only one of those can be used.
proportion	The proportion of individuals who will (after the causingElement) actually start the execution of the resultingElement

C.1.10 DiseaseState

This class defines one disease state in a disease model. For all health states of each disease model listed in the folder *models* (see D.2) one object is created. Each health state is described by the following parameters:

name	The unique name of this health state, which can be used for example in the formula of a DiseaseTest.
disease	The DiseaseModel this health state is part of.
infectiousity	The probability of transmitting the disease while being in this health state.
costsPerDay	How many costs (in pennies) per day occur if an individual is in this health state.
QALYdecrement	The loss of quality of life due to being in this health state.

C.1.11 Transition

A Transition connects to health state which each other. One is the health state which the individual comes from (fromState) and the other one is where the individual will be in after the transition (toState). Furthermore, a transition is defined by the following parameters:

formula	The time-to-event formula which calculates when the transition is going to happen. This formula should return an number of days which will be added to the current modelled day resulting in the event time.
costs	How much it costs (in pennies) to make this transition.

For each file in the *models/js*-folder, a transition object is created.

C.1.12 Dependency

Upon startup of the software, several Dependency objects are created. Each of these objects tells that after the change of a certain DiseaseState a Transition has to be recalculated. A dependency always states that either the existence of a transition or its calculated event time depends on the individual being in a certain health state. Dependencies are generated for all transitions on their “from states” and of all transitions on health states referenced in their time-to-event formulas.

C.1.13 DiseaseModel

One entity of this class is created for every file in the *models*-folder (see D.2). This object stores information about the first state an individual will be in after he/ she got infected, the so-called `infectedState` and the first State an individual will be in after he/ she has been successfully treated, the so-called `uninfectedState`. Furthermore, it contains a set of all health states included in the model as well as a set of all transitions in the model. To fully describe a disease model the following parameters are also stored:

`name`	The unique name of this disease, which can be used in the formulas.
`states`	Set of all health states used in this model.
`transitions`	Set of all transitions used in this model.
`uninfectedState`	First state an individual is in after successful treatment.
`infectedState`	First state an individual is in after an infection.
`restrictions`	A formula returning `true/ false`. With given parameters this formula can decide whether a certain individual will be simulated in this model. Can be to limit this model to individuals with certain age or sex.
`outsideInterval`	How often people in the modelled cohort get infected from outside the modelled cohort.
`proportionOutside`	How many people in the modelled cohort get infected from outside the modelled cohort.

C.1.14 Event

In a DES everything is controlled by the execution of events. Therefore these events also store chunks of data to trigger actions. At any time anything might happen in the software a new `Event`-object of a specific type is created. It might happen that these events are not actually executed due to events which happen before that. For more detail on this refer to section 3.4.3.

This is an abstract superclass for all different types of events. It only contains parameters which are needed to describe any type of event, these include:

`id`	A unique identification number.
`cycle`	The day at which this event will be executed

The class also holds the `nextID` value, which is used as the `id` of the next event which will be created.

C.1.14.1 MainQueueEvent

This class describes events which are executed in the main queue of the software. These events are either a lookup to an individual's queue (`PointerEvent`) or they trigger actions

which affect more than just a single individual or partnership but large proportions of the modelled cohort. During the runtime, no instances of this abstract class can be created.

ScreeningEvent This type of event starts a new `Offer`. At the end of each `screeningEvent` another one containing the same `Offer` object is created to guarantee that these screenings are continuously offered.

InfectionFromOutsideEvent This type of event triggers infections from the outside of the model. This is necessary as the simulated cohort is not big enough to keep track of every individual in the population. Therefore the modelled individuals will have sexual contacts with individuals from outside the cohort. These not modelled individuals might carry infections as well, which is why a small percentage of infections will happen through this mechanism in the software. The execution of this event will create `PersonDiseaseEvent`s for a randomly chosen subset of the simulated cohort.

PartnershipFormationInterval This triggers a new partnership formation interval. At the end of a partnership formation interval, the next one is started immediately to guarantee a constant creation of new partnerships. It holds all `conditionsForPartnershipFormation`. It will create `PersonPartnershipFormationEvent`s for a randomly selected subset of the cohort.

PointerEvent This event indicates that something might happen with an individual on this day. As the main queue is not kept up to date these pointers will sometimes cause unnecessary lookups, as the connected event has already been deleted from an individual's individual queue. To perform this lookup this event store information about the ID of an individual where a `PersonEvent` is suspected to happen in this cycle.

C.1.14.2 PersonEvent

These events affect a single individual or partnership in the model. in addition to the information held by the `Event` they also contain information on the costs (in pennies) of this event. This is an abstract superclass for all types of events which are no `MainQueueEvent`s.

C.1.14.3 PersonParameterEvent

This type of event contains the name of an attribute and a formula to calculate its new value.

PersonPartnershipFormationEvent This event is created by a `PartnershipFormationInterval`. It holds the same `conditionsForPartnershipFormation`.

PersonPartnershipEndingEvent For each partnership two `PersonPartnershipEnding` events are created. After the first execution the partnership is set inactive. The time which passes between the execution of the first and the second event is the partnership gap. After the execution of the second event, the partnership is deleted. This event type stores the `partnership` it is going to affect.

PersonContactEvent This event knows one `partnership` and represents one sexual contact between the individuals in this partnership. Whether a condom is used or not is calculated upon the execution of the event based on the `condomUsePercetage` of the `PartnershipType` of the associated partnership.

PersonTreatmentEvent This event executes a specific treatment with the given individual. This treatment might or not be successful.

PersonTestEvent This class describes the conduct of a disease test. It also holds the `notifierID`, which is the identification number of the individual who did a partner notification which triggered in this test. This is to avoid endless loops of the same partnes notifying each other. If the individual receives this test through any other pathway, but partner notification this parameter is set to 0.

PersonDiseaseEvent This event type describes the progression of one health state to another. As soon as an individual enters a new health state events for each transition departing from this health state are created. Only one, the first, of those events will be executed all others will be deleted.

The event holds information on the disease model it affects and the health state this individual will be in after this event has been executed successfully.

C.2 Example JavaScript

When time-to-event formulas are processed they might include attributes. For example, a transition from “asymptomatic chlamydia” to “no chlamydia” depends on the sex of an individual, as females tend to have longer periods of asymptomatic chlamydia than men. The corresponding formula might look like that:

```
if(male){90;}else{180;}
```

If we translate this into normal language it says: If the individual is a male, the event will occur in 90 days, in any other case in 180 days. But this code snippet would not be executable by a JavaScript interpreter on its own, as the interpreter doesn’t know what

“male” means. Therefore the statement has to be prepared before execution. To do so the name of the attribute (“male”) in the formula is replaced by the value the attribute holds. This changes the above-mentioned snippet to

```
if(false){90;}else{180;}
```

if it will be executed for a female, which will then output “180”. The snippet will be changed to

```
if(true){90;}else{180;}
```

if a male is taken into account. This will output “90”. If the formula calculates a negative number, no event will be added to the event queue.

Every attribute name in the formula is replaced by the value this attribute holds for a specific individual. This replacement is performed for all attributes, including all Boolean representations of health states, of an individual. Afterwards, the JavaScript interpreter can execute the snippet without any further information. If the formula contains the word “random”, it is replaced by a random value of the Java random number generator. The random number generator of the JavaScript interpreter is not used at this point, as each execution of a code snippet would lead to the creation of a new JavaScript random number generator. As newly created random number generators are likely to produce similar numbers, the overall distribution of those random numbers would be biased.

Appendix D

File Descriptions

The java code of the disease modelling tool does not contain any information about the diseases, the clinical pathways, or the sexual network it is going to model. It is just a framework which can be inputted in different ways to model different diseases or different settings. To fit the model to specific contexts these input files describing the diseases, the sexual network, and the clinical pathway must be specified. Within the next paragraphs, I describe how these files need to be structured.

The model needs a certain file and directory structure so that all important files can be found. Within the root folder, there must be four folders: *attributes*, *models*, *pathway*, and *social*. Additional files and folders will be ignored. All files and folders need to be named correctly (see corresponding paragraphs), otherwise, they will not be found by the software.

If the software is run using the user interface presented in section 4 the root folder should contain four folders named *bame*, *generalpopulation*, *msm*, *youngpeople*. Each of those folders contains the standard parametrisation for one of the sexual network types which have been included in the model. These folders have four sub-folders (*attributes*, *models*, *pathway*, and *social*), which are set up as described below.

D.1 Folder Attributes

This folder contains two files, *booleanAttributes.txt* and *doubleAttributes.txt*. These files list the attributes the model will use for its simulations. There are two folders within the *attribute* folder, which are *dependencies* and *init*. Other files and folders in the attributes folder will be ignored.

D.1.1 File booleanAttributes.txt

This file describes all attributes within the model which can store a boolean value. A boolean value can have two states, it is either true or false. Within the file, one line describes one attribute. This description contains the name (see D.5 for naming conventions) and the initial distribution of this attribute. The value in brackets gives the probability of this value being true upon the creation of a new individual. The probability is given as a value between 0 and 1 (both inclusive), with 0 equals 0% and 1 equals 100%. A boolean attribute called **female** which should be **true** for 50% of all newly generated individuals would be defined by using the following line:

```
female [0.5]
```

The file can contain as many attributes as the user needs to properly describe the model. Each attribute must be defined in a new line of the *booleanAttributes.txt* file.

The software also adds one Boolean attribute for each health state of each disease and sequelae model to the set of all Boolean attributes. These are either `true` if the person is currently in this health state, or `false` otherwise. In doing so, health states can also be used in the time-to-event formulas by referring to their name as defined in the corresponding `model.txt`-file.

D.1.2 File doubleAttribute.txt

This file describes all attributes which have a numeric value. Each line describes an attribute, starting with its name, see section D.5 for naming conventions. The information in brackets, separated by a space from the name describes the initial distribution of the value. It describes how all values of newly created individuals are initially distributed. An example line looks like:

```
age [n,16,24]
```

This will create an attribute called **age**, which is normally distributed between 16 and 24. Two types of distributions are currently possible:

Normal distribution	indicated by *n*. The first number to follow is the mean value minus one standard derivation, the next value describes the mean value plus one standard derivation. It is possible that values outside of these limits will be generated.
Uniform distribution	indicated by *u*. Uniformly distributed values between the first number (inclusive) and the second value (exclusive).

D.1.3 Folder Dependencies

Some attributes will change if the value of another attribute changes. These dependencies are described within the folder *dependencies*. Each file should be named in this manner:

ATTRIBUTE_NAME.DEPENDING_ATTRIBUTE.txt

If the value of the first attribute changes it might lead to a change of the value of the second attribute. The names of both attributes must be spelt as defined in the corresponding *booleanAttribute.txt* or *doubleAttribute.txt* file, with capitalisation taken into account. It is recommended to not have any additional files in this folder.

Each file follows the same structure. The first line specifies the delay (in days) of when the new value for the *DEPENDING_ATTRIBUTE* will occur. The second line gives the formula which should be used to calculate the new value of the attribute. For example, a dependency can be used to simulate the ageing process in the model. This would be kept in a file called *age.age.txt*, the content of the file could look like:

```
365
age+1;
```

In this case, 365 days after the value of **age** changed this dependency will increase the age again and thereby trigger the next dependency. The second line contains the formula which is used to calculate the new value of the attribute **age**. Please note that in the formula the old value of the attribute is used. The formula will increment the currently stored value of the **age** attribute by one year.

D.1.4 Folder Init

Some attributes cannot be initialised by only describing the distribution, as they depend on the values of other attributes. It is necessary to initialise them properly after the initial creation of all attributes. These initialisations are stored in the folder *init*. The files must be named exactly as the attributes they initialise and must be normal text-files (.txt). The initialisation file for the minimal partner age, would be named *minPartnerAge.txt* could contain the following information:

```
if(female){age-1.0;}else{  if(age<20){16.0;}else{age-5.0;}};
```

The third and last line contains a formula which calculates the value of the given attribute after the initialisation. In this case, the formula translates to: “If the individual is female the minimal age for her partner is one year under her current age. Otherwise (the individual is male) the minimum age of the partner is 16 as long as the individual is 20 years old or younger. If the male individual is older than 20 the minimum age is five years lower than the age of the man.”.

The first two lines describe a potential first event to change the value of this attribute. The first line describes the time when this event will happen, this can be a formula or a numeric value. The second line is the formula which calculates the new value of the attributes when the event happens. This structure is necessary to initialise the ageing process for example. If we have a look at the *age.txt*-file which initialises the age attribute this becomes clearer:

```
365-Math.floor((age%1.0)*365)
age+1;
Math.floor(age);
```

As we saw earlier the standard initialisation of the age attribute yields either normally or uniformly distributed values between the given thresholds. This means that non-integer values can appear as well. The formula in the third line resets the current age value to the closest lower integer value. Before that happens the first birthday of this individual is calculated, using the formula in line one. At this day the individual will age one year, as shown in the formula in line 2. All other birthdays from then on are covered by the previously described dependencies.

D.1.4.1 Execution Order Init

As the initialisation formulas can contain attribute names, they can also contain the names of attributes which must be initialised themselves as well. Therefore all initialisations must be sorted. The order must ensure that all necessary attributes to calculate an attribute’s initial value had been initialised before the formula is calculated. This means for example that, looking at the examples from above the attribute *age* must be initialised before *minPartnerAge* as the formula of the latter includes the first.

If there are circular dependencies no initialisation will be possible and the model run will be aborted. This could happen for example in a situation like this: `parameter_a` will be initialised as `parameter_b + 1` and `parameter_b` will be initialised using `parameter_a - 1`.

Whereas both formulas tell the same story there is no way to determine which has to be executed first.

D.2 Folder Models

This folder should contain one file for each disease model which is used in the model. Furthermore, there must be a folder *js*. The files describe who is eligible to be part of this model and which health states are within this model. In the *js*-folder the transitions between these health states are described.

D.2.1 Disease Model Files

The file type of these files is ".txt". In the first line, the restrictions which apply to this model are listed. These must be a boolean variable which has been defined in the *booleanAttribute.txt* file. A restriction to indicate that a certain model is only relevant for women could look like this:

```
female=true
```

This might be helpful when developing models for sequelae which can only affect women, for example, a PID model.

The following lines of the model list all health states in this model, one line per health state. The first health state in the list will be the "uninfected state", which is the health state an individual is in after successful treatment. The second health state in the list will be the "infected" state, which is the first health state an individual is in after an infection. A disease model must have at least two health states. The following syntax must be used to describe a health state:

```
NAME INFECTIOSITY INITIAL_POPULATION COST QALY_DECREMENT
```

NAME	Naming conventions apply, see D.5.
INFECTIVITY	The infectivity tells the per-contact-transmission-probability of the infection after condom-less sexual contact. It must be a value between 0 and 1, with 0 being no probability of transmission and 1 being a guaranteed transmission with each condom-less sexual intercourse. If -1.0 is used this means that an individual in this health state cannot be infected, e.g. to simulate immunity.
INITIAL_POPULATION	This value must be between 0 and 1. This value must add up to 1 over all health states. Otherwise, the population will completely be put into the "uninfected" health state.
COST	This determines the costs per day which arise if an individual is in this health state. It must be positive.
QALY_DECREMENT	The QALY-decrement describes the negative impact of this health state on an individual's health. These values will be subtracted and must be positive. It must be a value between 0 and 1.

D.2.2 Folder js

Within this folder, there should be one folder for each disease model. All other files and folders will be ignored. The names of these folders must correspond with the names of the disease models as stated in the disease model files. Within each of these folders, there are all transitions, which describe the natural progress of this disease. Each transition is stored in a separate ".js" file. These must be named in the following way:

FROM_STATE.TO_STATE.js

Whereas the `FROM_STATE` and the `TO_STATE` must be separate health states of the disease model in question, separated by a dot. The first line states the cost associated with this transition. This is useful to add one-time costs to a health state instead of inputting these costs as daily costs. The second line contains the formula, which calculates when this transition will occur. The result of the formula must be a positive integer value which will be interpreted as the difference in days between the calculation of the event time and the actual state change. All other lines in this file will be ignored.

D.3 Folder Pathway

The files and folders within this folder describe the clinical pathways modelled in the disease model. It contains 3 folders *offers*, *tests*, and *treatment* as well as two files: *pathway.txt* and *partnerNotification.txt*.

D.3.1 Folder Tests

Within this folder, all STI tests which can be performed in the model are listed. The filename is also the name of the test. Do not name it as the disease itself to avoid confusion.

The files follow a certain structure: The first line states the disease which this screening test for. The second line is the formula which returns a test result (`true`/ `false`). In the third line, the costs of conducting this test are stated. The last line tells the delay (in days) between taking the test and receiving the result. A file for a chlamydia test, being named *chlamydia_test.txt* could look like this

```
chlamydia
if(asymptomatic_chlamydia||symptomatic_chlamydia){if(random<0.97)
    {true;}else{false;}}else{if(random<0.99){false;}else{true;}};
250
3
```

The first line indicates that the test is looking at the *chlamydia* disease model. In the formula (second line) includes health states from the chlamydia model as well as the sensitivity and specificity of this test. the last two lines tell that the test cost £2.50 and it will take 3 days to receive the result of the test.

D.3.2 Folder Treatment

This folder contains all files, which describe all treatment included in the model. The filename is the name of the treatment. The first line states which disease is treated by this specific treatment. The formula in the second line returns the treatment success (`true`/ `false`). In the third line, the health state this individual will be in after successful treatment is stated. If this line is left empty it will be by default the uninfected state of the model. Explicitly stating a health state can be used to account for diseases where no curation is possible, e.g. for antiretroviral treatment for HIV. The penultimate line tells how long the treatment lasts, or in other words, how many days must pass until the individual is put into the health state of line three if the treatment was successful. In the last line, the costs for

this treatment are inputted.

If a certain drug can treat multiple diseases, multiple disease models and health states can be inputted in the file, separated by commas. The order of the disease models must correspond with the order of the health states.

A file describing doxycycline treatment for chlamydia could look like this (name of the file: *doxycycline.txt*):

```
chlamydia
if(random<0.79){if(random<0.95){true;}else{false;}}else{false;}
no_chlamydia
7
235
```

The first line tells that this treatment will only affect the individual's state in the *chlamydia* model. If the treatment is successful, the individual will be put into the health state *no_chlamydia* (see line 3). The formula takes the adherence for the treatment as well as the success rate of the treatment into account. Depending on those values the formula returns `true` or `false`. The doxycycline treatment costs £2.35 and takes 7 days.

D.3.3 Folder Offers

This folder contains proactive screening offers which are given to a specific set of individuals. Each file in this folder describes a separate screening offer. These files should have the same name as the screening offer, with a ".txt" file ending. The first two lines describe how many individuals get a screening offer. The first line shows how many per cent of the eligible individuals will get a screening offer. The second line tells the length of the interval in days over which these screenings are offered. In the third line, all screenings (see folder screening) which are included in this offer are listed, separated by spaces. The price for this offer is in the next line. These should be understood as the price of the administration for the offers rather than the test kit price, as they are already priced in the test files. The next line contains a formula which is used to check whether a certain individual is eligible to receive this offer. During the simulation this will be checked for each individual in the interval. Out of all eligible individuals, the proportion listed in the first line is then randomly drawn. This happens every x days, where x is the number stated in the second line. The last line specifies how many per cent of the approached people will take the test specimen.

A file which describes individuals who go to get tested without any specific reason, e.g.

symptoms could look like this:

```
0.05
365
chlamydia_test,gonorrhoea_test,syphilis_test,hiv_test
0
true;
1.0
```

This translates to plain English as follows: 5% (line 1 and line 6) of all individuals (line 5) in the model will go to get tested for chlamydia, gonorrhoea, syphilis, and HIV (line 3) once a year (line 2). This does not cost anything (line 4).

