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Methods and Quality of disease models incorporating more than two sexually transmitted infections: A protocol for a systematic review of the evidence

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Methods and Quality of disease models incorporating more than two sexually transmitted infections: A protocol for a systematic review of the evidence

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Abstract

Introduction

Disease models can be useful tools for policy makers to inform their decisions. They can help to estimate the costs and benefits of interventions without conducting clinical trials and help to extrapolate the findings of clinical trials to a population level.

Sexually transmitted infections (STI) do not operate in isolation. Risk-taking behaviours and biological interactions can increase the likelihood of an individual being co-infected with more than one STI.

Currently, few STI models consider co-infection or the interaction between STIs. We aim to identify and summarise STI models for multiple STIs and describe their modelling.

Methods and analysis

Six databases (Cochrane, Embase, PloS, ProQuest, Medline, and Web of Science) will be searched to identify studies which focus on the reporting of the methodology and quality of models for at least two different STIs. The quality of all eligible studies will be accessed using a percentage scale published by Kopec and al. We will summarise all used approaches to model multiple STIs in one model. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework will be used to report all outcomes.

Ethics and dissemination

Ethical approval is not required for this systematic review. The results of this review will be published in a peer reviewed journal and presented at a suitable conference. The findings from this review will be used to inform the development and implementation of a new multi-STI model.

Trial registration number

International Prospective Register for Systematic Reviews (PROSPERO) number CRD42017076837.

Strength and Limitations of this study

- We will summarise the methodology to model more than two STIs in a single disease model
- No limitations regarding the methodological approach of the models or the STIs simulated in the model
- Focus on the interacting feature of the disease modelling of STIs
- Key words: Sexually Transmitted Diseases, Theoretical Models, Economic Models

Introduction

Disease Modelling

Disease models attempt to simplify a complex topic to a single aspect of interest. Computational Disease Models for example examine the spreading of diseases within a population of interest and extrapolate the economic effect a potential intervention might have on this population [1, 2].With increasing computational power, disease modelling has become an important approach to inform health care decisions [3].

To set up a disease model either specialised modelling software (e.g. TreeAge [4]) or more general software (like Excel [5]) can be used. Specialised modelling software comes with a greater functionality, whereas non-expert users are more familiar with general software, which comes to the cost of longer calculation times to obtain results from the model [6].

In general disease model can be described using different dimensions. The most important dimensions to describe disease models are explained in the following paragraphs.

There are two types of approaches: individual-based disease models and compartment-based disease models. Individual-based models are computationally more intense as they simulate each person within the modelled cohort, whereas compartmental models look at proportions of the cohort which are in the same health state within the disease model. The modelled individuals of the model can be able to interact with each other, which is helpful to model infectious diseases but computationally more intense than the non-interacting modelling of population [1, 7].

The cohort of a disease model can either be open or closed. A closed cohort is defined at the beginning of the modelling process and no new individuals can enter a closed cohort model during the simulation process. An open cohort model allows new individuals to enter the simulation, i.e. keeping the simulated cohort the same size as modelled individuals might die during the calculated modelling time [8].

Disease Models can handle time in various ways. Markov-type models, for example, simulate time in a calendar-based manner, so that time always proceeds in steps of fixed length, also called cycles. Time could also be handled event-based, which means that the model skips periods when nothing happens and proceeds from one event to the next one [8-10].

Different modelling approaches might be suitable to answer various kind of questions depending on the modelling setting [1].

Sexually Transmitted Infections

STIs are infections that are primarily transmitted through sexual contact. There are many demographic, behavioural and biological risk factors for acquiring STIs including, rate of partnership change, condoms use and age [11]. As these risks apply to all STIs in the same way, people with one

STI may have a second one simultaneously.

There is also biological evidence that the presence of one STI can harm the tissue integrity of a patient or weaken the immune system of a patient and therefore make this patient more susceptible of catching another infection at the same time [12, 13].

Disease Modelling and STIs

Disease models for STIs have been used since the mid-80s. Systematics reviews of single STI models, e.g. for Chlamydia and Gonorrhoeae, have already been undertaken [14, 15]. Some of these single STI models have informed government policy like the National Chlamydia Screening Programme in the UK [16].

Rationale and research aims

Many disease models exist which examine single STIs, which is why there is good evidence on the methods to develop such a model [1, 3]. However, some STI interventions may impact on several STIs at once, reasoning the importance to include more than one infection in an STI model. We aim to summarise the literature on the simultaneous modelling of at least two different STIs and report on the methodology and quality of these models.

Registration

This review is registered with the international database of Prospectively Registers Systematic Reviews in health and social care (PROSPERO) under the registration number: CRD42017076837 (available at https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=76837).

Methods and analysis

Eligibility Criteria

Inclusion Criteria

- Models which examine STIs at a population or cohort level to describe the spreading of the disease.
- Models will have to cover at least two different STIs.
- Any methodological approach will be considered.
- Articles written in any language will be included in the review as long as an English title and abstract is provided.

Exclusion Criteria

- Any article which does not have enough detail to extract the relevant output (see Appendix B) for fully understanding the modelling approach will be excluded.
- If a model focusses on conditions other than STIs, e.g. cancer, diabetes or tuberculosis these studies will be excluded.
- If a model examines the interaction of a STI with a non-STI.
- All models which examine only one STI, even if the model includes different strains of the same STI.
- All models which examine the progression from HIV to AIDS without taking other STIs into account will be excluded.

Type of study being included and excluded

The search focusses on modelling studies, which also includes health economic analyses. As we want to extract much information only articles which aim to report in a detailed way on the disease model

and its development can be included. At least one of the objectives of the studies to be examined should be the detailed description of the model or the model development process.

The references of any review looking at multi-STI modelling studies will be included. We will add the mentioned modelling studies into the set of articles to be screened.

Clinical trials which have a modelling component and report on this with sufficient detail will be included.

Governmental documents and theses will be included.

Any other type of publication, for example, case reports or qualitative work, will be excluded.

Population

Models have to look at the sexually active part of a population. Models which only look at subgroups of the sexually active part of the population, such as homosexual men (MSM), sex workers or young people will be included as well.

Models which only look at congenital transmission will not be included in the study. We will include studies which look at any kind of horizontal transmission which could also be non-sexual transmission of STIs, e.g. through needle sharing.

Interventions

Relevant modelling studies could examine a variety of different interventions, for example screening, treatment or behaviour change approaches. This review does not aim to examine a certain type of intervention. This review will look at models which are able to simulate interventions for at least two STIs at the same time. Therefore articles reporting on models covering any intervention will be included.

If studies do not look at any specific intervention, but only introduce a model generally with the ability to examine several STIs at the same time, these studies will be included.

Selection Process

All researchers involved in article screening and data extraction will attend a meeting before starting the screening/ data extraction to develop a common understanding of the inclusion and exclusion criteria and to harmonise their understanding of the matter.

The PRISMA framework will be used to systematically report the results [17].

Outcomes

Outcomes

We want to get an overview over multi-STI disease models as well as the methodology used to implement these models. Therefore we will extract the following information:

- Modelling approach,
  - Entity level,
  - Open cohort vs closed cohort,
  - Interacting vs. 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,
- Input,
- Country,
- Output, and
- Customisability.

These data items and the reasons for including them are reported more detailed in Appendix B. Additionally data identifying the study as year of publication, authors, title, and journal are captured.

Quality Assessment

We will examine the quality of the included disease models. The quality will be assessed using a percentage scale [18]. In this percentage scale the quality of the model is examined in 17 dimensions, which are in grouped in five categories:

- Conceptual model,
- Parameters,
- Computer implementation,
- Evidence from examining model performance, and
- Evidence from examining the consequences of model-based decisions.

Each Dimension can be scored as “none” (= 0 points), “partial” (= 1 point) or “complete” (= 2 points). If some of the dimensions of the score are not applicable this particular dimension will not be included in the calculation. The sum of all points over all applicable dimensions for a model are divided by the total points a model could have reached to calculate the percentage as a quality indicator.

All reviewed studies will be reported in the final report, including their calculated percentage scale value.

Bias Assessment

We will examine whether published models tend to report a positive effect of the examined intervention, so that we can uncover a potential publication bias.

Subgroup analysis

It might be possible to use the same methodology to model STIs in a low-income country and in a high income country or in a low prevalence vs high prevalence setting. Whereas the input of these models might and most certainly will differ, the technological approach in both settings could be the same. This is why we do not focus the search on a particular setting, but examine the different income subgroups separately later on.

Information Sources

The following databases will be used to search for disease models: Cochrane, Embase, PloS, ProQuest, Medline, and Web of Science. Grey literature will be searched to find additional material using OpenGrey and New York Academy of Medicine Grey Literature Report. Conference

Proceedings will be found using Web of Science and EMBASE. PhD theses will be searched using ProQuest, Web of Science, OpenGrey and the DART-Europe portal.

We will not contact authors to understand papers with incomplete information, as we regard the completeness of information given in an article as a quality indicator. The details provided in an article should be sufficient to understand and evaluate the described model.

Before starting the title and abstract screening pilot searches will be carried out to see whether the search terms yields all known key articles. If the potentially relevant articles are not found we will amend the search terms.

Search strategy

The search term will be adapted for different search engines and database to fit their syntax. The Medline (via Ovid) version of the search term can be found in appendix A. The general search strategy is split into three main fields; “disease models”, “sexually transmitted infections” and “the interacting feature”. For each field an individual search term was developed. These search terms were combined using “AND”.

The search term is set up to have a high sensitivity to avoid missing potentially important articles. On the other hand the search term has a lower specificity, which will be compensated by manually sieving out the irrelevant search results.

The search is planned to be carried out in autumn 2017.

Study records and data management

The result list from different search engines and databases will be downloaded. We will import these search results into a new and empty Endnote database. To guarantee the reproducibility of results a backup of this database will be saved.

Endnote [19] will be used to remove duplicates. An automated check for duplicate titles and year of publication will be applied. Each possible duplicate will be deleted manually to prevent deleting non-duplicates. Another backup after the duplicate elimination will be stored.

The remaining unique articles will be imported into a Microsoft Access database [20]. The inclusion and exclusion criteria will be applied by examining the title and abstract by FS. AH will check a random sample of 10% of all articles for eligibility. Conflicts will be resolved by RH. After the title and abstract screening a backup of the Access database will be saved.