D.3.4 File pathway.txt

This file establishes the connections between screenings and treatments. Each line describes a different pathway, using the following syntax.

CAUSINGEVENT RESULTING_EVENT DELAY PROPORTION MULTIPLE_PATHWAYS

The first attribute is the name of a causing event, this can be a test which will then be followed by a treatment. But it can also be a treatment which will then be followed by another test, e.g. for retesting after treatment. It could also be a test to be followed by a test or a treatment followed by another treatment, e.g. for continuous treatment like ART. After the processing of the causing event, a certain period will have to pass before the resulting event will be processed (`DELAY`).

If the causing element was a test, the resulting event will only be triggered if the test returned positive. For some instances, the resulting event should be triggered only if the test was negative. In these cases, a negative number for the `PROPORTION` has been inputted. If the causing event was a treatment the resulting event will always be triggered. The next number tells how many per cent of the cases the resulting event will be added to the event queue. The last attribute tells whether this attribute will be evaluated on its own, or whether this is one of many pathways starting from the causing element of which one can be randomly chosen. If the attribute is set to "false" this attribute will be evaluated together with other attributes from this causing element. If set to "true" this pathway will be evaluated independently.

The following two lines are taken from a the *pathway.txt* file and showcase possible effects of an HIV-test for high-risk individuals:

```
hiv_hr_test antiretroviral 7 0.95 false
hiv_hr_test prep 7 -0.95 false
```

After a high-risk individual had an HIV-test the individual is offered either ART (if the test was positive) or PrEP (if the test was negative). The individual will accept this offer in 95% of all cases and the treatment starts 7 days after the test.

D.3.5 File partnerNotification.txt

This file describes the partner notification process by stating three key attributes, each one in a separate line. The order of the attributes is this:

```
Probability of notifying current partner(s)
Probability of notifying past partners
How long to look back
Current Delay
Past Delay
```

The first attribute states how likely it is to notify the current partner, or the current partners if the individual has concurrent partnerships. For each partner, a random number is drawn. If the value is below the threshold this partner will be notified.

The next two attributes have to be looked at together. The latter attribute defines how long ago a partnership could have been ended so that the partner could or should still be notified. The second attribute tells the likelihood of notifying them. For each past partnership, a separate random value between 0 and 1 is drawn so that some partners might get notified and others might not.

The last two attributes define the delay in days between a positive test result of the infected individual and the day when the partner will be tested. After this delay, the notified partner will receive the same screening as the infected partner received.

D.4 Folder Social

This folder only contains two files, *partnershipFormation.txt* and *socialmodel.txt*. It is not recommended to have more files in this folder. These files describe the partnership formation and ending process. Per definition, sexual contact can only occur in partnerships.

D.4.1 File partnershipFormation.txt

This file can contain several formulas (returning `true`/`false`), one per line. Each formula contains one condition which must be fulfilled in order to not stop the partnership formation algorithm. In these formulas, the attributes of the potential partner can be accessed by putting the prefix "other_" before the name of the attribute.

These formulas can be used to check whether the sexual orientation of an individual matches with the sex of the potential partner:

```
if(male){other_attractedToMale;}else{other_attractedToFemale}
if(other_male){attractedToMale;}else{attractedToFemale}
```

These formulas can also check whether the age of the potential partner is within the preferred partner age range of an individual:

```
age > other_minPartnerAge
age < other_maxPartnerAge
other_age > minPartnerAge
other_age < maxPartnerAge
```

And lastly, whether a partner has reached their preferred number of partnerships:

```
other_currentPartnerships < other_prefNumberPartners;
currentPartnerships < prefNumberPartners;
```

As the formulas in this file will only be executed once during the partnership formation algorithm, they should include each formula twice, one time from the individuals perspective and one time from the potential partners perspective.

D.4.2 File socialmodel.txt

This file is one of the most influential ones of all files. It describes how often partnerships build and which kind of partnerships are built. In the first line contains two parameters the first one is the *proportion of the population looking for a partnership within the partnership formation interval*, or short *proportion* for the remainder of this section. The second one is

the *partnership formation interval* or short *interval* for the remainder of this section. The unit of the interval is “days”, as for all other duration attributes as well. Within the interval a proportion of people is randomly selected, not looking at their current partnership status. All selected individuals will be matched with another randomly drawn individual once in the interval. Whether these individuals could start a partnership is determine by the formulas listed in *partnershipFormation.txt*. If all formulas return true another random number is drawn, this number is compared to the *partnership building probability*, which is held in the second line of the *socialmodel.txt* file.

All remaining lines define different partnership types, one per line. To describe a partnership type the following values must be written, separated by a space

NAME	The name of the partnership is mostly for analysis purposes to differentiate the partnerships after the simulation.
PROPORTION	Describes how many of all new partnerships will be of this type. The proportions over all different partnership types should add up to 1.0. If they do not add up to 1.0, they will be inputted by default so that all partnership types have the same likelihood of creation.
MINIMUM_DURATION	The minimum and maximum duration describe the duration of a partnership. Upon the formation of a partnership, a uniformly distributed random number between those borders is drawn to calculate the partnership ending events of the partnership. The MINIMUM_DURATION must be smaller than the MAXIMUM_DURATION. Both values must be greater than 0.
MAXIMUM_DURATION	opposite of MINIMUM_DURATION.
FREQUENCY_OF_SEX	The frequency determines how often sexual contact occurs per day in this partnership type. This value cannot be greater than 1.0 or smaller than 0. Each input will be randomly blurred so that the gap between two sexual contacts changes slightly each time.
CONDOM_USE	Describes how many sexual contacts of this partnership type will include condoms. Before each sexual contact, a random number is drawn. If this number is greater than the given value, no condom will be used and an infection could potentially occur. Otherwise, a condom will be used. This means that within the same partnership the individuals might use a condom for sexual intercourse and might not in the next one. Condom security is assumed to be 100% in the model.
GAP	Defines the gap between after this partnership ended before the individuals in this partnership can start a subsequent partnership.

D.5 Naming Conventions

While setting up models and inputting them into the disease model tool the user must give names to attributes, health states, etc. It is worthwhile to spend some time to understand what kind of names are possible and which are not. The following rules apply:

- Do not use a full stop in any name
- All names must be unique
- Do not start a name with “other_”
- except for the health states which represent death, no other health state should end with "_dead"
- Only use numbers, letters, and underscores ("_")
- Do not use name consisting only of numbers
- do not use JavaScript reserved words, such as: true, false, if, else, etc. A full list of all reserved words can be found online[1].
- Tip: Write all lowercase, to avoid confusion e.g. between a lowercase L and a capitalised i.

Any health state name which ends with “_dead” will be assumed to be a state where the individual died. Therefore these individuals will be removed from the model. Naming health states in this way should be avoided if this effect is not desired.

As the names of diseases, health states, treatments, tests etc. are used to label output of the software, e.g. graphs and tables it recommended to use names which are easy to understand and meaningful instead of abbreviations or constructs like `attribute_1`.

[1] `https://www.w3schools.com/js/js_reserved.asp`

Appendix E

Advisory Group

This section contains the questionnaire which was distributed online using EU survey (see E.1) and the interview guide for the semi-structured interviews which were conducted afterwards (see E.2). Interviewees were also given an information sheet (see E.3).

E.1 Questionnaire

You have been contacted to fill in this questionnaire because you are involved in sexual health service planning and/ or commissioning. I would be delighted if you – as a potential user of my STI disease modelling software - could find some time to fill in this short questionnaire, which will assess your expectations and priorities towards the features of this modelling software.

What Is it About

- Sexually transmitted infections (STI) heavily influence the health of an individual.
- Disease models support decision makers in finding cost-effective STI interventions.
- There is evidence for interaction (biological and social) between STIs.
- Disease models are often hard to use

I am developing a new software, which simultaneously incorporates the most important STIs in England and interactions between those. I plan to create easy-to-use user interfaces for this software, based on your needs. I further explain PhD project, the purpose of the modelling software, and this questionnaire in a short video (4:35min): https://youtu.be/tr5mLM4I_r8

Understanding the Target User Group

Which type of organisation do you belong to? *(single choice)*

- Local Authority
- NHS England
- Public Health England
- Clinical Commissioning Group
- Sexual Health Service Provider
- Other, please specify

Which type of organisation do you belong to? *(free text)*

In what way are you involved with the commissioning of sexual health/ reproductive health/ HIV decisions? *(free text)*

In what way are you involved with service planning and service delivery? *(free text)*

Infections Covered by the Model

Which of the following STIs would you like to see included in the software, please rank (with 1 is the top priority, each rank can only be given once) *(ranking)*

- chlamydia,
- genital herpes,
- genital warts,
- gonorrhoea,
- hepatitis B,
- hepatitis C,
- HIV,
- HPV,
- mycoplasma infection,
- syphilis, and
- trichomoniasis.

Is there any STI missing? If so, please name them and their suggested rank: *(free text)*

Relevant Interventions

What health promotion interventions are currently being the top priority within your service/ borough? *(multiple choice)*

- Point of Care Testing for HIV
- Opportunistic Screening for Chlamydia
- Systematic Screening for HIV
- Systematic Screening for other STIs
- Condom distribution schemes
- HPV vaccination
- Hepatitis B vaccination
- Hepatitis A vaccination
- Pre-exposure Prophylaxis for HIV
- Post-exposure Prophylaxis for HIV
- Behavioural Interventions on Individual Level
- Behavioural Interventions on Group Level, e.g. based on similar experiences
- Behavioural Interventions on Community Level, e.g. school-based
- Preventive campaigns (e.g. posters, TV)
- Treatment for HIV
- Treatment for STIs (not HIV)
- Other, please specify

What health promotion interventions do you think will be highly prioritised within the next two years in your service/ borough? *(multiple choice)*

- Point of Care Testing for HIV
- Opportunistic Screening for Chlamydia
- Systematic Screening for HIV

- Systematic Screening for other STIs
- Condom distribution schemes
- HPV vaccination
- Hepatitis B vaccination
- Hepatitis A vaccination
- Pre-exposure Prophylaxis for HIV
- Post-exposure Prophylaxis for HIV
- Behavioural Interventions on Individual Level
- Behavioural Interventions on Group Level, e.g. based on similar experiences
- Behavioural Interventions on Community Level, e.g. school-based
- Preventive campaigns (e.g. posters, TV)
- Treatment for HIV
- Treatment for STIs (not HIV)
- Other, please specify

Are there any interventions you may want to implement, but not able to because of given financial restrictions? *(single choice)*

Usage of Software

How would you imagine to use this software in your service? *(multiple choice)*

- Understanding the potential impact of changes in current interventions
- Examining the effect of new interventions
- Extrapolating research study results
- I would not use this software
- Other, please specify

Result Presentation

Which types of result presentation would you prefer to see? *(multiple choice)*

- **Raw Data**: Data on the STI prevalence, quality of life values, and costs (e.g. per week), e.g. in an Excel workbook for further analysis on your own, with descriptive analysis in the software
- **Cost per patient**: How much money is spent on average on every person accessing the service.
- **Cost per Infection prevented**: Comparing two interventions to see how much money was spent to prevent a given number of infections.
- **Cost-effectiveness Analysis**: Comparing two interventions in terms of their costs and health outcomes
- Other, please specify

Further Research

As part of the next stage of the research, we want to speak to volunteers about the design of the user interfaces. This will happen in a one-hour meeting at a location of your choice.

May I, therefore, contact you for an interview?

If yes, please leave your e-mail address here, otherwise, leave blank. Your e-mail address will not be linked to your answers to the questionnaire. *(free text)*

E.2 Semi-structured Interview Topic Guide

General Introduction

duration: *10 min*

My name is Fabian Sailer. I am a second year PhD student at University College London. Information and consent sheet. Talk through information sheet which contains:

- General introduction to the project
- Objective of research
- Why have you been chosen

Sign consent form and give participant another copy of consent form and the information sheet.

Aim of today: I have developed a set of initial user interface drafts and would like your feedback on these. We will look at these drafts of user interfaces. During today's interview, I will ask you to "think aloud" so that I can understand what you are thinking while using these interfaces.

Scene Setting Questions

duration: *10 min*

Understanding the Professional Role

1. What is your professional role? Can you tell me what your job includes, what kind of work do you do on a day to day basis?
2. What are the main decisions you have to make in terms of STI interventions? *funding, designing, evaluating*
3. Which are the main competing interests in terms of decision making? *Competing financial aspects, competing political interests, moral dilemmas*

Understanding the Previous Disease Model Use

4. What experience do you have with disease models? ("any" then continue, "none" then go to 9.) *Look at the outcome of published models, creating models, informing models, used models to inform decisions you had to take*
5. Where did you get this model from? *Published source, specifically created, reused, developed it on your own*

6. What were the advantages of the model you used? Why?
7. What were the disadvantages of the model you used? Why?
8. How easy was it to use this model? (then start looking at user interface drafts) Why?
9. Have you ever considered using a disease model (for) decision making?
10. What are the advantages of disease models from your point of view? Why?
11. What are the disadvantages of disease model from your point of view? Why?
12. Why did you decide to not use the model? (then start looking at user interface drafts)

User Interface Drafts

duration: *25 min*

Think aloud, pen and paper prototypes/ wireframes.

- How would you approach . . .
- If you would need to . . . , how would you do it
- Do you like the look and feel of this interface?
- List of parameters: Which of those are relevant for you to be changed?

Closing Questions

duration: *10 min*

Understanding Barriers in Implementing This Software

1. From your point of view: What are the biggest advantages/ disadvantages of the software? Why?
2. Do you think you could benefit from this software? If yes in which way and why? If no why so?
3. Do you think you would use this software? If so in which way and why? If not why?
4. What kind of (global/ local) barriers you can identify in terms of using this software in practice?

Thanking and End

duration: *5 min*

Do you have anything else you want to say?

Would you want to have a look at the final software and see how your input influenced the outcome (end of this year)?

Thank you for participating and your time.

E.3 Information Sheet

Title of Study

Expert Engagement in User Interface Development for new disease modelling software

Department

Research Department of Primary Care and Population Health

Name and Contact Details of the Researcher(s)

Rachael Hunter – r.hunter@ucl.ac.uk Fabian Sailer – f.sailer@ucl.ac.uk

Name and Contact Details of the Principal Researcher

Rachael Hunter – r.hunter@ucl.ac.uk

1. Invitation Paragraph

Thank you for expressing your interest in participating in this study and thereby helping me with my PhD. This study is to understand user preferences for modelling software. Participation in the study is voluntary.

Before you decide to participate it is important for you to understand why the research is being done and what participation will involve. Please take time to read the following information carefully and discuss it with others if you wish.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

2. What is the Project's Purpose?

To understand the demands and to satisfy the needs of decision makers in health care of a disease modelling software. This project aims to develop graphical user interfaces for a disease modelling software developed by Fabian Sailer in the course of his PhD.

3. Why Have I Been Chosen?

You are eligible for participating in this study as you are or work with policy and decision makers in sexual health. You expressed initial interest to participate in this study after an invitation was published.

4. Do I Have to Take Part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. You can withdraw

at any time without giving a reason and without it affecting any benefits that you are entitled to.

5. What Will Happen to Me If I Take Part?

You will be asked to participate in a single face-to-face interview. This interview will take approximately one hour.

6. Will I Be Recorded and How Will the Recorded Media Be Used?

Notes will be taken during the interview. No audio or video recording of the meetings is planned.

7. What Are the Possible Disadvantages and Risks of Taking Part?

You do not have to expect any disadvantages or risks beyond those of a standard office day.

8. What Are the Possible Benefits of Taking Part?

The user interfaces which are developed in the course of this study will be used to input a disease modelling software for STIs. This modelling software might, therefore, be more user-friendly and accessible to the future users, like you.

9. What If Something Goes Wrong?

If you want to raise a complaint about the research project, you can at any time contact the principal researcher Rachael Hunter (r.hunter@ucl.ac.uk), as she is only involved in the project in a supervisory role. If you feel that your complaint is not handled satisfactorily you can also contact the Chair of the UCL Research Ethics Committee (ethics@ucl.ac.uk).

10. Will My Taking Part in This Project Be Kept Confidential?

All the information that we collect about you during the course of the research (including the fact that you participate in the study) will be kept strictly confidential. You will not be able to be identified in any ensuing reports or publications.

11. Limits to Confidentiality

Confidentiality will be respected unless there are compelling and legitimate reasons for this to be breached. If this was the case we would inform you of any decisions that might limit your confidentiality.

12. What Will Happen to the Results of the Research Project?

Your input in the advisory group will be used to develop user interfaces for an STI modelling software. This software is a key part of Fabian Sailer's PhD. It will be disseminated after the finalisation.

13. Data Protection Privacy Notice

The data controller for this project will be University College London (UCL). The UCL Data Protection Office provides oversight of UCL activities involving the processing of personal data, and can be contacted at data-protection@ucl.ac.uk. UCL's Data Protection Officer is Lee Shailer and he can also be contacted at data-protection@ucl.ac.uk. Your personal data will be processed for the purposes outlined in this notice. The legal basis that would be used to process your personal data will be the provision of your consent. You can provide your consent for the use of your personal data in this project by completing the consent form that has been provided to you. Your personal data will be processed so long as it is required for the research project. If we are able to anonymise or pseudonymise the personal data you provide we will undertake this, and will endeavour to minimise the processing of personal data wherever possible. If you are concerned about how your personal data is being processed, please contact UCL in the first instance at data-protection@ucl.ac.uk. If you remain unsatisfied, you may wish to contact the Information Commissioner's Office (ICO). Contact details, and details of data subject rights, are available on the ICO website at: https://ico.org.uk/for-organisations/data-protection-reform/overview-of-the-gdpr/individuals-rights/

14. Who is Organising and Funding the Research?

The research is organised by the UCL Research Department for Primary Care and Population Health. Fabian Sailer is funded by the School for Primary Care Research of the National Institute of Health Research.

16. Contact for Further Information

Fabian Sailer – f.sailer@ucl.ac.uk

Thank you for reading this information sheet and for considering to take part in this research study.

Appendix F

Presentation of the User Interfaces Included in the Software

The first user interface which is displayed after starting the software lets the user decide on which STIs shall be simulated and which sexual network should be used, see Figure F.1. The user has to select at least one STI and exactly one sexual network, otherwise the "Next Step"-button is disabled.

Even if a user did not select all STI all of them will be simulated during the model run. The selection at the start-up of the software only facilitates the input. As the model simulates interactions between STIs it is not possible to examine an isolated STI with it.