FS will conduct the full text screening for all articles and AH will check a random sample of 10% of all articles. Another backup of the Access database will be made after the completion of this step.

The remaining articles are eligible for data extraction, which will be done by FS. AH will do the data extraction for a random sample of 10% of all eligible articles. Conflicts will be solved by RH.

Electronical input forms to capture the information retrieved from the title and abstract screening, the full text screening, and data extraction will be developed. These forms will be used by all researcher (FS, AH, RH) involved in article screening and data extraction. The forms will be developed in Microsoft Excel and basic VBA programming. The information extracted with the help of these forms are also stored in Excel workbooks, one for each researcher. These workbooks will then be imported into the Microsoft Access database for further processing, quality assessment, bias assessment and analyses.

Discussion and dissemination

We will publish the results in a peer-reviewed journal and present them at a suitable conference.

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Contributors

FS is the guarantor. FS developed and refined the study protocol with comments from JS, RH, and GR. FS will be responsible for the literature search. FS and AH will carry out the data extraction. FS will do the analysis, interpretation and report writing in cooperation with RH, JS, and GR. All authors read and approved the final manuscript.

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Amendments

This is the first version of the protocol. No amendments have been made to this version so far. If the protocol has to be amended, all amendments will be listed in a table in the final report on the results of the review.

Competing Interests

None declared

Provenance and peer review

Not commissioned. Externally peer reviewed.

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Appendix A

This is the search strategy used to search Medline via the Ovid interface. This strategy has been adapted to meet the constraints in terms of syntax and thesaurus of other databases. The exact search strategies for other databases as well as the rationale for each search term are available from the authors upon request.

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

Appendix B

We will extract the following information from all eligible article. Each data item and a short explanation are given in a separate paragraph. We will also store information which identifies the study, which is: year of publication, authors, title, abstract, and publishing journal.

Modelling approach

We will extract the general approach the modellers used. This can be for example “Discrete Event Simulation” or “Markov Microsimulation”. This approach will be described in more detailed by the following items.

Entity level

This item will be used to describe whether an individual-based or a compartment-based approach is used, which means whether the model simulates each simulated patient individually or whether they are put into subgroups of the population, for example “infected” and “non-infected”.

Open cohort vs closed cohort

We will extract 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).

Interacting vs. non interacting population

We will extract information on whether the individuals in a model can interact in some form with each other or whether they are mostly independent from each other.

If they can interact with each other we will look whether a sexual contact network is used to describe this model and how this network is described.

Time handling

We will look at how time is simulated in a model. Does it proceed in slices of fixed length or does the model jump from one event to the next.

Data origin

We will look at the inputted cohort of the model. Is it based on a real life cohort or is generated hypothetical data used. If hypothetical data is used we will look at the origin for the authors’ assumptions.

Cohort Size

We will look 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.

Time horizon

We will extract data on the time horizon of the model which can be useful to understand the purpose of the model.

Modelling software

We will extract the data on the modelling software which was used to set up the model. This could be either specialised modelling software or more general tools like spreadsheet tools.

List of included STIs

We will list all STIs which were examined in this model.

Interaction

We will extract data on whether the simulated STIs are modelled in parallel or whether they interact in some form. If possible we will describe how the interaction affects the STIs.

List of sequelae of STIs

Additionally to the STIs, we will look at (long-term and short-term) sequelae which are included in the model.

Interventions

We will look at the intervention which were simulated by the model and whether the model recommends the implementation of this intervention.

Economic component

We will extract information on the economic component of the model, if there is any. We will extract the type (or types) of analysis this model is able to perform.

Input

We will collect all parameters which can be inputted by a user.

Country

We will extract information on the country (or countries) of the modelling study. The Region will be mapped to a high-, middle- or low-income region based on the World Bank definition of July 2017 [1], see also Table 1.

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

Table 1 Mapping of average gross national income per capita to income group by World Bank definition

Output

We will collect all output parameters which can be calculated by a model.

Customisability

Based on the possibility to generalise a model we will try to extract information on the generalisability. This means whether the model can be used by other researcher for other research questions.

References

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Checklist PRISMA-P

For submission: Methods and Quality of disease models incorporating more than two sexually transmitted infections: A protocol for a systematic review of the evidence

Checklist filled by Fabian Sailer

Item No	Section and Topic	Addressed where
Administrative Information		
1a	Title: Identification	Page 1, Line 10-12: Title
1b	Title: Update	N/A in this submission
2	Registration	Page 1, Line 54: Abstract: last paragraph; Page 3, Line 25-28: Introduction: registration
3a	Authors: Contact	Page 1, Line 14-22 & Page 7, Line 8-26: Authors & Author affiliations
3b	Authors: Contributions	Page 7, Line 27-32: Contributors
4	Amendments	N/A in this submission
5a	Support: Sources	Page 7, Line 27-31: Funding
5b	Support: Sponsor	Page 7, Line 27-31: Funding
5c	Support: Role of sponsor or funder	Page 7, Line 27-31: Funding
Introduction		
6	Rationale	Page 3, Line 16-22: Introduction: Rationale and research aims
7	Objectives	Page 3, Line 16-22: Introduction: Rationale and research aims
Methods		
8	Eligibility Criteria	Page 3, Line 31- Page 4, Line 35: Methods and analysis: Eligibility Criteria
9	Information sources	Page 1, Line 40: Abstract: Methods and analysis; Page 5, Line 53 – Page 6, Line 14: Methods and analysis: Information Sources
10	Search strategy	Page 6, Line 15-27: Methods and Analysis: Search strategy; Page 10-11: Appendix A
11a	Study Records: Data Management	Page 6, Line 29-57: Methods and analysis: Study records and data management
11b	Study Records: Selection Process	Page 4, Line 36-42: Methods and analysis: Selection Process
11c	Study Records: Data Collection Process	Page 6, Line 46-57: Methods and analysis: Study records and data management
12	Data Items	Page 4, Line 44 – Page 5, 18: Methods and analysis: Outcomes; Page 12-14: Appendix B
13	Outcomes and Prioritization	Page 4, Line 43 – Page 5, Line 18: Methods and analysis: Outcomes
14	Risk of bias in individual studies	Page 5, Line 19-40: Methods and analysis: Quality Assessment
15a	Data synthesis	N/A in this review
15b	Data synthesis	N/A in this review
15c	Data synthesis	Page 5, Line 45-52: Methods and analysis:

		Subgroup Analysis
15d	Data synthesis	Page 5, Line 38-39: Methods and analysis: Quality Assessment, last paragraph
16	Meta-bias(es)	Page 5, Line 41-44: Methods and analysis: Bias Assessment
17	Confidence in cumulative evidence	Page 5, Line 19-39: Methods and analysis: Quality Assessment

We are confident that we addressed all of the above mentioned items of the PRISMA-P checklist in a sufficient manner.

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Primary Subject Heading:	Sexual health
Secondary Subject Heading:	Health economics, Health informatics, Infectious diseases
Keywords:	SEXUAL MEDICINE, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, HEALTH ECONOMICS, INFECTIOUS DISEASES

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Disease models can be useful tools for policy makers to inform their decisions. They can help to estimate the costs and benefits of interventions without conducting clinical trials and help to extrapolate the findings of clinical trials to a population level.

Sexually transmitted infections (STI) do not operate in isolation. Risk-taking behaviours and biological interactions can increase the likelihood of an individual being co-infected with more than one STI.

Currently, few STI models consider co-infection or the interaction between STIs. We aim to identify and summarise STI models for two or more STIs and describe their modelling.

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Trial registration number

International Prospective Register for Systematic Reviews (PROSPERO) number CRD42017076837.

Strength and Limitations of this study

- This review will summarise the methodology which was used to model more than two STIs in a single disease model.
- This review is not limited to a certain kind of modelling approach or intervention.
- Focus on summarising different techniques to model interacting STIs, excluding the potential interactions of STIs with other non-sexually transmitted infections
- Key words: Sexually Transmitted Diseases, Theoretical Models, Economic Models

Introduction

Disease Modelling

Disease models attempt to simplify a complex topic to a single aspect of interest. Computational Disease Models for example examine the spreading of diseases within a population of interest and extrapolate the economic effect a potential intervention might have on this population [1, 2].With increasing computational power, disease modelling has become an important approach to inform health care decisions [3].

To set up a disease model either specialised modelling software (e.g. TreeAge [4]) or more general software (like Excel [5]) can be used. Specialised modelling software comes with a greater functionality, whereas non-expert users are more familiar with general software, which comes to the cost of longer calculation times to obtain results from the model [6].

In general disease model can be described using different dimensions. The most important dimensions to describe disease models are explained in the following paragraphs.

There are two types of approaches: individual-based disease models and compartment-based disease models. Individual-based models are computationally more intense as they simulate each person within the modelled cohort, whereas compartmental models look at proportions of the cohort which are in the same health state within the disease model. The modelled individuals of the model can be able to interact with each other, which is helpful to model infectious diseases but computationally more intense than the non-interacting modelling of population [1, 7].

The cohort of a disease model can either be open or closed. A closed cohort is defined at the beginning of the modelling process and no new individuals can enter a closed cohort model during the simulation process. An open cohort model allows new individuals to enter the simulation, i.e. keeping the simulated cohort the same size as modelled individuals might die during the calculated modelling time [8].

Disease Models can handle time in various ways. Markov-type models, for example, simulate time in a calendar-based manner, so that time always proceeds in steps of fixed length, also called cycles. Time could also be handled event-based, which means that the model skips periods when nothing happens and proceeds from one event to the next one [8-10].

Different modelling approaches might be suitable to answer various kind of questions depending on the modelling setting [1].

Sexually Transmitted Infections

STIs are infections that are primarily transmitted through sexual contact. There are many demographic, behavioural and biological risk factors for acquiring STIs including, rate of partnership

change, condoms use and age [11]. As these risks apply to all STIs in the same way, people with one STI may have a second one simultaneously.

There is also biological evidence that the presence of one STI can harm the tissue integrity and therefore make a patient more susceptible of catching another infection at the same time [12, 13].

Disease Modelling and STIs

Disease models for STIs have been used since the mid-80s. Systematics reviews of single STI models, e.g. for chlamydia and gonorrhoea, have already been undertaken [14, 15]. Some of these single STI models have informed government policy like the National Chlamydia Screening Programme in the UK [16].