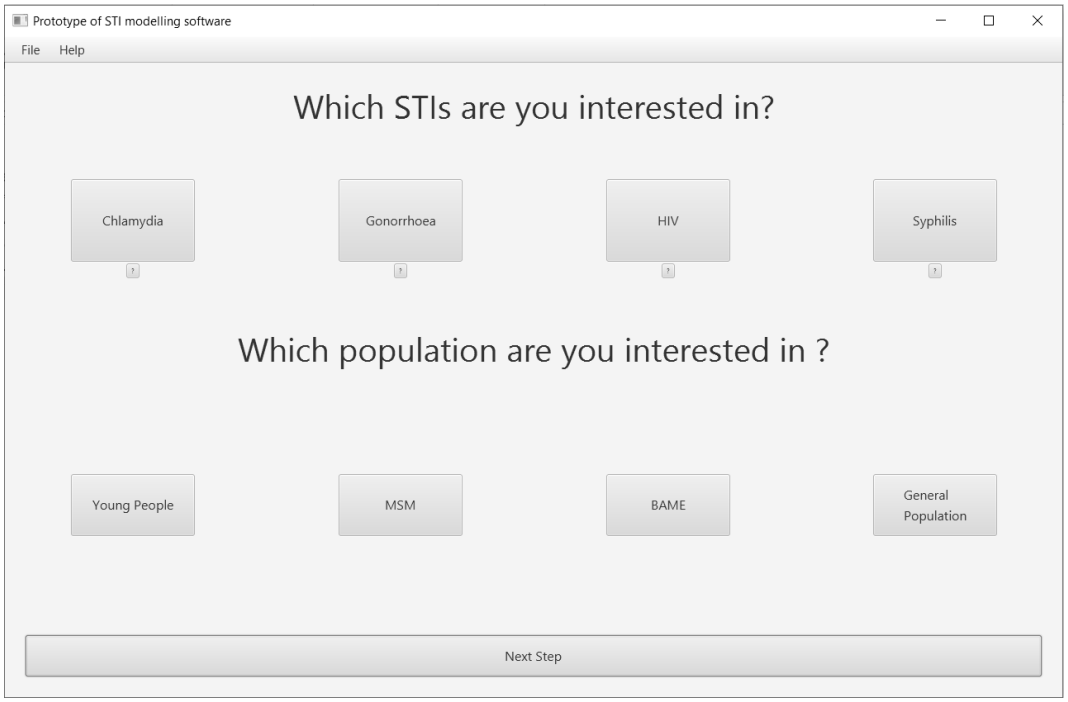

Figure F.1: User interface which is shown after startup

In the next input mask, the user can amend the sexual network, see Figure F.2. The user interface is pre-filled with the default values for the selected sexual network, see section 7 on how these were derived. In this user interface, similar to the following user interface, the user can specify separate input values for the standard arm and the intervention arm of the simulation.

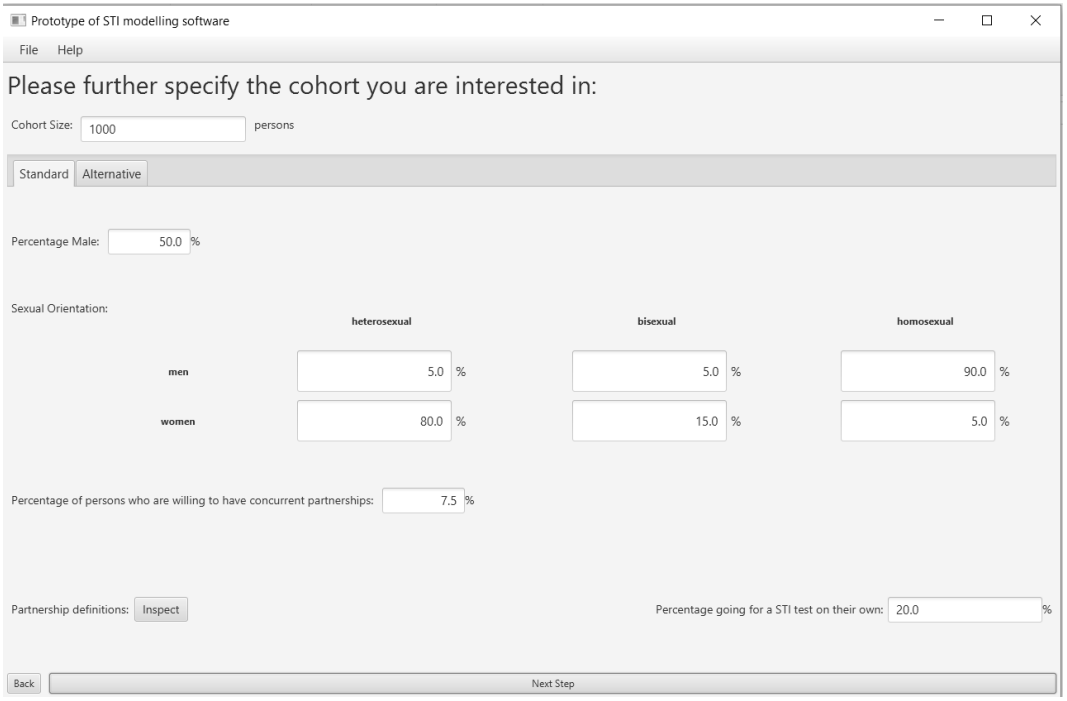

Figure F.2: User interfaces to amend the sexual network

Depending on which STIs the user selected on the first screen, not all of the user interfaces in Figure F.3 are shown. The user interfaces which belong to the selected STIs in the first user interface are shown one after each other and allow the user to edit parameters which define treatment pathways for each STI.

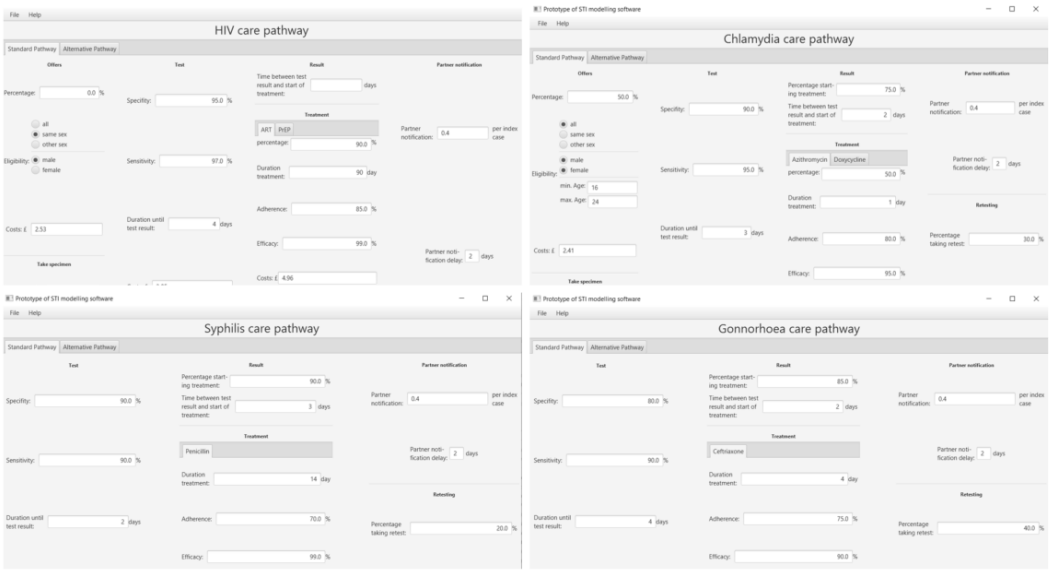

Figure F.3: User interfaces to amend the treatment pathways

After specifying the input for all standard and alternative treatment pathways, an overview is displayed to the user. They can return to any user interface and edit values if needed. After confirming the input on the overview input mask, a user interface which shows the process on the simulation progress is displayed. At the end of the simulation the results of the simulation are presented to the user, i.e. as in Figure F.4.

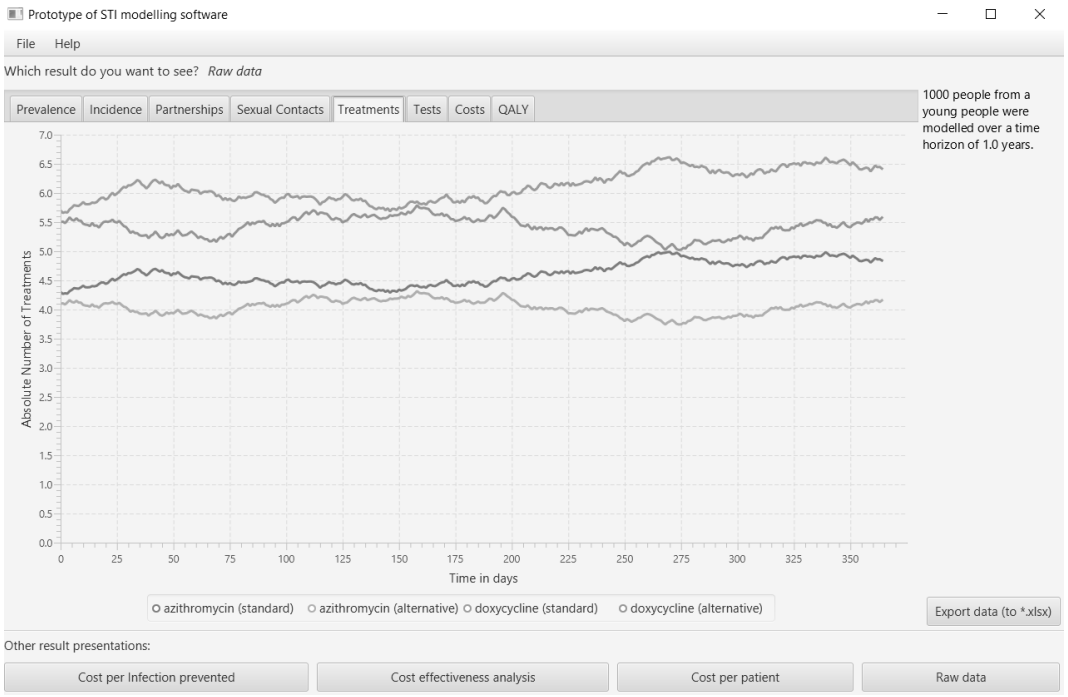

Figure F.4: User interfaces to show the modelling results

The software can display various types of results. It is possible to export any displayed result and the databases which were used to run the simulations into *.csv files so that they can be processed with other software, such as Excel or R.

Appendix G

Additional Material for Disease Models

Parameter Origin Graphs

This parameter origin search is visualised in what I call "review graphs". All review graphs in this section are structured the same way. Solid boxes stand for studies which I could access. Dotted boxes indicate studies which I could not access, but which were used as a reference elsewhere. Bold font says that it is a modelling study. The graph is sorted so that newer studies are on the right-hand side and older ones are on the left-hand side. There is no fixed time scale to these graphs. For reasons of readability sometimes these boxes are not in absolute chronological order, especially when many studies are examined at the same time. Arrows indicate that a certain study referenced another on. More information can be found in Appendix G.

In the next few paragraph I explain how the default parametrisation of the chlamydia model was derived from the literature.

Individuals will stay in *incubation period of chlamydia* for a certain amount of time, depending on their sex. Figure G.1 shows a review of different values used for this duration for females, figure G.2 shows the same parameter origin graph for males.

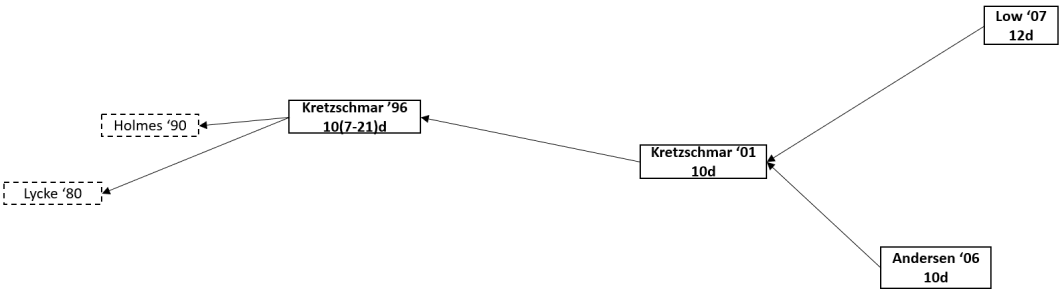

Figure G.1: Review graph for the duration of the incubation period (female) of chlamydia

Chlamydia models from Low [287], Andersen [288] and two models of Kretzschmar [166, 185] were used to parametrise the *incubation period* duration. Kretzschmar et al. based their estimation on studies of Holmes [289] and Lycke [290], which were not accessible for me. The review for males included the same articles.

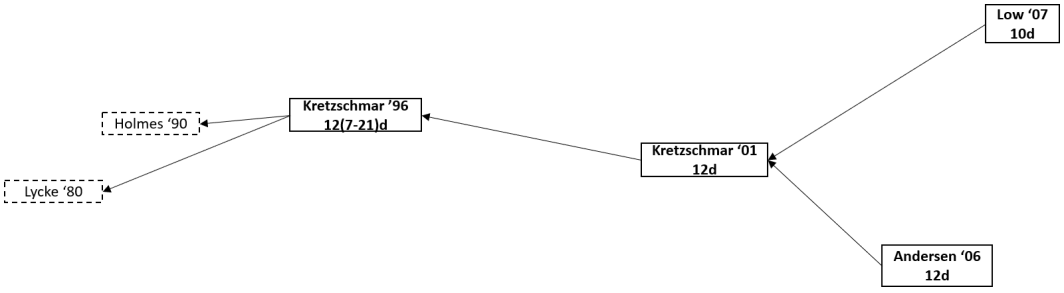

Figure G.2: Review graph for the duration of the incubation period (male) of chlamydia

Most authors, except Low et al. agree on durations for the incubation period of 10 days for females and 12 days for males. Low et al. used the values of Kretzschmar et al. as a reference for their values and do not give a justification why they changed values. Therefore I decided to use 10 days for females and 12 days for male individuals as default input values for the model.

After the *incubation period* the infection becomes either symptomatic or asymptomatic. In both cases, the individuals are infectious in contrast to the incubation period where they are not. The proportion of individuals showing symptoms varies between sexes. Various potential values for the proportion of asymptomatic infections are shown in figures G.3 and G.4 for women.

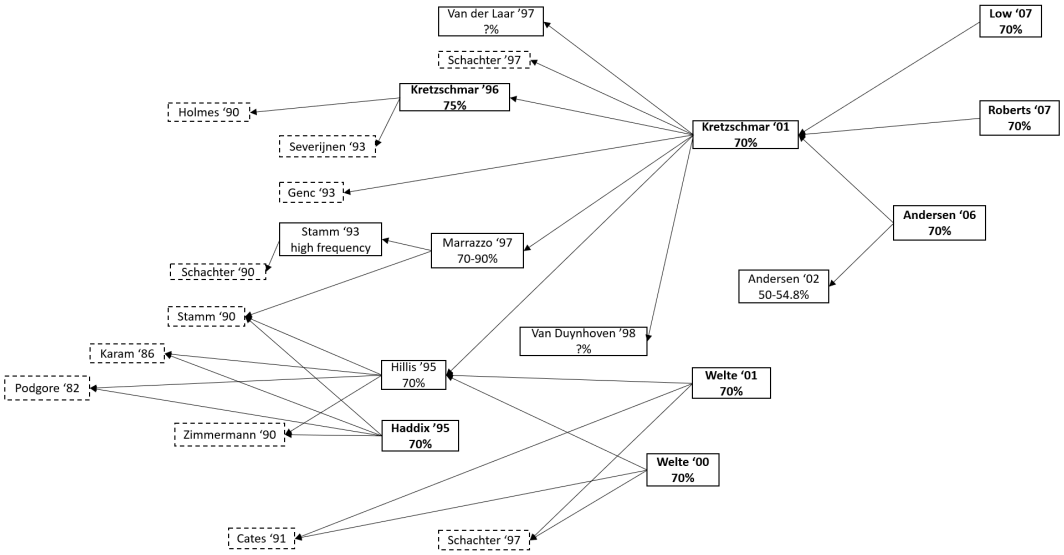

Figure G.3: Review graph for the asymptomatic proportion of chlamydia (female) - part 1

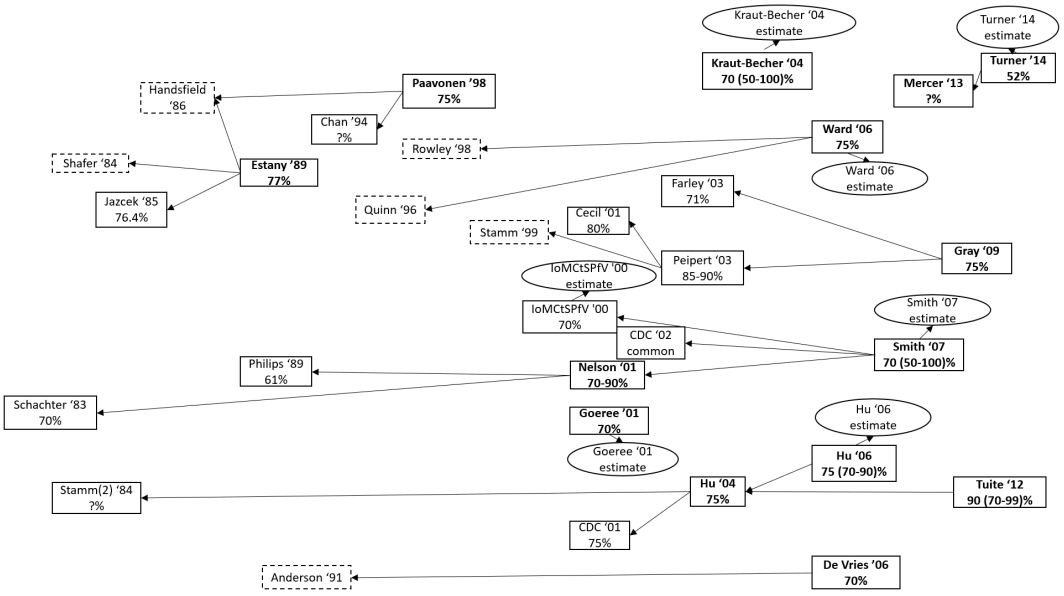

Figure G.4: Review graph for the asymptomatic proportion of chlamydia (female) - part 2

Most models use values originating from the 1980s, even if younger sources are used, they form a chain of citations rooting in the 1980s. No trend in the parameter values is visible, therefore it is likely that new research and studies would not yield new results. Unfortunately, not all the older studies were accessible which is why I could not always verify the used values. By looking at the studies which examined the proportion of women being asymptomatic we can see that all values are approximately 75%. On the other hand, the same value origin graph for males looks different, see figure G.5.

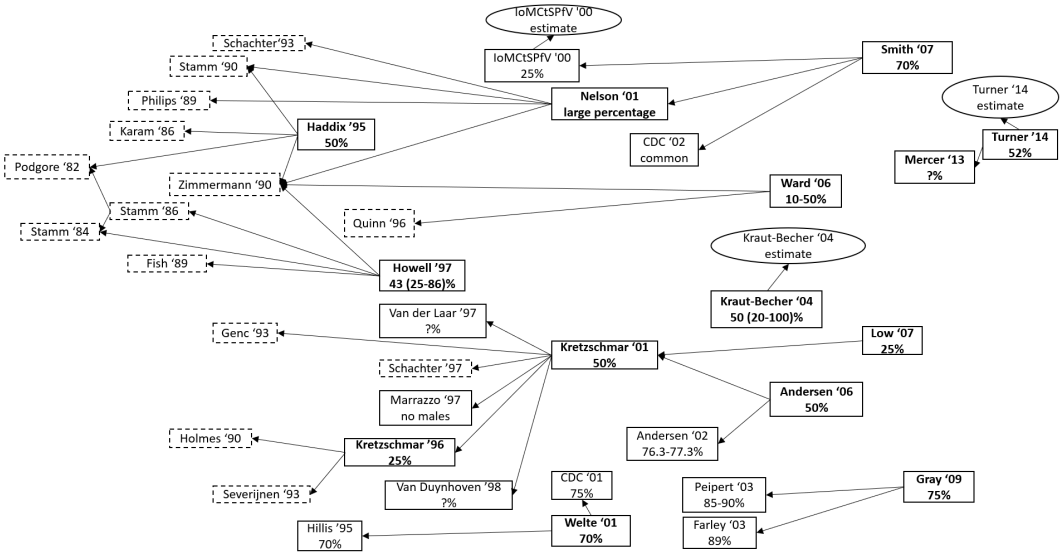

Figure G.5: Review graph for the asymptomatic proportion of chlamydia (male)

The duration of untreated chlamydia infection depends on the sex of the patient and whether the individual is symptomatically or asymptomatically infected. I examine the duration of a treated infection in the description of the clinical pathway model for chlamydia infections. Different values which have been used for the duration of asymptomatic female chlamydia infection are shown in figure G.6.

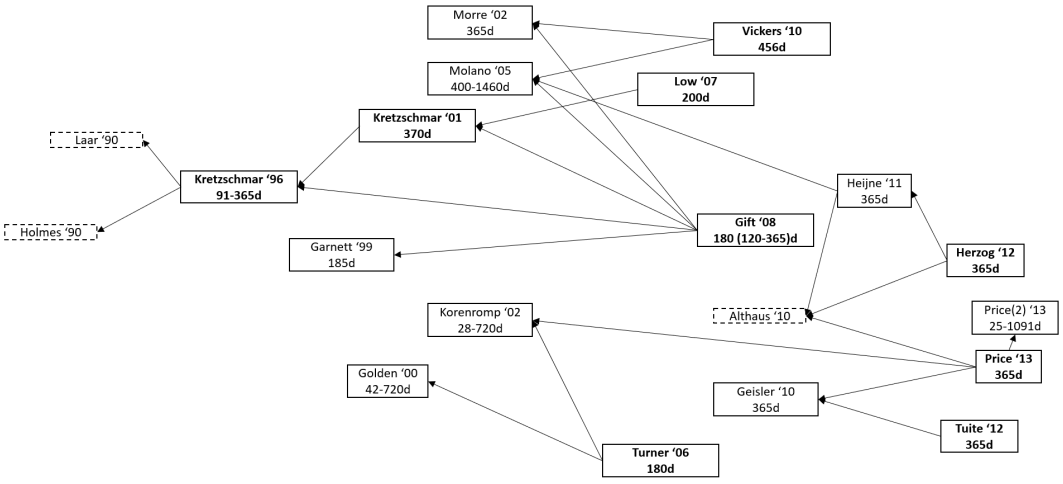

Figure G.6: Duration of untreated asymptomatic female chlamydia

All studies used durations between half a year and slightly over one year. Nevertheless, most models and other studies used one year as an estimation for the duration of untreated female chlamydial infection, which is why I used this value as a default input for this parameter.

The parameters used by other models for the duration of male asymptomatic chlamydia is shown in figure G.7.

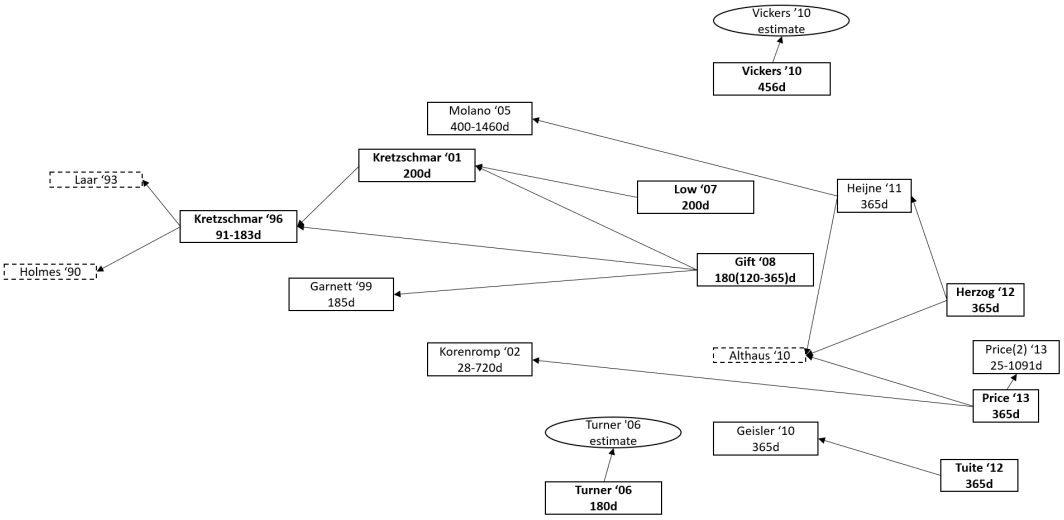

Figure G.7: Duration of untreated asymptomatic male chlamydia

As we can see, the values are very similar to the "female" parameters which is why the duration of untreated female infection is also used for the duration of untreated male infection.

Symptomatic infections are known to be shorter, as the parametrisation of most models suggests, see figure G.8 for females and figure G.9 for males.

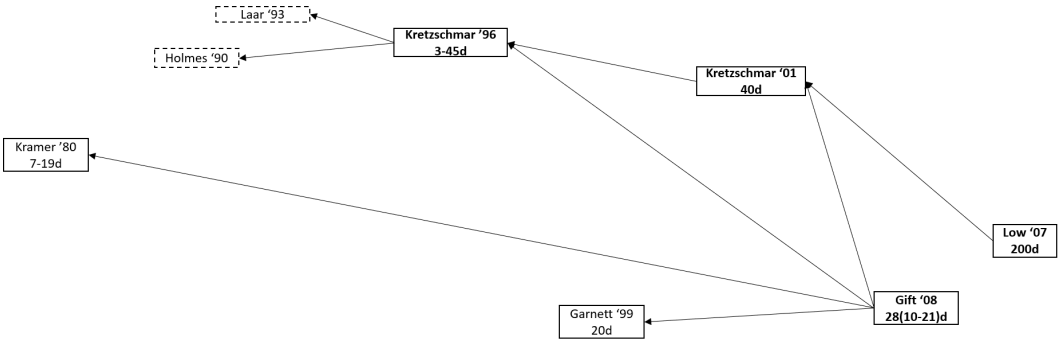

Figure G.8: Duration of untreated symptomatic female chlamydia

We can see that the duration of a male infection is in all models estimated to be shorter. I describe the male duration with a mean duration of three weeks.

I assume in the clinical pathway model, that a proportion of individuals with symptomatic chlamydia infection will seek treatment. This will be explained in more detail in chapter 6. Therefore the above-mentioned durations are upper limits which only apply if

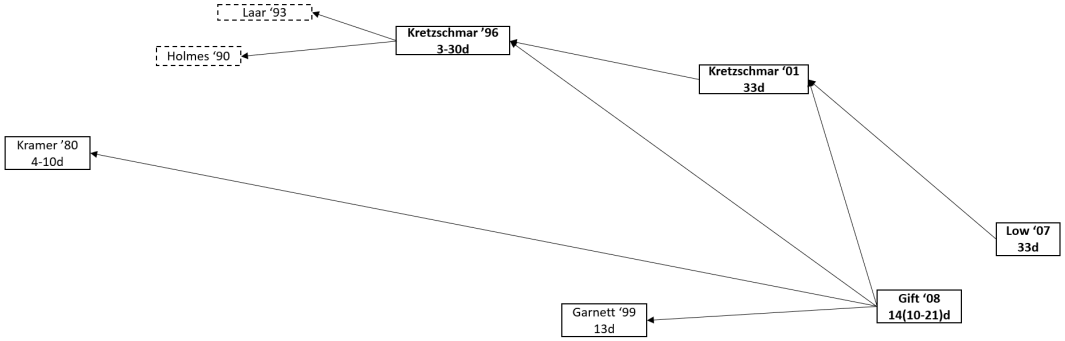

Figure G.9: Duration of untreated symptomatic male chlamydia

the treatment shows to not be effective for this patient on this occasion.

There is also not enough information on the duration of naturally gained transient chlamydia immunity in humans. Two models which included immunity, based their estimation for the duration of transient immunity on information gained from animal studies. Figure G.10 shows the value origin diagram for transient immunity.

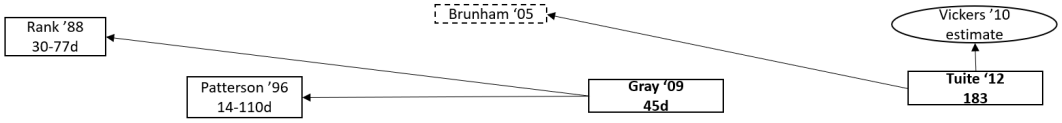

Figure G.10: Transient chlamydia immunity

Parameter Origin References

Gonorrhoea

Duration Incubation Period

Table G.1: Duration of the incubation period of gonorrhoea

reference	duration [days]	comment	references
[211]	[2,5]	♂	[291]
[291]	n/a	value not found	n/a
[292]	5.5	♂	
[292]	9.5	♀	
[211]	10	♀	[292, 293]
[211]	[1,14]	♂	[294]
[293]	n/a	article not accessible	n/a
[294]	3.4 [2,5]	♂	[295]
[294]	10	♀	[292, 293]
[295]	3.4 [1,9]		
[166]	5	♂	
[166]	10	♀	

Proportion Symptomatic Gonorrhoea

Table G.2: Proportion of symptomatic gonorrhoea in women

reference	percentage	comment	references
[211]	[20%, 80%]		[296]
[166]	55%		
[297]	60%		
[188]	[20%, 70%]		[298]
[298]	n/a	only asym. gon.	
[190]	35% [0%, 50%]		[299, 300]
[165]	48%		
[212]	32%		
[213]	36%		[301]
[301]	45%		
[302]	34.80%		

Table G.3: Proportion of symptomatic gonorrhoea in men

reference	percentage	comment	references
[211]	80%		[291]
[291]	17.86%		
[166]	90%		
[297]	95%		
[190]	35% [0%, 70%]		[299, 300]
[165]	35%		
[212]	5%		
[213]	59%		[301]
[301]	66%		
[302]	53.3%		

duration symptomatic gonorrhoea

Table G.4: Duration of symptomatic gonorrhoea in men

reference	duration [days]	comment	references
[303]	55 [10, 100]		[304, 305]
[304]		article not found	
[305]		article not found	
[211]	[10, 50]		
[291]	21 [12, 90]		
[166]	16		
[297]	13		
[306]	[10, 50]		
[307]	274 [183, 365]		
[212]	21		
[308]	69 [51, 91]		
[213]	13		[297]

Table G.5: Duration of symptomatic gonorrhoea in women

reference	duration [days]	comment	references
[303]	55 [10, 100]		[304, 305]
[304]		article not found	
[305]		article not found	
[211]	[10, 50]		
[166]	23		
[297]	20		
[306]	[10, 50]		
[212]	24		
[308]	69 [51, 91]		
[213]	20		[297]

Duration Asymptomatic Gonorrhoea

Table G.6: Duration of asymptomatic gonorrhoea in men

reference	duration [days]	comment	references
[303]	55 [10, 100]		[304, 305]
[304]		article not found	
[305]		article not found	
[211]	[10, 50]		
[291]	21 [7, 165]		
[166]	9		
[297]	185		
[306]	[10, 50]		
[212]	333		
[308]	69 [51, 91]		
[213]	185		
[219]	183		

Table G.7: Duration of asymptomatic gonorrhoea in women

reference	duration [days]	comment	references
[303]	55 [10, 100]		[304, 305]
[304]		article not found	
[305]		article not found	
[211]	[10, 50]		
[166]	157		
[297]	185		
[306]	[10, 50]		
[212]	333		
[308]	69 [51, 91]		
[213]	185		
[219]	183		

Infectivity

Table G.8: Infectivity of asymptomatic gonorrhoea

reference	infectivity per contact	comment	references
[166]	[15%, 60%]	from ♂	
[166]	[6.25%, 25%]	from ♀	
[297]	80%	from ♂	
[297]	60%	from ♀	
[306]	[5%, 20%]		
[165]	10%		
[212]	50%	from ♂	
[212]	30%	from ♀	
[309]	[2.43%, 84.02%]	depending on oral/ anal	
[213]	60%	per partnership, from ♂	
[213]	80%	per partnership, from ♀	
[219]	50%	from ♂	
[219]	20%	from ♀	
[167]	22%		

Table G.9: Infectivity of symptomatic gonorrhoea

reference	infectivity per contact	comment	references
[211]	[5%, 20%]	per day in partnership	[310, 311]
[311]	[19%, 53%]	per act	
[310]	22.1%	per act	
[166]	[15%, 60%]	from ♂	
[166]	[6.25%, 25%]	from ♀	
[297]	80%	from ♂	
[297]	60%	from ♀	
[306]	[5%, 20%]		
[212]	95%	from ♂	
[212]	80%	from ♀	
[309]	[2.43%, 84.02%]	depending on oral/ anal contact	
[213]	60%	per partnership, from ♂	
[213]	80%	per partnership, from ♀	
[167]	22%		

HIV

Duration

Table G.10: duration of chronic HIV I

reference	duration [days]	comment	references
[312]	2044		[313]
[313]	718		
[314]	767		
[315]	730		
[316]	480		[317]
[317]	1260		
[215]	[1095, 1825]		
[318]	2008		[319, 320]
[319]	n/a		
[320]	n/a		
[219]	2738		
[172]	n/a		
[321]	[6840, 7050]		
[322]	365		
[323]	478		
[324]	995		

Table G.11: duration of chronic HIV II

reference	duration [days]	comment	references
[325]	72		
[312]	1351		[313]
[313]	604		
[315]	657		
[316]	480		[317]
[317]	1260		
[326]	1095		
[327]	2008		
[215]	[730,1460]	for chronic HIV II and chronic HIV III	
[318]	1314		[319, 320]
[319]		not free	
[320]		not free	
[219]	2738	for the whole infection	
[321]	[6840, 7050]	for the whole infection	
[322]	1132		
[221]	2770		
[323]	599		
[324]	898		

Table G.12: duration of chronic HIV III

reference	duration [days]	comment	references
[325]	834		
[313]	604		
[328]	420		
[315]	657		
[316]	300		[317]
[317]	1260		
[326]	1460		
[327]	548		
[215]	[730,1460]	together with chronic HIV III	
[318]	1168		[319, 320]
[319]		not free	
[320]		not free	
[219]	2738	for the whole infection	
[172]	[135,336]		
[321]	[6840, 7050]	for the whole infection	
[329]	4015		[330, 331, 332]
[330]	2190		
[331]		value not found	
[332]		value not found	
[333]	930		
[322]	1205	for chronic HIV III and AIDS	
[220]	4015		[329, 330, 331, 332]
[221]	2770	for chronic HIV II and III	[334]
[323]	949		
[324]	1020		

Table G.13: duration of AIDS

reference	duration [days]	comment	references
[335]	730 [183, 1825]		
[336]		not a paper, only presentation	
[337]	375		
[313]	373		
[314]	840		
[326]	1460		
[327]	840		
[215]	280		
[321]	[6840, 7050]	for the whole infection	
[330]	730		
[333]	570		
[338]	[240, 255]		
[322]	1205	for chronic HIV III and AIDS	
[220]	241		
[339]			
[340]			
[334]	276 [66, 708]		
[221]	730		
[224]			
[341]	[1020, 1200]		
[342]	913		
[324]	1110		

Mortality

Table G.14: mortality of chronic HIV I

reference	mortality	comment	references
[314]	1%	per year	
[318]	0.02%	per year	[319, 320]
[319]		article not available	
[320]		article not available	
[172]	0.06%	per year	
[330]	5.5%	per five years	
[322]	0.06%	per month	
[343]	[0.019%, 0.028%]	per month	
[344]	0.4%	per year	

Based on these values an excess mortality due to *chronic HIV I* of 1% per year was assumed. Using an average time of 2.725 years in *chronic HIV I* this results in a overall mortality of 2.7% for *chronic HIV I*.

Table G.15: mortality of chronic HIV II

reference	mortality	comment	references
[327]	0.7%	per year	
[318]	0.28%	per year	[319, 320]
[319]		not free	
[320]		not found	
[172]	0.12%	per year	
[330]	15%	per 5 years	
[338]	[0.33%, 0.66%]	per month	[345, 346, 347]
[322]	0.06%	per month	
[341]	0.8%	per month	[342]
[342]	2.3% [1.15%, 13.78%]	per 6 months	
[343]	[0.018%, 0.027%]	per month	
[344]	0.4%	per year	

Based on these values an excess mortality due to *chronic HIV II* of 0.7% per year was assumed. Using an average time of 2.461 years in *chronic HIV II* this results in an overall mortality of 1.7% for *chronic HIV II*.

Table G.16: mortality of chronic HIV III

reference	mortality	comment	references
[327]	4.2%	per year	
[318]	2.24%	per year	[319, 320]
[319]		not free	
[320]		not found	
[172]	[0.34%, 0.72%]	per year	
[330]	32.3%	per 5 years	
[333]	3.65%	per month	
[338]	[0.33%, 0.66%]	per month	[345, 346, 347]
[322]	0.12%	per month	
[341]	1.1%	per month	[342]
[342]	3.99% [2.81%, 10.34%]	per 6 months	
[343]	[0.02%, 0.096%]	per month	
[344]	0.8%	per year	

Based on these values an excess mortality due to *chronic HIV III* of 2.24% per year was assumed. Using an average time of 2.795 years in *chronic HIV III* this results in an overall mortality of 6.1% for *chronic HIV III*.

Syphilis

Incubation Period

Table G.17: duration of the incubation period of syphilis

reference	duration [days]	comment	references
[214]	25 [0,31]		[348]
[202]	30 [10,90]		
[349]	25 [21,28]		
[350]	[21,28]		
[167]	21		
[217]	28		
[351]	27%		

Duration Primary Infection

Table G.18: duration of primary syphilis

reference	duration [days]	comment	references
[214]	[46,47]		[352]
[353]	180	whole infectious period	
[202]	45		
[219]	365	whole infectious period	
[216]	183		
[221]	365	whole infectious period	
[354]	43 [21, 75]		
[349]	[19, 46]		
[350]	[45, 60]		
[173]	21 [6, 90]		
[217]	46 [14, 84]		
[351]	45		

Duration Secondary Infection

Table G.19: duration of secondary syphilis

reference	duration [days]	comment	references
[214]	108 [30, 365]		
[215]	180	whole infectious period	
[202]	110		
[219]	365	whole infectious period	
[221]	365	whole infectious period	
[354]	104 [64, 155]		
[349]	108 [30, 365]		
[350]	[100, 140]		
[173]	108 [15, 180]		
[217]	108 [90, 120]		
[351]	108		

Duration Recurrent Syphilis

Table G.20: duration of a period of recurrent syphilis

reference	duration [days]	comment	references
[350]	90		

Probability Recurrent Syphilis

Table G.21: duration of early latent syphilis

reference	probability	comment	references
[349]	23.6%	90% in first year	
[350]	25%		

Duration Early Latent Syphilis

Table G.22: duration of early latent syphilis

reference	duration [days]	comment	references
[214]	46 [15, 130]		
[218]	182		
[219]	1800		
[216]	365		
[349]	183 [30,368]		
[350]	365		
[173]	231 [90, 339]		
[351]	207		

Duration Late Latent Syphilis

Table G.23: duration of late latent syphilis

reference	duration [days]	comment	references
[218]	3650		
[215]	5475		
[219]	1800		
[216]	5475		
[354]	4004 [2485, 6181]		
[349]	lifelong		
[350]	lifelong		
[173]	5475 [730, 10950]		

Time-to-Event Formulas

In this section the time-to-event formulas which are used to define the gonorrhoea, syphilis, and HIV are shown.