Rationale and research aims

Many disease models exist which examine single STIs, which is why there is good evidence on the methods to develop such a model [1, 3]. However, some STI interventions may impact on several STIs at once. For example, interventions to increase condom use have shown to decrease the prevalence of STIs [17, 18], whereas a Cochrane did not find significant evidence that increased condom use will result in decreased transmission rates for STIs [19]. This ambiguous situation underlines the importance to include more than one infection in an STI model to further examine potential effects of interventions targeting more than one STI at the same time. We aim to summarise the literature on the simultaneous modelling of at least two different STIs and report on the methodology and quality of these multi STI models.

Registration

This review is registered with the international database of Prospectively Registers Systematic Reviews in health and social care (PROSPERO) under the registration number: CRD42017076837 (available at https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=76837).

Methods and analysis

Eligibility Criteria

Inclusion Criteria

Articles will be included if they:

- Report on a disease model as one of the main aims of the paper
- Examine STIs at a population or cohort level to describe the spreading of the disease.
- Cover two or more different STIs.
- Contain an English title and abstract.

Other inclusion criteria by characteristic

- **Type of study:** governmental documents, journal articles, clinical trials with modelling component, theses
- **Populations:** sexually active population (or subgroups of it), examining at least horizontal STI transmission
- **Interventions:** Any kind of intervention

Exclusion Criteria

Articles will be excluded if they:

- Do not provide enough detail to extract the relevant output (see Appendix A) to reproduce

the modelling approach.

- Focus on conditions other than STIs, e.g. cancer, diabetes or tuberculosis.
- Examine the interaction of a STI with a non-STI.
- Examine only one STI, even if the model covers different strains of the same STI.
- Examine the connection of a STI and its sequelae, e.g., the progression from human immunodeficiency virus (HIV) infection to acquired immunodeficiency syndrome, without taking other STIs into account.

Other exclusion criteria by characteristic

- **Type of study:** qualitative work, case reports
- **Populations:** solely regarding vertical transmission

Type of study

The search focusses on modelling studies, which also includes health economic analyses. As we want to extract much information, only articles which aim to report in a detailed way on the disease model and its development can be included. At least one of the objectives of the studies to be examined should be the detailed description of the model or the model development process.

The references of any review looking at multi-STI modelling studies will be included. We will add the mentioned modelling studies into the set of articles to be screened.

Clinical trials which have a modelling component and report on this with sufficient detail will be included.

Governmental documents and theses will be included.

Any other type of publication, for example, case reports or qualitative work, will be excluded.

Populations

Models have to look at the sexually active part of a population. Models which only look at subgroups of the sexually active part of the population, such as homosexual men, sex workers or young people will be included as well.

The review focusses on articles which examine horizontal transmission, e.g. through sexual contact. If an article only simulates vertical transmission, i.e. mother to child transmission (congenital transmission), it will not be included in the study. If an article considers horizontal and vertical transmission it will be included in the review. We will include studies looking at any kind of horizontal transmission. This could also be non-sexual transmission of STIs, e.g. through needle sharing.

Interventions

Relevant modelling studies could examine a variety of different interventions, for example screening, treatment or behaviour change approaches. This review does not aim to examine a certain type of intervention. This review will look at models which are able to simulate interventions for at least two STIs at the same time. Therefore articles reporting on models covering any intervention will be included.

If studies do not look at any specific intervention, but only introduce a model generally with the ability to examine several STIs at the same time, these studies will be included.

Outcomes

Outcomes

We want to get an overview over multi-STI disease models as well as the methodology used to implement these models. Therefore we will extract the following information:

- Modelling approach,
  - Entity level,
  - Open cohort vs closed cohort,
  - Interacting vs. 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 data item "output" will capture the different outputs model can calculate. These can be economic outcomes, like "cost per infection prevented" or "costs per QALY gained" or other numeric outcomes such as the "total number of infections". All parameters which can be inputted in the model or have been used by the researchers are captured using the data item "input". We will also capture the degree to which "input" parameters can be modified if/when additional evidence becomes available or to modify the model to ask a different research question. This will be captured in the "customisability" data item. All data items and the reasons for including them are reported more detailed in Appendix A. Additionally data identifying the study as year of publication, authors, title, and journal are captured.

Information Sources

The following databases will be used to search for disease models: Cochrane, Embase, PLOS, ProQuest, Medline, and Web of Science. Grey literature will be searched to find additional material using OpenGrey and New York Academy of Medicine Grey Literature Report. Conference Proceedings will be found using Web of Science and EMBASE. PhD theses will be searched using ProQuest, Web of Science, OpenGrey and the DART-Europe portal.

We will not contact authors to understand papers with incomplete information, as we regard the completeness of information given in an article as a quality indicator. The details provided in an article should be sufficient to understand and evaluate the described model.

Before starting the title and abstract screening pilot searches will be carried out to see whether the search terms yields all known key articles. If the potentially relevant articles are not found we will amend the search terms.

Search strategy

The search terms will be adapted for different search engines and database to fit their syntax. The Medline (via Ovid) version of the search term can be found in appendix B. The general search strategy is split into three main fields; “disease models”, “sexually transmitted infections” and “the interacting feature”. For each field an individual search term was developed. These search terms were combined using “AND”.

The search terms are set up to have a high sensitivity to avoid missing potentially important articles. On the other hand the search term has a lower specificity, which will be compensated by manually sieving out the irrelevant search results.

The search is planned to be carried out in autumn 2017.

Selection Process

All researchers involved in article screening and data extraction will attend a meeting before starting the screening/ data extraction to develop a common understanding of the inclusion and exclusion criteria and to harmonise their understanding of the matter.

FS and AH will independently do the title and abstract screening, with FS screening all articles and AH screening 20%. During the title and abstract screening FS and AH will not know the year of the study, the authors, and the journal the study was published in. Arising conflicts will be solved by RH. If the second and third reviewer find that the first reviewer is over exclusive and has missed some papers we will increase the percentage of papers reviewed by two reviewers by 10% and repeat the process.

All articles eligible for full text screening will be independently screened by FS and AH, with FS screening all articles and AH screening 20%. RH will solve any conflicts.

The data extraction will be done independently by FS and AH. If any conflicts arise, a meeting will be set up to find consensus, if necessary this will be moderated by RH.

The PRISMA framework will be used to systematically report the results [20].

Quality Assessment

We will examine the quality of the included disease models. The quality will be assessed using a percentage scale [21]. In this percentage scale the quality of the model is examined in 17 dimensions, which are in grouped in five categories:

- Conceptual model,
- Parameters,
- Computer implementation,
- Evidence from examining model performance, and
- Evidence from examining the consequences of model-based decisions.

Each Dimension can be scored as “none” (= 0 points), “partial” (= 1 point) or “complete” (= 2 points). If some of the dimensions of the score are not applicable this particular dimension will not be included in the calculation. The sum of all points over all applicable dimensions for a model are divided by the total points a model could have reached to calculate the percentage as a quality indicator.

Bias Assessment

We will examine whether published models tend to report a positive effect of the examined intervention, so that we can uncover a potential publication bias.

Analyses

All reviewed studies will be reported in the final report, including their calculated percentage scale of the quality assessment value.

We will report how often each modelling approach has been used and how high the average percentage scale for each modelling approach was. We will report on the distribution of years in which the study has been conducted to understand potential trends in multi STI modelling.

To understand which STI interaction have been the most relevant, we will set up a graph to show which STIs have been modelled together most frequently.

Subgroup analysis

We will use the percentage scale of the quality assessment to differentiate between models with higher and lower quality. We will compare these subgroups individually to examine the differences between those.

We will examine whether articles obtained through grey literature searches differ from articles obtained through searches in published literature databases.

To examine trends in the usage and variations in quality of modelling approaches we will examine all modelling approaches separately.

It might be possible to use the same methodology to model STIs in a low-income country and in a high income country or in a low prevalence vs high prevalence setting. Whereas the input of these models might and most certainly will differ, the technological approach in both settings could be the same. This is why we do not focus the search on a particular setting, but examine the different income subgroups separately later on.

Study records and data management

The result list from different search engines and databases will be downloaded. We will import these search results into a new and empty Endnote database. To guarantee the reproducibility of results a backup of this database will be saved.

Endnote [22] will be used to remove duplicates. An automated check for duplicate titles and year of publication will be applied. Each possible duplicate will be deleted manually to prevent deleting non-duplicates. Another backup after the duplicate elimination will be stored.

All articles will be imported into a Microsoft Access database [23]. After title and abstract screening and after full text screening copies of the database will be saved.

Electronical input forms to capture the information retrieved from the title and abstract screening, the full text screening, and data extraction will be developed. These forms will be used by all researcher (FS, AH, RH) involved in article screening and data extraction. The forms will be developed in Microsoft Excel and VBA programming. The information extracted with the help of these forms are also stored in Excel workbooks, one for each researcher. These workbooks will then be imported into the Microsoft Access database for further processing, quality assessment, bias assessment and analyses.

Discussion and dissemination

The aim of this review is to describe the quantity and quality of published multi STI models. A limitation of this is that we will not be able to conduct a meta-analysis of the findings. We will summarise all results, but we will not be able to produce aggregate figures such as funnel plots as it is likely that the models included in the review will report a range of outcomes with no single identifiable outcome to evaluate.

We will summarise the methodology which has been used to model STIs and assess the quality of existing multi STI models. We will not assess whether the most suitable approach to answer the research question of interest has been chosen by the authors of those disease models.

The modelling of STIs interacting with non-STIs, e.g. HIV and tuberculosis, although being clinically important [24], will not be examined in this review, as it will not answer our research question and is beyond the remit of the review.

We will publish the results in a peer-reviewed journal and present them at a suitable conference. The findings of this review will be used to inform the development of a multi STI disease model, incorporating the most important STIs in an UK setting.

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Contributors

FS is the guarantor. FS developed and refined the study protocol with comments from JS, RH, and GR. FS will be responsible for the literature search. FS and AH will carry out the data extraction. FS will do the analysis, interpretation and report writing in cooperation with RH, JS, and GR. All authors read and approved the final manuscript.

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Amendments

This is the first version of the protocol. No amendments have been made to this version so far. If the

protocol has to be amended, all amendments will be listed in a table in the final report on the results of the review.