Chlamydia Model

Incubation Period of Chlamydia to Asymptomatic Chlamydia

```
if(male){if(random < 0.75){9.0;}else{11.0}}
else if(random < 0.8){9.0;}
else{11.0};
```

Incubation Period of Chlamydia to Symptomatic Chlamydia

```
if(male){10.0;}else{12.0;}
```

Asymptomatic Chlamydia to Transient Chlamydia Immunity

```
if(male){21.0 + random*159.0;}
else{60.0 + random * 396.0;}
```

Asymptomatic Chlamydia to No Chlamydia

```
if(male){21.0 + random*159.0;}
else{60.0 + random * 396.0;}
```

Symptomatic Chlamydia to Transient Chlamydia Immunity

```
if(male){14.0 + random * 19.0;}
else{21.0 + random * 435.0;}
```

Symptomatic Chlamydia to No Chlamydia

```
if(male){14.0 + random*19.0;}
else{21.0 + random * 435.0;}
```

Transient Chlamydia Immunity to No Chlamydia

```
45.0 + random * 27.0;
```

Gonnorhoea Model

Incubation Period of Gonnorhoea to Asymptomatic Gonnorhoea

```
if(male){if(random < 0.5){4.0;}
else{6.0}}
else{if(random < 0.66){9.0;}
else{11.0}};
```

Incubation Period of Gonnorhoea to Symptomatic Gonnorhoea

```
if(male){5.0;}
else{10.0;};
```

Asymptomatic Gonnorhoea to No Gonnorhoea

```
50.0 + random*135.0;
```

Symptomatic Gonnorhoea to No Gonnorhoea

```
if(male){10.0 + random * 40.0;}
else{20.0 + random * 60.0;}
```

Syphilis model

Incubation Period of Syphilis to Primary Syphilis

```
if(male){if(random < 0.325){20.0;}
else{22.0;}}
else if(random < 0.186){20.0;}
else{22.0;}}
```

Incubation Period of Syphilis to Secondary Syphilis

```
21.0;
```

Primary Syphilis to Secondary Syphilis

```
21.0+random*21.0;
```

Secondary Syphilis to Early Latent Syphilis

```
100.0+50.0*random;
```

Early latent Syphilis to Late Latent Syphilis

```
183.0;
```

Early latent Syphilis to Recurrent Syphilis

```
if (random < 0.243){182.0;}
else{184.0;}
```

Recurrent Syphilis to Early Latent Syphilis

```
21.0;
```

Early Latent Syphilis to Recurrent Syphilis

```
if (random < 0.243){182.0;}
else{184.0;}
```

Late Latent Syphilis to Tertiary Syphilis

```
if (random<0.4){1825.0+3650.0*random}
else{-1.0;}
```

HIV model

Primary HIV infection to Asymptomatic Infection

```
1.0;
```

Primary HIV infection to Acute Retroviral Syndrome

```
if (random>0.5){0.0;}
else{2.0;}
```

Acute Retroviral Syndrome to chronic HIV 1

```
35.0;
```

Asymptomatic Infection to chronic HIV 1

```
35.0;
```

chronic HIV 1 to HIV Dead

```
if (random<0.027016){random*993.0;}
else{995.0;}
```

chronic HIV 1 to chronic HIV 2

```
994.0;
```

chronic HIV 2 to HIV Dead

```
if (random<0.017139){random*897.0;}
else{899.0;}
```

chronic HIV 2 to chronic HIV 3

```
898.0;
```

chronic HIV 3 to HIV Dead

```
if (random<0.061356){random*1019.0;}
else{1021.0;}
```

chronic HIV 3 to AIDS

```
1020.0;
```

AIDS to HIV Dead

```
1110.0;
```

Sequelae Models

PID

Model Structure

We assume that female individuals who are not successfully treated or left completely untreated for a chlamydia or gonorrhoea infection have a possibility of developing PID. This transition and all further health states of the PID model are shown in Figure G.11. Also, female individuals who are currently not infected with chlamydia or gonorrhoea are likely to develop PID if they had at least one episode of chlamydia or gonorrhoea in their past. The likelihood of getting PID increases with the total number of episodes they had during their simulated life.

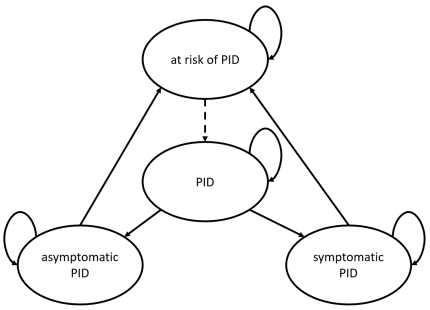

Figure G.11: PID model structure

The health state *PID* exists for technical reasons. It is easier to collect all female individuals which develop PID in one health state and separate the ones with symptomatic PID from those with asymptomatic PID in a second step. In the chlamydia and gonorrhoea model, this is done similarly with the *incubation period* state.

Transition Probabilities

To parametrise this model a review of other models was conducted.

The duration of a PID infection was set to an average of 14 days based on the review graph shown in Figure G.12.

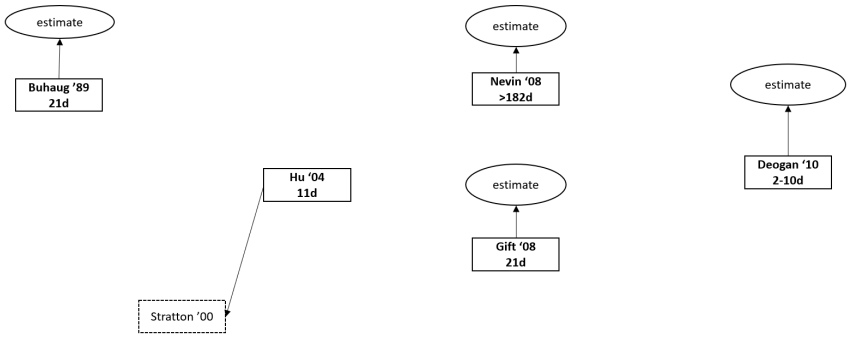

Figure G.12: Parameter origin graph for the duration of PID

The parameter origin graph for the proportion of female individuals who will get an episode of PID after an initial chlamydial (or gonorrhoea) infection is shown in Figures G.13, G.14, G.15, G.16, G.17, and G.18.

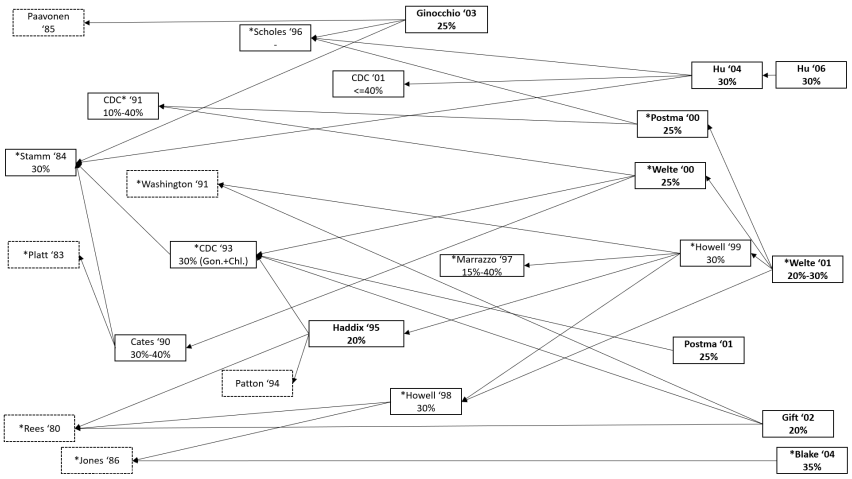

Figure G.13: Parameter origin graph for the probability of developing PID 1/6

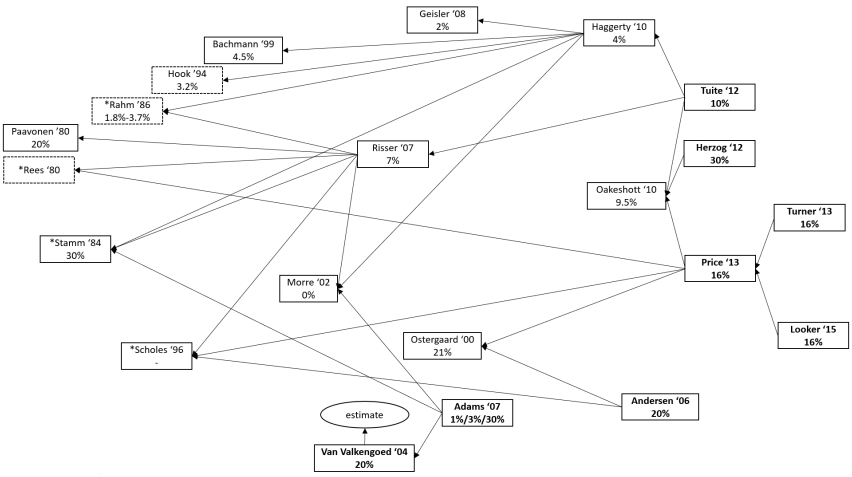

Figure G.14: Parameter origin graph for the probability of developing PID 2/6

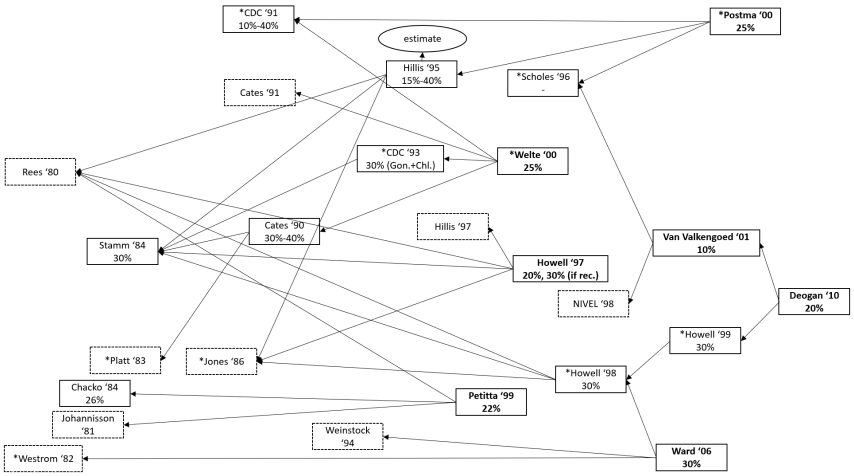

Figure G.15: Parameter origin graph for the probability of developing PID 3/6

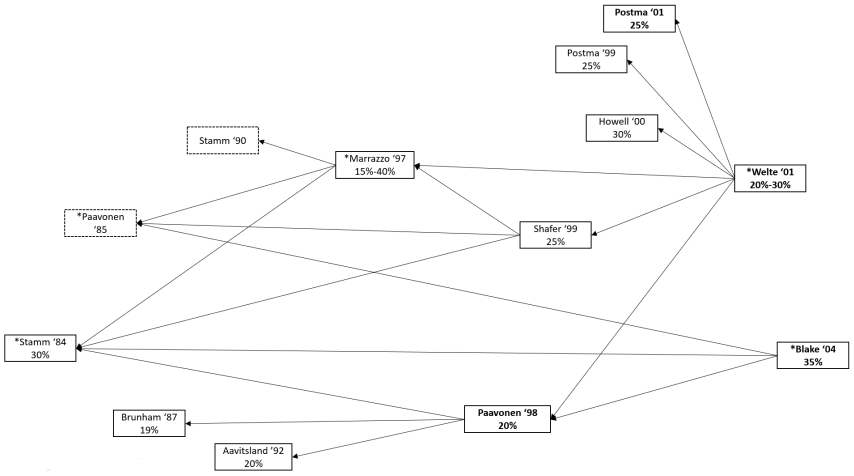

Figure G.16: Parameter origin graph for the probability of developing PID 4/6

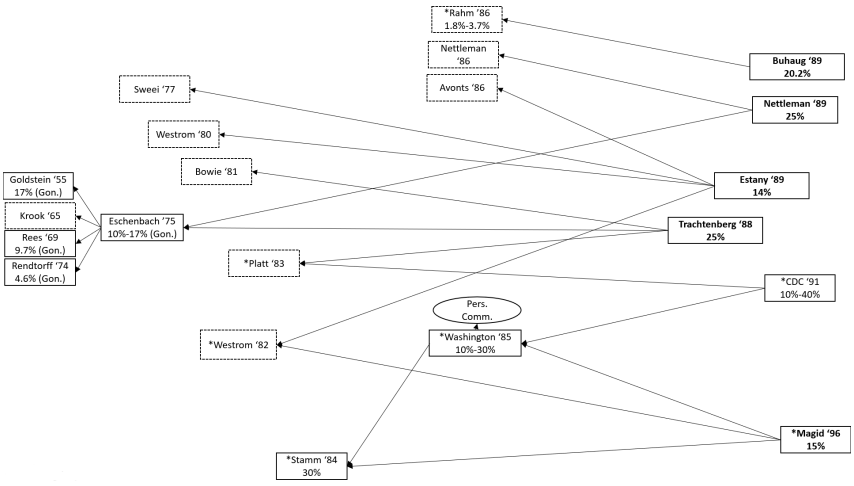

Figure G.17: Parameter origin graph for the probability of developing PID 5/6

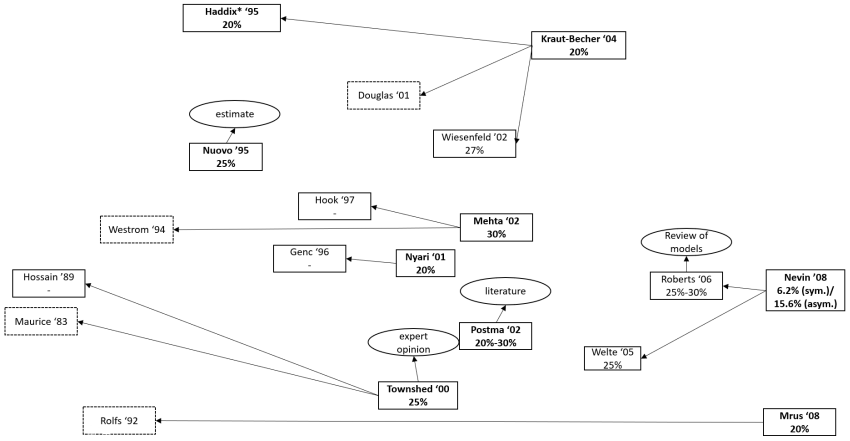

Figure G.18: Parameter origin graph for the probability of developing PID 6/6

The review graphs for the proportion of symptomatic PID infections are shown in Figures G.19, G.20, G.21, G.22, and G.23.

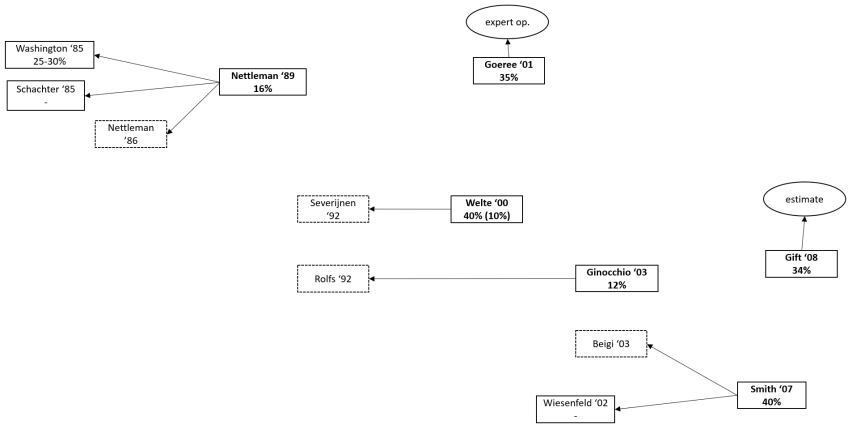

Figure G.19: Parameter origin graph for the proportion of symptomatic PID 1/5

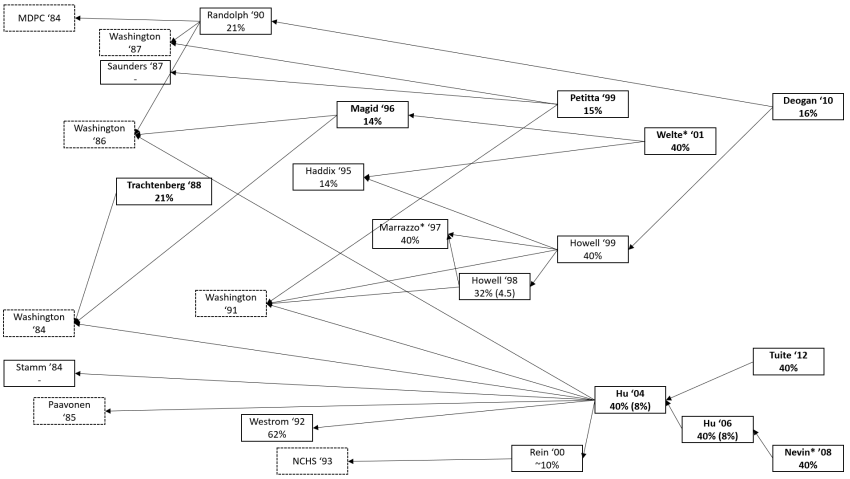

Figure G.20: Parameter origin graph for the probability of developing PID 2/5

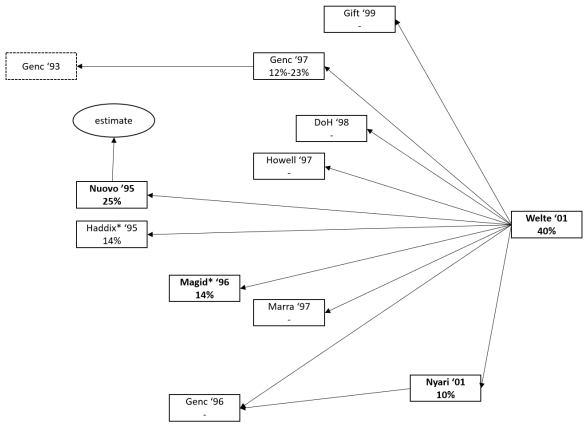

Figure G.21: Parameter origin graph for the probability of developing PID 3/5

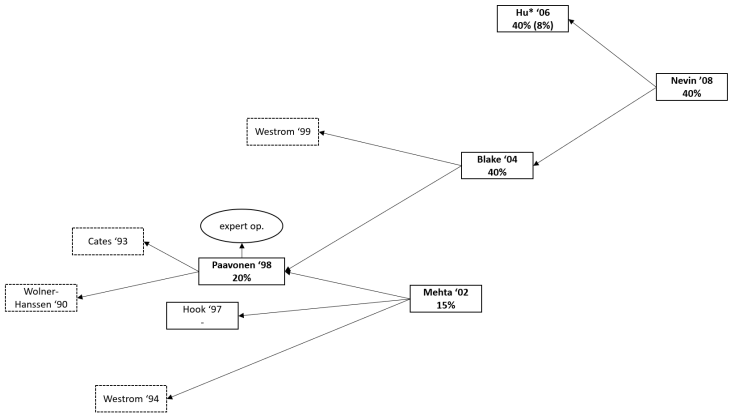

Figure G.22: Parameter origin graph for the probability of developing PID 4/5

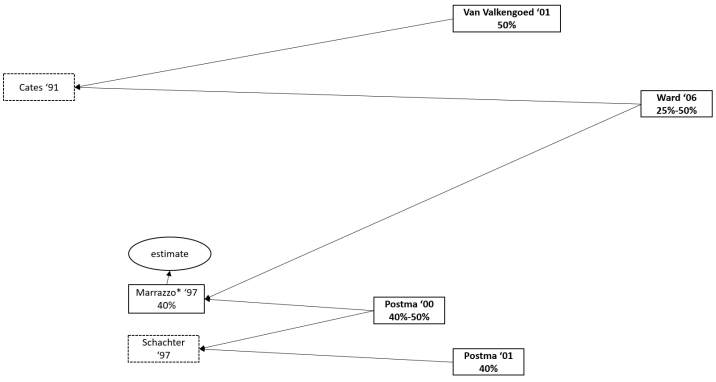

Figure G.23: Parameter origin graph for the probability of developing PID 5/5

The estimates for the percentage of female individuals developing PID after an untreated or not successfully treated episode of chlamydia ranged from 0% to 40%. Figure G.24 shows the distribution of these values.

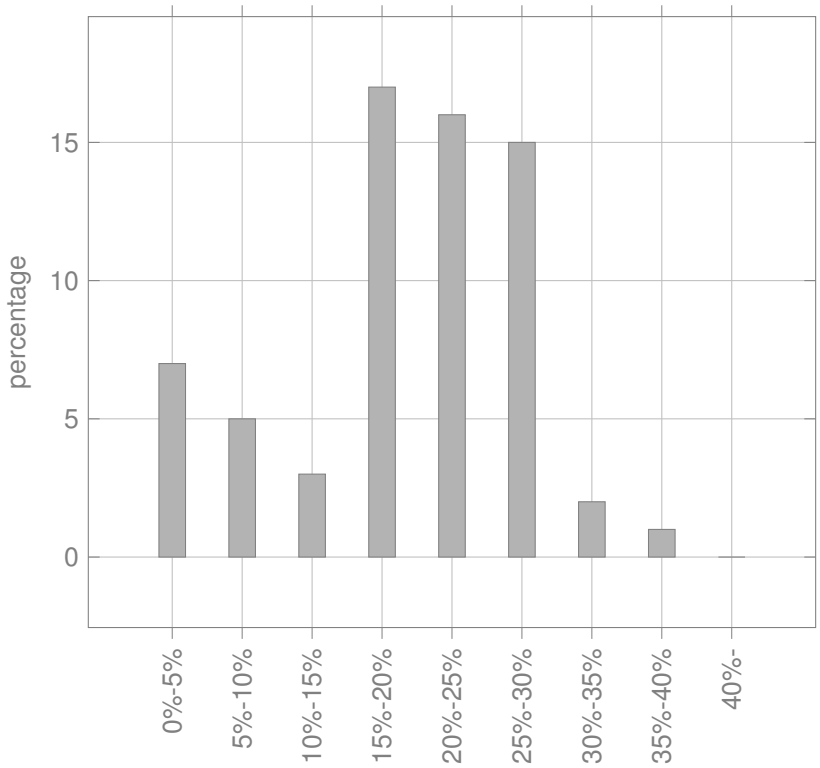

Figure G.24: Distribution of PID likelihood values

The shape of this distribution looks like two overlapping distributions. The left-hand side – up to 15% might be the distribution for women who were not successfully treated for chlamydia or gonorrhoea whereas the distribution for completely untreated PID is shown from 15% upwards, with a slight overlap up to 25%. The high middle block in the distribution is partly due to the reason that many studies and models cited Stamm et al. [355] who calculated the proportion to be 30%. I assume in my model that the proportion of women who develop PID is the same unless they are not successfully treated, I used the median value, which was 20.60% (average value: 20.55%) to parametrise my model.

The proportion of women who developed symptomatic PID differed within all regarded models. The distribution of all values can be found in Figure G.25.

Again, we can see two overlapping distributions. I assume this is due to the fact that the studies used different definitions for the term “symptomatic”. A part of the studies defined it as showing symptoms, others used it as the need for hospitalisation. In my model, I will

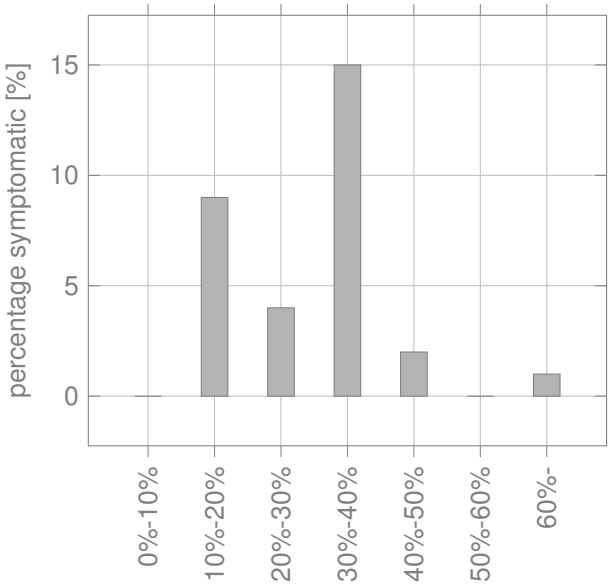

Figure G.25: Proportion symptomatic PID

use the term symptomatic PID as the first group of models did. This means that within the group of symptomatic cases of PID there is a subgroup which needs hospitalisation for treatment. This will be accounted for in the costing of the health state. After deleting all studies from the review which defined “symptomatic” as “hospitalisation”, we get a slightly left-skewed distribution with one outlier. The median of this distribution is 36.5% (average value: 31.29%) which was then used as the default value for the proportion of women showing symptoms.

The natural duration of PID did not differ between symptomatic and asymptomatic PID in all reviewed models. All of them based their parametrisation on estimates, taken from the model of Hu et al. published in 2004 [199] which referenced an article from Stratton which was not accessible to us [356]. Due to outliers on the right-hand side, we decided to use a strongly right-skewed distribution with a median of 21 days to aggregate all estimates.

Further Sequelae Models

Utility Decrements

Table G.24, on the other hand, shows the utility decrements for the sequelae of chlamydia. These models are, as explained earlier, connected to, but not solely, the chlamydia model.

Table G.24: Quality of life decrements for chlamydia sequelae

Sequela	Min decrement	Max decrement	Best est. for decrement
Cervicitis			
Symptomatic Cervicitis	0.1	0.6	0.25
Asymptomatic Cervicitis	0.1	0.3	0.158
Pelvic Inflammatory Disease (PID)			
Severe PID	0.15	0.74	0.4
Mild PID	0.1	0.57	0.26
Tubal Infertility			
Tubal Infertility	0.05	0.871	0.28
Chronic Pelvic Pain (CPP)			
CPP	0	0.5	0.22
Severe CPP	0.2	0.75	0.41
Ectopic Pregnancy (EP)			
EP	0.02	0.85	0.32
Neonatal conjunctivitis			
Neonatal conjunctivitis	0.001	0.03	0.019
Neonatal Pneumonia			
neonatal pneumonia	0.037	0.21	0.13
severe neonatal pneumonia	n/a	n/a	0.45
Male Infertility			
Male infertility	0.05	0.871	0.28
Epididymitis			
epididymitis	n/a	n/a	0.17
severe epididymitis	n/a	n/a	0.53
chronic epididymitis	n/a	n/a	0.17
Urethritis			
Asymptomatic urethritis Symptomatic urethritis	0.002	0.6	0.15
Reactive Arthritis			
Reactive arthritis	0.11	0.6	0.23

The quality decrement for the “not infected” health state for each of those models is not explicitly listed, as it is 0.0 in each case.

The quality decrement for chronic epididymitis has been set to the same value as for non-severe epididymitis.

Due to the scarcity of data, the decrement for male infertility was set to the same value as for female tubal infertility.

Some of the values in these tables are not directly taken from studies, as they were published as absolute utility values of a certain health state. In this case, I subtracted the

mentioned value from 1 (e.g. perfect health) to calculate the QALY decrement. The study of Walleser et al. [357] was not available for me and subsequently, its values are not used to calculate utility decrements.

The best estimate for the decrement is the mean value over all different estimates, this is also the value I use as a standard input in the model whereas the values for min and max decrement are used as threshold values for the extreme value analyses and the sensitivity analyses.

Unused Models

During this PhD project, some STI models have been developed which were ultimately not used in the first release of the software. This was since I started drafting model structures for diseases models before the final selection of which models to include in the software. Subsequently some of the STIs for which I already drafted a model structure have been removed from the list of STIs to include in the software.

As these models might be used in future releases or contain some relevant information for other readers, the intermediate results of the model development process are shown here.

I did not do a systematic search to input parameters of these models. They are, in this state, completely based on the corresponding treatment guideline, as published from BASHH.

Herpes

The herpes model displayed in figure G.26 is based on the BASHH guideline on herpes [358]. The disease process refers to an untreated individual. No care pathways have been developed to alter the natural process of a herpes infection.

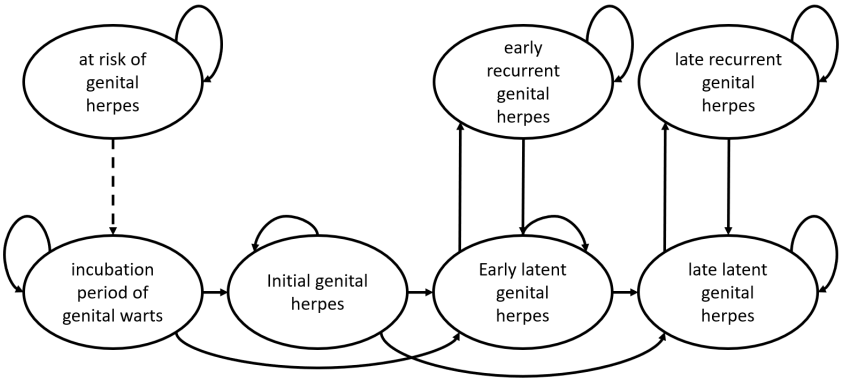

Figure G.26: Model structure of the herpes model

An infection can occur after sexual contact with a previously infected individual. The

first health state after an infection is the incubation period of herpes which lasts between 2 and 14 days. Individuals in this health state cannot further spread the disease.

After the incubation period, a majority of individual develop an initial herpes infection. Depending on the severity of the infection the infectivity of this health state is between 15% and 90% per sexual contact. The initial herpes infection lasts one to three weeks. Some individuals skip this phase and directly go into the early latent phase of herpes.

During *early latent herpes*, 0.25% - 10% of all sexual contacts with an infected individual will lead to an infection. Females in this health state will have approximately four episodes of recurrent herpes per year (male individuals five). The recurrent infections last four to seven days and have an infectivity per sexual contact of 10% - 50%. Early latent herpes lasts one up to fifteen years.

After early latent herpes, individuals will enter the health state late latent herpes. The infectivity of this health state is 0%.30% of all individuals in this health state will have at least one relapse per year. The time between two relapses is at least 6 months.

Hepatitis C

The model structure of the hepatitis C model is displayed in figure G.27. No parameters have searched to input the model.

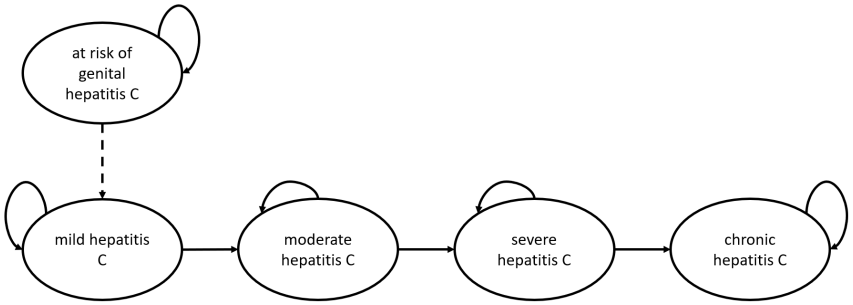

Figure G.27: Model structure of the hepatitis C model

After an infection, individuals will enter the health state *mild hepatitis C*. If the individual is not treated their health state can worsen and become *moderate hepatitis C* or even *severe hepatitis C*. Individuals in these three health states can still be treated and return to the *no hepatitis C* health state.

Untreated individuals who were in the health state *severe hepatitis C* will get *chronic hepatitis C*.

Hepatitis is linked to liver damages. Therefore cirrhosis can be caused by hepatitis C as well. The cirrhosis model structure which has been developed is shown in figure G.28.

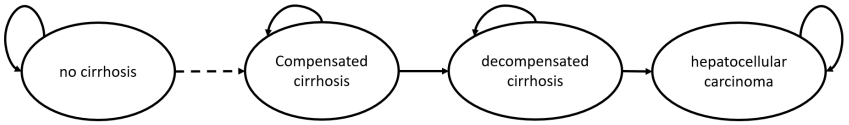

Figure G.28: Model structure of the cirrhosis model

A cirrhosis process starts with compensated cirrhosis. Individuals may proceed to decompensated cirrhosis which increases the probability of developing hepatocellular carcinoma. It is not possible to reverse the progression of carcinoma once a certain health state is reached. Though hepatocellular carcinoma can be treated i.e. with a liver transplant.

Hepatitis B

The model structure of the hepatitis B model is shown in figure G.29.

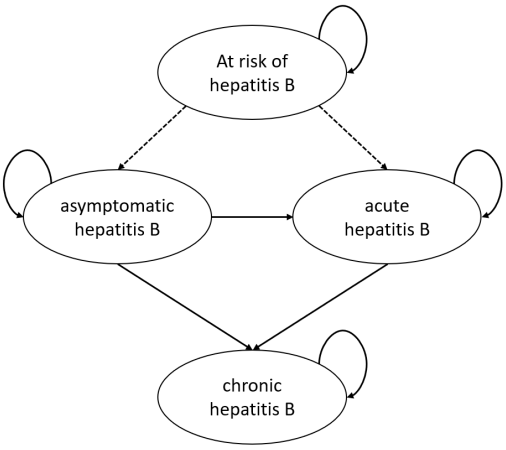

Figure G.29: Model structure of the hepatitis B model

After an infection, individuals might be in the health state *asymptomatic hepatitis B* or *acute hepatitis B*. *Asymptomatic* infections might become *acute*. Individuals in these health state can be treated and return to the health state no hepatitis B. If left untreated the hepatitis B infection can become chronic which might result in liver damage.

Mycoplasma Infection

The mycoplasma infection model structure, see Figure G.30, consist of three health states, no mycoplasma infection, asymptomatic mycoplasma infection and symptomatic mycoplasma infection.

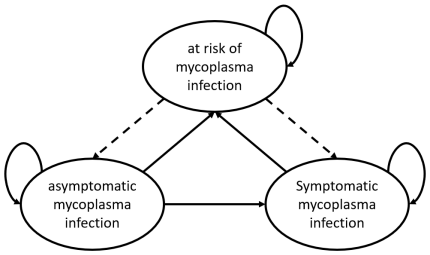

Figure G.30: Model structure of the mycoplasma infection model

After an infection, individuals will be put into the other two health states by chance. The infection will cure on its own but can also be treated. Successful treatment will decrease the duration of the infection.

Trichomonas

The trichomonas model follows an SI model structure, see figure G.31. Individuals can return from the infected state by treatment or if the infection cures on its own.

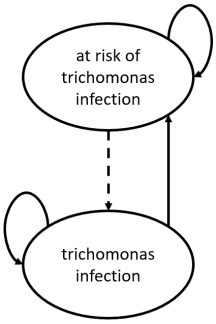

Figure G.31: Model structure of the trichomonas model

Human Papillomavirus

Human Papillomavirus is known to cause genital warts and might also be a risk factor for cervical cancer, depending on the type. The model structure in figure G.32 reflects this.

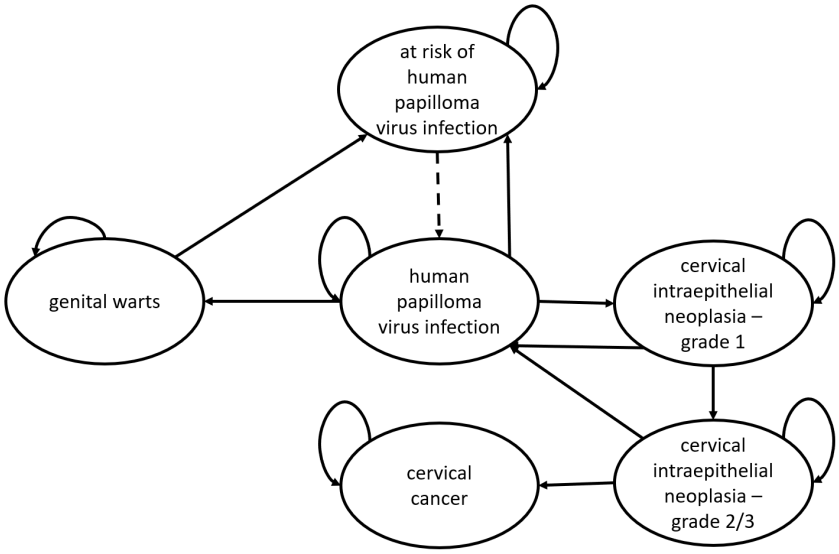

Figure G.32: Model structure of the HPV and genital warts model

Depending on the strain individuals might either proceed into the health state *genital warts* or Cervical intraepithelial neoplasia (CIN) 1. Treatments can decrease the time individuals spend in *genital warts*. *Rarely genital* warts cure on their own.

If individuals who are in the health state CIN 1 are not successfully treated they will proceed to have CIN 2 and CIN 3. The latter two states are aggregated in one health state in the suggested model structure.

If they are still not treated successfully, CIN 2/3 is also a risk factor for cervical cancer.

Appendix H

Supplementary Material for the Sexual Networks

Parameter Definitions

The final set of attributes of individuals which are used in the generic framework to describe a sexual network are summarised in Table H.1.

Table H.1: Parameters of individuals defining the sexual network and their definitions.

attributeName	definition
`male`	whether the simulated individual is male. For simplification reasons and due to the scarcity of data, the gender spectrum was projected to a binary value. Fixed throughout the whole simulation for each individual.
`age`	simulated age in years. Will increase during the simulation,
`attractedToMen`	tells whether this individual would start a partnership with another individual whose `male`-attribute is set to `true`
`attractedToWomen`	tells whether this individual would start a partnership with another individual whose `male`-attribute is set to `false`
`minPartnerAge`	states the minimum `age` of a partner, if a potential partner is younger no partnership will be built
`maxPartnerAge`	states the maximum `age` of a partner, if a potential partner is older no partnership will be built
`maxNumberOfConcurrentPartnerships`	states how many concurrent partnerships this individual is willing to have, e.g. "1" means that this individual is monogamous.

No numeric values was assigned to these attributes here as this depends on the specific sexual network which they will describe, see section 7.2.3. These attributes of an individual are not enough to describe the sexual network, therefore the attributes in Table H.2 in are part of the sexual network framework as well but can not be assigned to an individual.

Table H.2: Model parameters defining the sexual network and their definitions.

attributeName	definition
`numberPartnershipTypes`	how many different partnership types can be defined in a specific sexual network
`minDuration`	*per partnership type*; defines the minimum duration of this specific partnership type
`maxDuration`	*per partnership type*; defines the maximum duration of this specific partnership type
`frequencySexualContact`	*per partnership type*; defines the rate at which sexual contacts occur (on average) in this partnership type
`condom use`	*per partnership type*; defines the likelihood of condom use in this partnership type
`gapAfterPartnership`	*per partnership type*; how many days individuals will not start a new partnership after the old one ended
`percentageInType`	*per partnership type*; how many newly build partnerships will be of this specific type
`meetingInterval`	how often individuals are looking for new partnerships
`meetingPercentage`	how many individuals are looking for new partnerships within one `formationInterval`
`formationProbability`	how likely it is to form a partnership after all conditions (e.g. partnes's age within the own age preference range) have been checked

These parameters are used in JavaScript code snippets, which describe the formation and ending of partnerships. Those code snippets are presented in the next section.

JavaScript Code Snippets

Natsal-3 describes the proportion of homosexual, bisexual and heterosexual individuals in the population, stratified by sex. In the software homo-, bi- and heterosexuality are defined by three dichotomous attributes. These are `male`, `attractedToFemale`, `attractedToMale`. No attribute `female` was used for this as the gender is represented in a binary value. Therefore all individuals, which are not `male` are assumed to be female. To allow the partnership formation algorithm these attributes have to mutually match, as shown in the following JavaScript code snippet:

```
if (male)[other_attractedToMale;] else [other_attractedToFemale]
if (other_male)[attractedToMale;] else [attractedToFemale]
```

These expressions will only return true, and thereby potentially allowing a partnership if the sex of one individual is attractive for the other individual and vice versa.

The next important condition to be true in order to start a sexual partnership is described by the following code snippet:

```
age > other_minPartnerAge
age < other_maxPartnerAge
other_age > minPartnerAge
other_age < maxPartnerAge
```

This checks whether the age of an individual is within the age range of the potential partner and vice versa. The preferred partner age depends on their own age as well on the sex.

The last pre-partnership condition is defined in the following code snippet:

```
other_currentPartnerships < other_prefNumberPartners;
currentPartnerships < prefNumberPartners;
```

This guarantees that individuals cannot have an infinite number of partners at the same time.

Appendix I

Validation of Sexual Networks Using Deterministic Sensitivity Analysis

To examine the effect of each parameter on the disease incidence, I performed a one-way DSA. The DSA presented in this chapter is on the *young people* sexual network. The relevant outcome was the number of chlamydia infections. Each simulation was run for five years, with 1000 individuals in it. General mortality was not considered, and no clinical pathway models were activated. No chlamydia sequelae models were activated for this DSA.

A pilot run has shown that the mean number of chlamydia infections stabilizes after ten simulations with a standard derivation of 135 infections. I ran each parametrization ten times and calculated the mean of all ten results.

The base values of the deterministic sensitivity analysis are the values which were found to produce the best match with the Natsal-3 study data. This standard parametrisation was presented in the previous section, see 7.2.3. I manually selected values of interest around those default values to understand the effect of these parameters towards the overall number of new chlamydia cases. Where possible these extreme values were taken from the literature review which was used to find the default values. All the following figures are structured the same way. The dashed line indicates the number of chlamydia infections calculated by the deterministic sensitivity analysis, whereas the bar shows the number of infections for the baseline value.

I.1 Infectivity Chlamydia

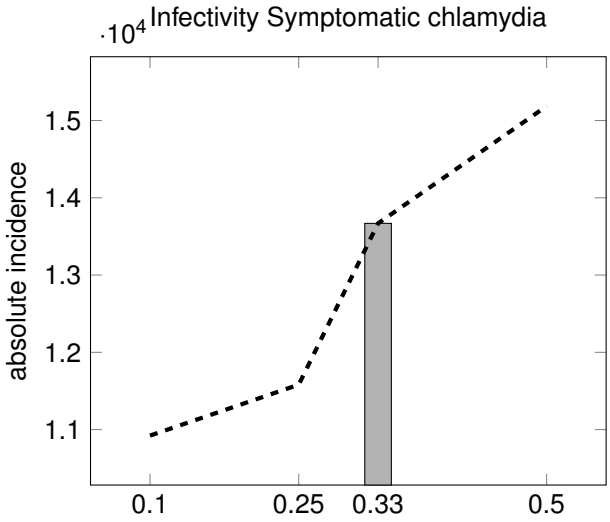

Figure I.1: Sensitivity Analysis: infectivity symptomatic chlamydia

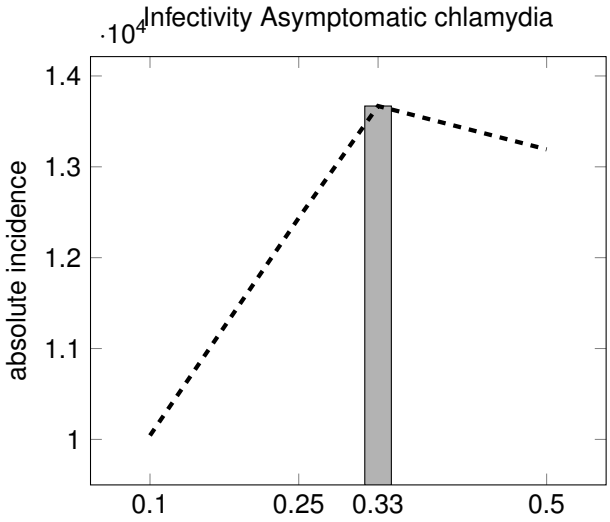

Figure I.2: Sensitivity Analysis: infectivity asymptomatic chlamydia

The infectivity of chlamydia, symptomatic (Figure I.1) as well as asymptomatic (Figure I.2) was included in the deterministic sensitivity analysis as control parameters. I wanted to see whether the total number of infections increases with higher infectivity. Both Figures confirmed the hypothesis. The slope for the graph showing the number of infections in relation to the infectivity of asymptomatic chlamydia is steeper than the same graph for the symptomatic chlamydia infections. This can be explained by the fact that an asymptomatic infection lasts longer. Therefore the likelihood of being in a partnership within this time is

higher than for symptomatic infections.

The probability of infection is the risk per sexual contact multiplied with the number of contacts. It increases with a higher number of contacts. Due to the long-lasting nature of an asymptomatic chlamydia infection compared to symptomatic chlamydia infections more contacts can occur. Therefore, the likelihood of an infection is higher. The infectivity had a higher impact on short partnerships as within those only about ten sexual contacts occur. Whereas in longer partnerships much more contacts occur and therefore infections are much more likely to happen only because of the high number of contacts. This mechanism only holds true in this analysis, as no condom use was activated and no screening and treatment measures were activated to avoid potential biases.

Overall, these graphs showed the expected trend and therefore increase the trust we can put into this analysis.

I.2 Percentage Two Partnerships

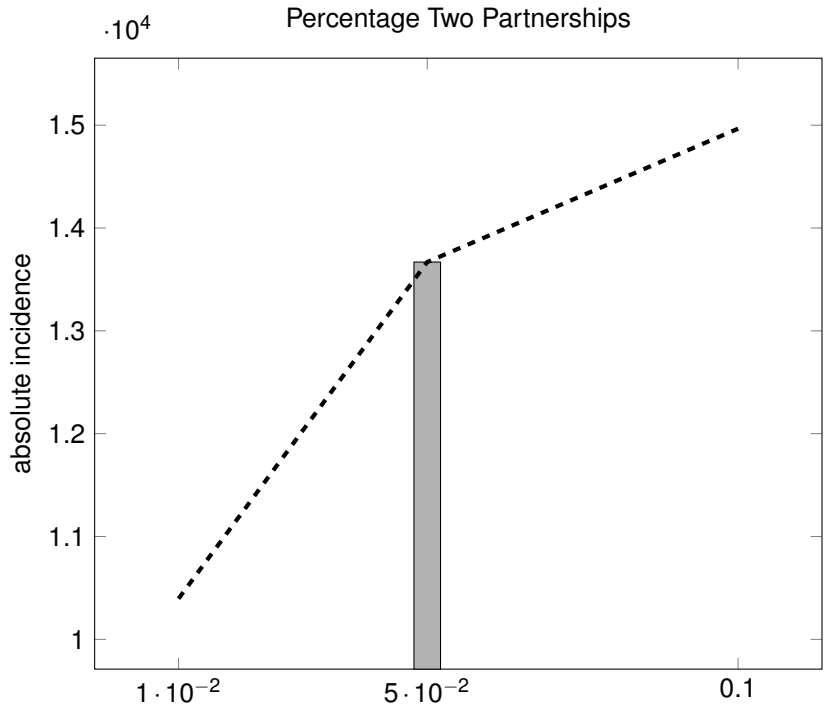

Figure I.3: Sensitivity Analysis: percentage two partnerships

With an increasing proportion of people accepting concurrent partnerships, see Figure I.3, at the same time the overall number of chlamydia infections increases. This trend reflects current knowledge of sexual networks, as a higher number of partnerships in the sexual

network results in more potential pathways for an STI to spread within the simulated population of interest.

This parameter, as well as the two parameters to follow, are those where no real-world evidence is available. Therefore the sensitivity analysis of these parameters is of great interest to show how these parameters influence the overall modelling output despite not having good evidence to parametrize them. It is good to see that this parameter does not largely influence the outcome, as no real-world evidence is available to input it.

I.3 Meeting Percentage

The meeting percentage, see Figure I.4, together with the length of the meeting interval determines how many partnerships could possibly be started as they determine how many individuals start looking for partners.

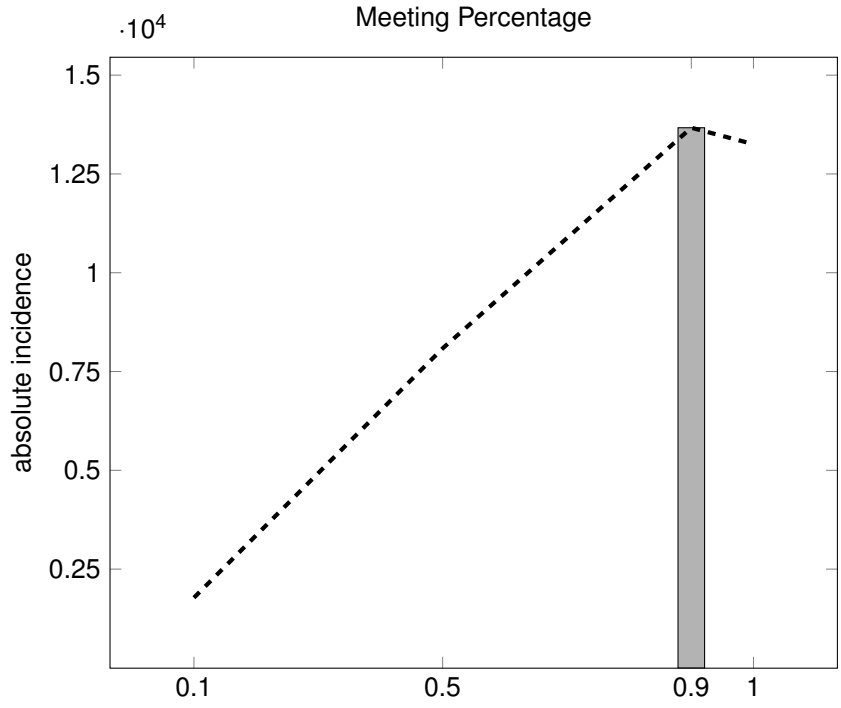

Figure I.4: Sensitivity Analysis: meeting percentage

If more individuals look for partners the number of partnerships increases, which leads to an increased number of sexual contacts and ultimately of infections within the software. This mechanism explains the previous figure well.

I.4 Length Meeting Interval

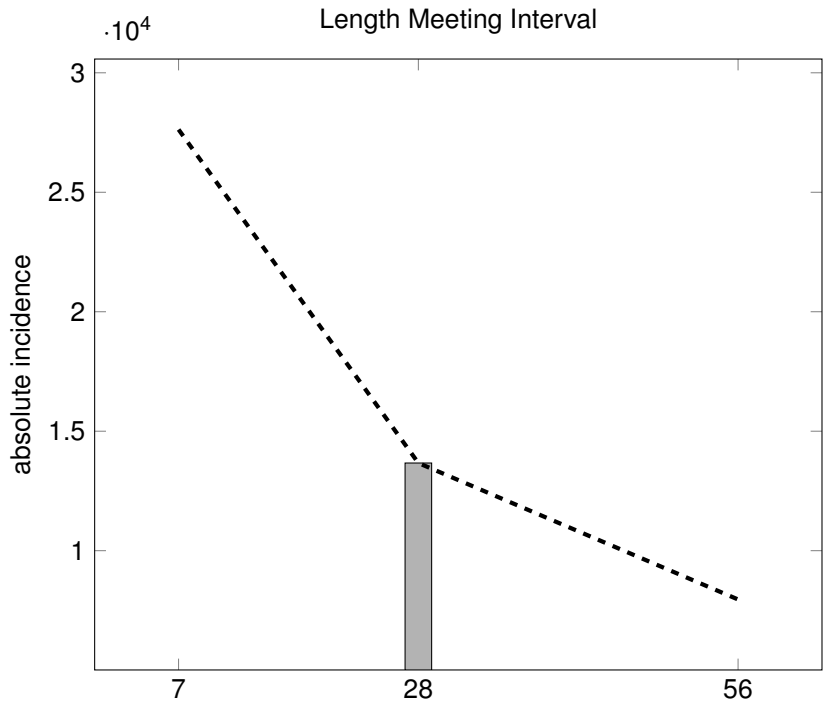

Figure I.5: Sensitivity Analysis: length meeting interval

If the same number of individuals tries to build partnerships more often, see Figure I.5, this will also lead to more partnerships and therefore more infections. The total number of infections decreases with an increased length of the meeting interval.

These two parameters both showed the expected effect. Based on this sensitivity analysis it is hard to compare their impact on the impact of other parameters. It is necessary to examine the relative effect of these parameters close in a tornado analysis, where each parameter is altered by the same proportion to show its relative effect compared to other parameters. This is described in section 7.3.2.

I.5 Partnership Formation Probability

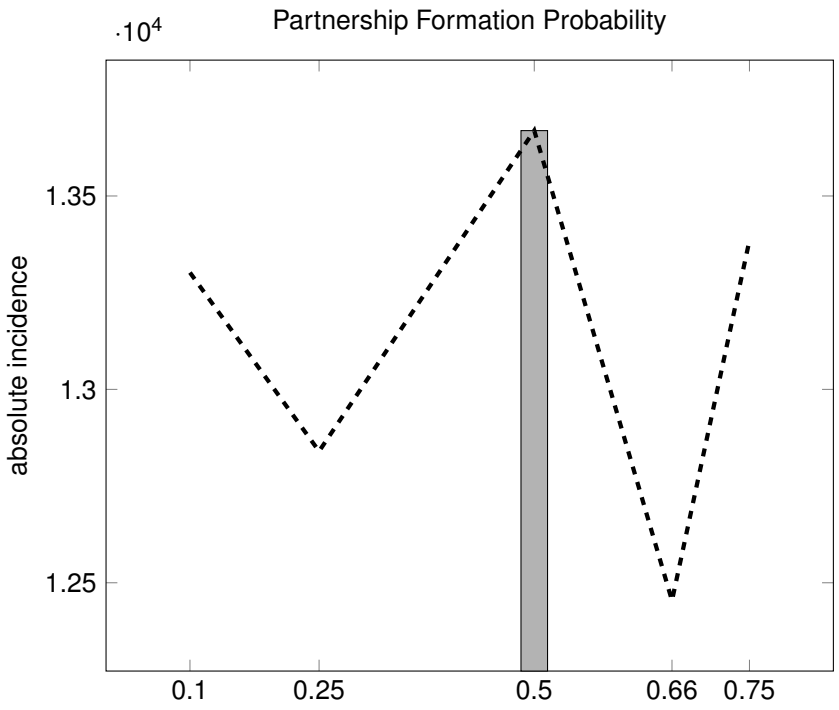

Figure I.6: Sensitivity Analysis: partnership formation probability

This parameter directly influences the number of partnerships. The number of partnerships increases in line with the proportion of all partnerships which are build, see Figure I.6.

I.6 Percentage Short Partnerships

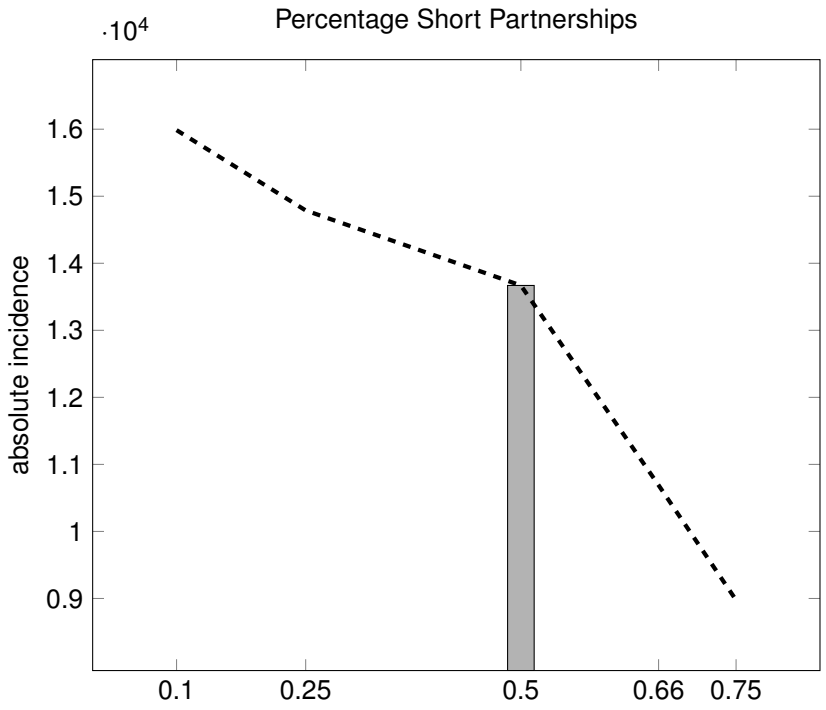

Figure I.7: Sensitivity Analysis: percentage short partnerships

When the proportion of short partnerships within all partnerships increases, the number of infections increases as well, see Figure I.7 This is likely to be explained by the fact that short partnerships end quicker and therefore enable more partnerships in the same period than a network with mainly long partnerships. As explained earlier, an increased number of partnerships ultimately leads to an increased number of infections.

At the lower end of this figure, we can see another interesting effect. With a lower proportion of short partnerships to be built, the total number of infections seems to level. To understand this effect it is important to acknowledge that this proportion only describes the type of partnerships to be built. The proportion of existing long and short partnerships depends on this parameter but is not distributed in the same way. In fact, there are, after the warm-up period, at any point during the simulation more active long partnerships than active short partnerships. With this knowledge, we can understand that an increased proportion of long partnerships yield more active long partnership. This leads to more individuals in partnerships which cannot start a partnership anymore. New infections in this scenario mostly occur due to the promiscuous nature of the network.

With a sexual network which mainly focusses on long partnerships, it might also hap-

pen that STIs within this network become extinct as relationships last longer than the natural healing process of the infection lasts.

These things considered; it is important to include an adequate proportion of short partnerships in the sexual network. On the other hand, a network which solely looks at short partnerships does not reflect the nature of a real-world sexual network.

I.7 Duration Short Partnerships

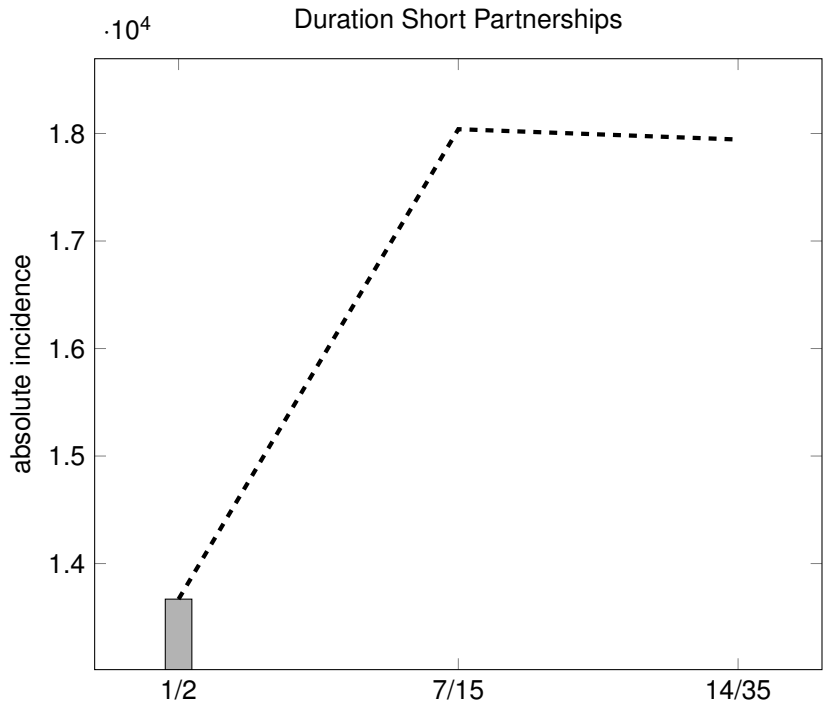

Figure I.8: Sensitivity Analysis: duration short partnerships

The partnership duration of a short partnership seems to peak at the baseline value, as Figure I.8 illustrates. There are two underlying effects to explain this behaviour.

Firstly, we have to remind ourselves that due to the baseline infectivity of 33% not every sexual contact with an infected individual will lead to an infection. On average three contacts are necessary to infect a partner. The shorter a partnership is the more likely it becomes that this number of sexual contacts necessary to yield an infection will not be reached in a short partnership. The total number of infections decreases slightly if partnerships become very short.

Another mechanism having the same effect is seen if the partnership duration increases. This lead to short and long partnerships becoming more similar. Therefore in-

dividuals stay longer in their current partnerships and the overall number of partnerships decreases, with the previously described effect of fewer infections happening.

I.8 Frequency of Sexual Contact Short Partnerships

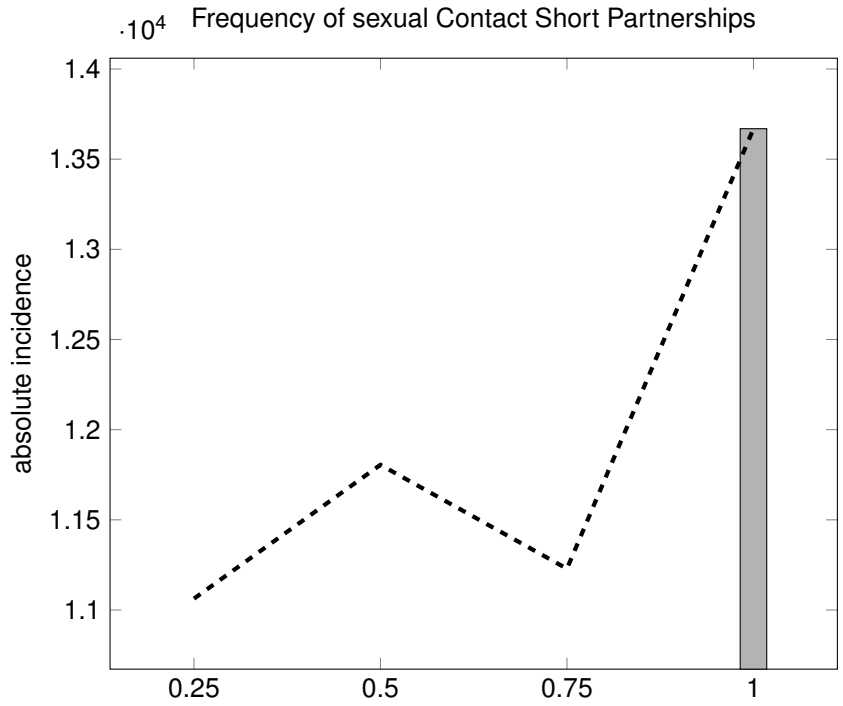

Figure I.9: Sensitivity Analysis: frequency contact short partnerships

If the number of sexual contacts within a short partnership decreases the number of total infections decreases as well. The mechanism behind this effect was explained in the previous paragraphs, as due to the lower number sexual contacts within a partnership it becomes less likely that the partnership with an infected individual will result in an infection.

Nevertheless, even for only one sexual contact every four days the total number of infections still is 70% of the baseline value, as shown in Figure I.9. This indicates that in this sexual network a majority of all infections occur within long partnerships.

I.9 Gap After Short Partnership

The duration of this gap is an important parameter as it defines how quickly after each other partnerships can occur. This is one of the most important factors for the spreading of STIs.

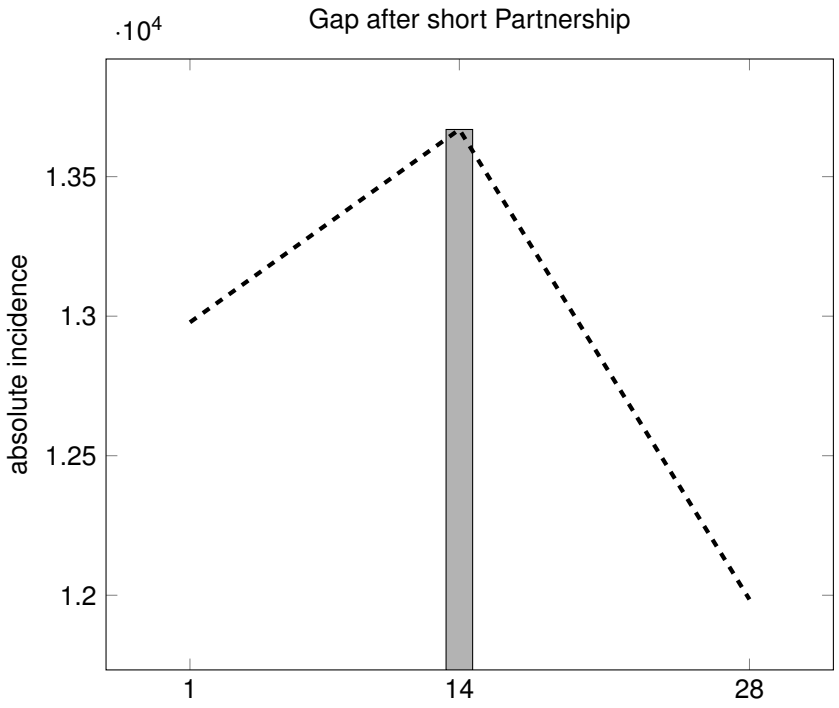

Figure I.10: Sensitivity Analysis: gap after short partnership

In Figure I.10 we can see an indicator for the same important mechanism as earlier. A longer gap after a partnership means that this individual will not be able to start a new partnership earlier on. The overall number of possible partners for individuals currently looking for a partnership decreases. Ultimately this leads to a lower number of partnerships and therefore fewer infections.

I.10 Duration Long Partnerships

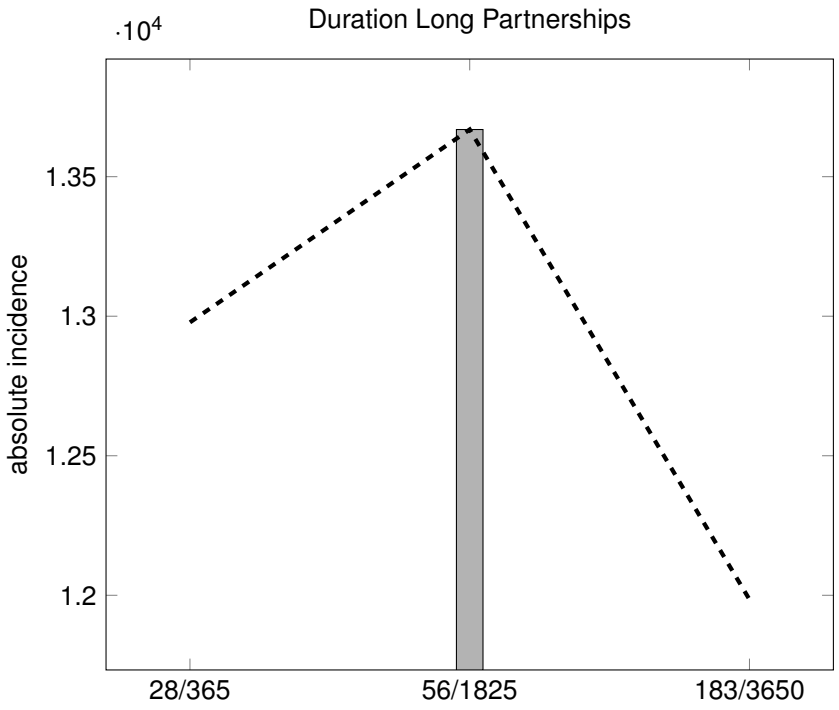

Figure I.11: Sensitivity Analysis: duration long partnerships

With increased duration of long partnerships, see Figure I.11, the number of infections decreases, as the total number of partnerships decreases as well.

I.11 Frequency Sexual Contact Long Partnerships

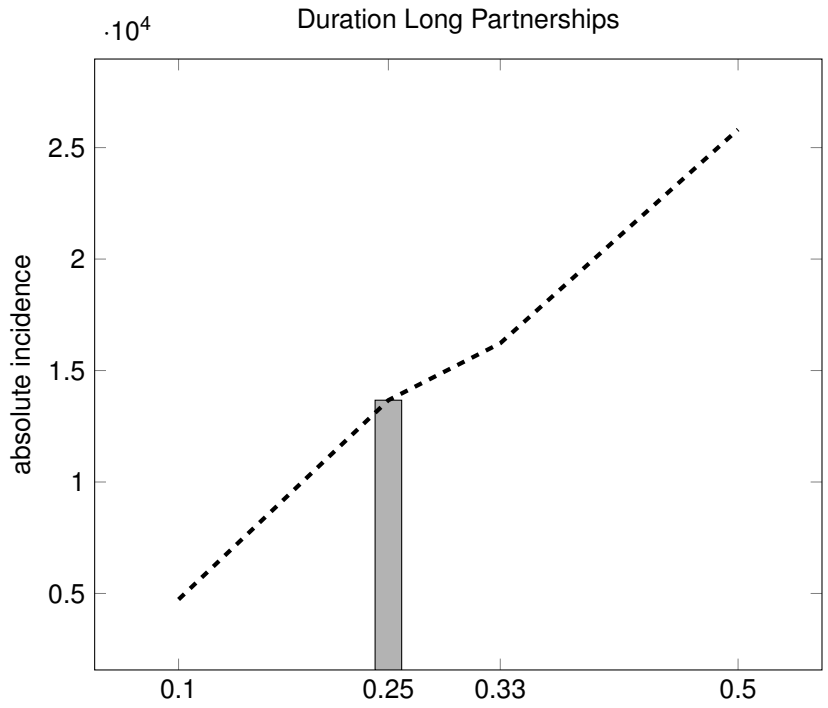

Figure I.12: Sensitivity Analysis: frequency contact long partnerships

Changes of the frequency of sexual contact within long partnerships, as demonstrated in Figure I.12, within the range from once in ten days up to every second day do not show a proportionally big effect. We can see that higher contact frequency will lead to more infections. But due to the long duration of long partnerships, an infection will happen within those anyway.

The number of infections drops when the contact frequency becomes too small, in this case, 0.05 per day. This approximately translates into one sexual contact every twenty days. Combined with the infectivity of 33%, which says that on average only the third sexual contact will lead to an infection. This means that the infection will occur on average on day 60 of the relationship. If we look at the baseline minimum duration of the sexual relationship (=56 days) we can see that long relationships without infection are possible. This explains the drop at the left end of the figure.

I.12 Gap After Long Partnership

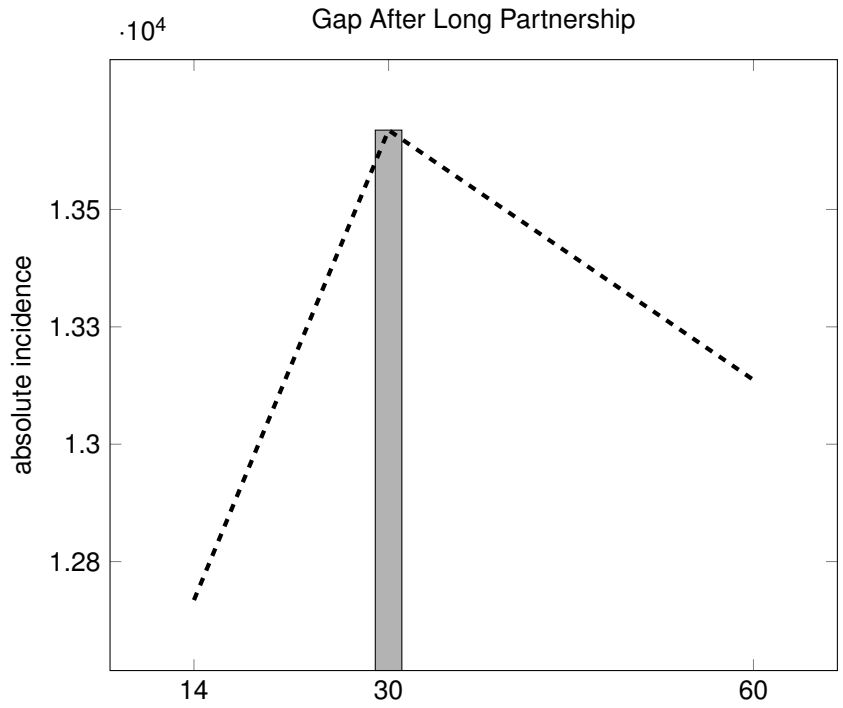

Figure I.13: Sensitivity Analysis: gap after long partnership

In Figure I.13 we can observe the same trend as for the gap after short partnerships. The local minimum at 14 days is not significant. Overall the slope is much shallower than the one already seen for short partnerships. This is since individuals who end a long-term partnership are more likely to not have any STI at this point as possibly prevalent STIs at the beginning of the partnership will have cured within the partnership.

Individuals who end a long-term partnership and look for new partnerships are under the risk of getting infected again. Assuming that they had monogamous long-term partnerships, they will very likely not carry any pathogens at this point and therefore not contribute to the spread of the disease. After a short partnership, a high proportion of those leaving a short partnership will contribute to the further spreading of the STI within the cohort, as they could be still infected.

Appendix J

Looking Back on Research Question, Aims and Objectives

In this appendix I have a look at the research question, aims, and objectives stated in the beginning of the thesis and reflect on how they were addressed by the project.

Research Question

1. Is it feasible to develop a health economic disease model for multiple sexually transmitted infections, which incorporates the most important sexually transmitted infections in England?

I have developed a software which is able to run health economic evaluations, such as cost per infection prevented and CUA. Utility values and costs have been assigned to events and health states in the software. The software contains at its current stage four distinct STIs and various sequelae. It can be debated whether the four STIs in the model, namely chlamydia, gonorrhoea, HIV, and syphilis, are the most important STIs in England. The process which was used to select the STIs found consensus from different professional areas, such as academic, clinical expertise and experience from decision makers in sexual health care. Potential future users of the model decided which STIs should be included in the model. This means that the included STIs are at least the most important STIs from the perspective of decision makers in sexual health care in England, which is the target audience of the software.

2. Is this model valid and effective considering decision makers in health care as potential users?

The validity of each bit of the model, such as disease models, sexual networks, and

clinical pathways has been presented at the end of each corresponding chapter. In the previous chapter, a possible application of the software has been showcased. As the software was able to simulate values which were close to the reported values, this is an indicator for the overall validity of the model. The intended audience for the software, were decision makers in sexual health services, which means that user interfaces were developed for them and the in- and output of the model was optimised for them. Whether this software is effective for them remains to be seen until the software will be used as a decision-support tool.

Aims

1. To develop a user-friendly multi sexually transmitted infection model as a decision support tool for decision makers in health care.

I equipped the software with user interfaces which were developed with the intention to be user-friendly for decision makers. Therefore their input from the questionnaire study and face-to-face interviews was used to decide on relevant input parameters and the kind of results which have to be displayed as well as how they have to be displayed.

2. To calculate the economic and health outcomes of sexually transmitted infections with this model in order to compare and evaluate different sexually transmitted infection interventions, either planned or existing.

I used the software to simulate the observed outcome of the MenSS-trial. In a second step, the software was used to show the impact of a potential intervention, which has not been conducted in the trial, on the same cohort and calculate its effect on the total cost and utilities.

3. To validate this model.

As already stated above, I validated each bit of the software individually. During the simulation of the MenSS-trial, I could show that the software is able to simulate real-world results with input from the same trial.

Objectives

1. Systematically review the evidence of models which simulate at least two sexually transmitted infections in one disease model to examine employed methodology and the quality of those models.

I describe in chapter 2 the systematic review I conducted. During the review, I have seen that there is no multi-STI model with a health economic component, which could be used in an English setting. The review showed that only four other models used a discrete event simulation approach, whereas compartmental, mathematical models were the most used approach. Most of the models, which were included in the review, were of average quality.

2. Determine the most suitable modelling approach to simulate multiple sexually transmitted infections in one disease model.

I found that three approaches, compartmental mathematical models, Markov models, and DES are the most suitable approaches for this kind of disease model. As the usage of an individual-based model was inevitable, because otherwise it would not be possible to simulate co-infections on an individual-based level, I deleted compartmental mathematical from this list because they do not allow to track single individuals over time. To decide between Markov microsimulations and DES, I developed a prototype (see Appendix B) which showed that for my setting a DES approach was superior as it was faster in calculating the same results as the Markov approach whilst being easier to input. The software itself is built on three separate sub-models so that the different tasks of modelling STIs can be distributed between them. These simulate the natural progress of the disease, the influence health care can have on the natural progress, and the spread of the disease within a population. In chapter 3 this three-fold approach is described in-depth.

3. Prioritise prevalent sexually transmitted infections in England with respect to their importance for the National Health Service and thereby for inclusion in the model.

In section 4.2.2.1 I describe how the STIs, which were included in the model, were selected. The process started by looking at the incidence of STIs in England and getting expert opinions on those STIs. Based on that information my supervisors and I selected 10 STIs which we considered to be most relevant. In the questionnaire, which was distributed to decision makers during the user interface development the potential future users could prioritise those STIs. The top four STIs from this selection were included in the model.

4. Create a set of disease models, which are able to interact, reflecting the prioritised sexually transmitted infections.

In chapter 5 I describe the development of disease models for chlamydia, gonorrhoea, HIV and syphilis and their corresponding sequelae. These models consist of health states and transitions between those. The transitions are described as formulas. These formulas refer to health states of other models to connect the individual models and make them interact with each other.

5. Develop models for clinical pathways to describe existing and hypothetical interventions.

In section 6 I describe how I simulate interventions such as treatment for STIs or systematic screening in the software. These clinical pathways consist of two different types of pathway elements, tests, and treatments. Those can be linked to each other, to describe the flow of an individual through the health care system, e.g. to describe mechanisms like partner notification.

6. Develop a sexual contact network model, which describes the formation and resolving of partnerships in the United Kingdom using available nationwide data.

Based on the decision of decision makers in sexual health I included four different sexual networks in the software. These were young people, MSM, BAME, and a general population network. All sexual networks assume that a relationship exists to allow sexual contacts between two individuals. The different sexual networks use different partnership building algorithms, e.g. due to different proportions of homo-, bi-, and heterosexual individuals, and different initial prevalences for included STIs.

7. Examine the validity of these models by using internal and external validation techniques.

I validated each of the three major parts of the software. The disease models have been face-validated by clinical STI experts, the sexual networks have been validated by comparing it to results from the Natsal-3 study, the clinical pathways have been face-validated by decision makers.

8. Develop user interfaces for this disease model with an agile development process in cooperation with its future users, e.g. decision makers in health care, to ensure the interface will suit their needs.

In Chapter 4 I describe the user interfaces which I developed in cooperation with decision-makers in sexual health care. The user interface development started with a questionnaire to understand the needs and working environment of future users. Based on this questionnaire, a topic guide for a semi-structured interview was set up and a first user interface draft was drawn using pen and paper methodology. In face-to-face interviews with future users the pen and paper user interface drafts were iteratively refined, translated into wireframes, validated, and finally included in the software.

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