Competing Interests

None declared

Provenance and peer review

Not commissioned. Externally peer reviewed.

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Appendix A

We will extract the following information from all eligible article. Each data item and a short explanation are given in a separate paragraph. We will also store information which identifies the study, which is: year of publication, authors, title, abstract, and publishing journal.

Modelling approach

We will extract the general approach the modellers used. This can be for example “Discrete Event Simulation” or “Markov Microsimulation”. This approach will be described in more detailed by the following items.

Entity level

This item will be used to describe whether an individual-based or a compartment-based approach is used, which means whether the model simulates each simulated patient individually or whether they are put into subgroups of the population, for example “infected” and “non-infected”.

Open cohort vs closed cohort

We will extract 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).

Interacting vs. non interacting population

We will extract information on whether the individuals in a model can interact in some form with each other or whether they are mostly independent from each other.

If they can interact with each other we will look whether a sexual contact network is used to describe this model and how this network is described.

Time handling

We will look at how time is simulated in a model. Does it proceed in slices of fixed length or does the model jump from one event to the next.

Data origin

We will look at the inputted cohort of the model. Is it based on a real life cohort or is generated hypothetical data used. If hypothetical data is used we will look at the origin for the authors’ assumptions.

Cohort Size

We will look 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.

Time horizon

We will extract data on the time horizon of the model which can be useful to understand the purpose of the model.

Modelling software

We will extract the data on the modelling software which was used to set up the model. This could be either specialised modelling software or more general tools like spreadsheet tools.

List of included STIs

We will list all STIs which were examined in this model.

Interaction

We will extract data on whether the simulated STIs are modelled in parallel or whether they interact in some form. If possible we will describe how the interaction affects the STIs.

List of sequelae of STIs

Additionally to the STIs, we will look at (long-term and short-term) sequelae which are included in the model.

Interventions

We will look at the intervention which were simulated by the model and whether the model recommends the implementation of this intervention.

Economic component

We will extract information on the economic component of the model, if there is any. We will extract the type (or types) of analysis this model is able to perform.

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 store the year in which the study actually has been conducted. If this year is not reported in the article we will assume that the study has been conducted in the year of the publication.

Input

We will collect all parameters which can be inputted by a user.

Country

We will extract information on the country (or countries) of the modelling study. The Region will be mapped to a high-, middle- or low-income region based on the World Bank definition of July 2017 [1], see also Table 1.

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

Table 1 Mapping of average gross national income per capita to income group by World Bank definition

Output

We will collect all output parameters which can be calculated by a model.

Customisability

Based on the possibility to generalise a model we will try to extract information on the generalisability. This means whether the model can be used by other researcher for other research questions.

References

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Appendix B

Basically, we used the same search strategy for all databases. But due to different thesauri and syntaxes the search strategy had to be amended to fit with the requirements of each database. Within this appendix the search strategies for all databases are listed.

Medline and Embase

This was the baseline search strategy. This strategy was used to derive the search strategies for all other databases.

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

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

Dart Europe

Dart Europe is, compared with Embase and Medline, a fairly 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

OpenGrey

Preiliminary 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 diseases”

PLOS and ProQuest

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, we decided to search for all terms in the title and abstract only.

ProQuest does not support thesaurus search or advanced syntax, which is why we had to simplify the search strategy as well. We decided to search anywhere but in the full text. We searched for scholary articles, dissertations, theses, working papers, reports, conference papers, and conference proceedings. We did not search for wire feeds, newspapers, trade journals, magazines, blogs, podcassts, and websites.

Due to the similar requirements we 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

Web of Science

Web of Science does not use a thesaurus. The database does not have a limited suffix search, which is why we replaced those with unlimited suffix searches. The adjacent operator is the same as of the Cochrane search tool. As Web of Science access also non medicinal journals, we decided to not use any abbreviations to decrease the possibility of picking up 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

Checklist PRISMA-P

For submission: Methods and Quality of disease models incorporating more than two sexually transmitted infections: A protocol for a systematic review of the evidence

Checklist filled by Fabian Sailer

Item No	Section and Topic	Addressed where
Administrative Information		
1a	Title: Identification	Page 1, Line 10-12: Title
1b	Title: Update	N/A in this submission
2	Registration	Page 1, Line 54: Abstract: last paragraph; Page 3, Line 25-28: Introduction: registration
3a	Authors: Contact	Page 1, Line 14-22 & Page 7, Line 8-26: Authors & Author affiliations
3b	Authors: Contributions	Page 7, Line 27-32: Contributors
4	Amendments	N/A in this submission
5a	Support: Sources	Page 7, Line 27-31: Funding
5b	Support: Sponsor	Page 7, Line 27-31: Funding
5c	Support: Role of sponsor or funder	Page 7, Line 27-31: Funding
Introduction		
6	Rationale	Page 3, Line 16-22: Introduction: Rationale and research aims
7	Objectives	Page 3, Line 16-22: Introduction: Rationale and research aims
Methods		
8	Eligibility Criteria	Page 3, Line 31- Page 4, Line 35: Methods and analysis: Eligibility Criteria
9	Information sources	Page 1, Line 40: Abstract: Methods and analysis; Page 5, Line 53 – Page 6, Line 14: Methods and analysis: Information Sources
10	Search strategy	Page 6, Line 15-27: Methods and Analysis: Search strategy; Page 10-11: Appendix A
11a	Study Records: Data Management	Page 6, Line 29-57: Methods and analysis: Study records and data management
11b	Study Records: Selection Process	Page 4, Line 36-42: Methods and analysis: Selection Process
11c	Study Records: Data Collection Process	Page 6, Line 46-57: Methods and analysis: Study records and data management
12	Data Items	Page 4, Line 44 – Page 5, 18: Methods and analysis: Outcomes; Page 12-14: Appendix B
13	Outcomes and Prioritization	Page 4, Line 43 – Page 5, Line 18: Methods and analysis: Outcomes
14	Risk of bias in individual studies	Page 5, Line 19-40: Methods and analysis: Quality Assessment
15a	Data synthesis	N/A in this review
15b	Data synthesis	N/A in this review
15c	Data synthesis	Page 5, Line 45-52: Methods and analysis:

		Subgroup Analysis
15d	Data synthesis	Page 5, Line 38-39: Methods and analysis: Quality Assessment, last paragraph
16	Meta-bias(es)	Page 5, Line 41-44: Methods and analysis: Bias Assessment
17	Confidence in cumulative evidence	Page 5, Line 19-39: Methods and analysis: Quality Assessment

We are confident that we addressed all of the above mentioned items of the PRISMA-P checklist in a sufficient manner.

BMJ Open

Methods and Quality of disease models incorporating more than two sexually transmitted infections: A protocol for a systematic review of the evidence

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Methods and Quality of disease models incorporating more than two sexually transmitted infections: A protocol for a systematic review of the evidence

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Sexually Transmitted Diseases; Models, Theoretical; Economics, Medical; Review Literature as Topic

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Excluding title page, references, figures: 3310

Abstract

Introduction

Disease models can be useful tools for policy makers to inform their decisions. They can help to estimate the costs and benefits of interventions without conducting clinical trials and help to

extrapolate the findings of clinical trials to a population level.

Sexually transmitted infections (STI) do not operate in isolation. Risk-taking behaviours and biological interactions can increase the likelihood of an individual being co-infected with more than one STI.

Currently, few STI models consider co-infection or the interaction between STIs. We aim to identify and summarise STI models for two or more STIs and describe their modelling.

Methods and analysis

Six databases (Cochrane, Embase, PLOS, ProQuest, Medline, and Web of Science) were searched on 27. November 2018 to identify studies which focus on the reporting of the methodology and quality of models for at least two different STIs. The quality of all eligible studies will be accessed using a percentage scale published by Kopec et al. We will summarise all used approaches to model two or more STIs in one model. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework will be used to report all outcomes.

Ethics and dissemination

Ethical approval is not required for this systematic review. The results of this review will be published in a peer reviewed journal and presented at a suitable conference. The findings from this review will be used to inform the development of a new multi-STI model.

Trial registration number

International Prospective Register for Systematic Reviews (PROSPERO) number CRD42017076837.

Strength and Limitations of this study

- This review will summarise the methodology which was used to model more than two STIs in a single disease model.
- This review is not limited to a certain kind of modelling approach or intervention.
- Focus on summarising different techniques to model interacting STIs, excluding the potential interactions of STIs with other non-sexually transmitted infections
- Key words: Sexually Transmitted Diseases, Theoretical Models, Economic Models

Introduction

Disease Modelling

Disease models attempt to simplify a complex topic to a single aspect of interest. Computational Disease Models for example examine the spreading of diseases within a population of interest and extrapolate the economic effect a potential intervention might have on this population [1, 2].With increasing computational power, disease modelling has become an important approach to inform health care decisions [3].

To set up a disease model either specialised modelling software (e.g. TreeAge [4]) or more general software (like Excel [5]) can be used. Specialised modelling software comes with a greater functionality, whereas non-expert users are more familiar with general software, which comes to the cost of longer calculation times to obtain results from the model [6].

In general disease model can be described using different dimensions. The most important

dimensions to describe disease models are explained in the following paragraphs.

There are two types of approaches: individual-based disease models and compartment-based disease models. Individual-based models are computationally more intense as they simulate each person within the modelled cohort, whereas compartmental models look at proportions of the cohort which are in the same health state within the disease model. The modelled individuals of the model can be able to interact with each other, which is helpful to model infectious diseases but computationally more intense than the non-interacting modelling of population [1, 7].

The cohort of a disease model can either be open or closed. A closed cohort is defined at the beginning of the modelling process and no new individuals can enter a closed cohort model during the simulation process. An open cohort model allows new individuals to enter the simulation, i.e. keeping the simulated cohort the same size as modelled individuals might die during the calculated modelling time [8].

Disease Models can handle time in various ways. Markov-type models, for example, simulate time in a calendar-based manner, so that time always proceeds in steps of fixed length, also called cycles. Time could also be handled event-based, which means that the model skips periods when nothing happens and proceeds from one event to the next one [8-10].

Different modelling approaches might be suitable to answer various kind of questions depending on the modelling setting [1].

Sexually Transmitted Infections

STIs are infections that are primarily transmitted through sexual contact. There are many demographic, behavioural and biological risk factors for acquiring STIs including, rate of partnership change, condoms use and age [11]. As these risks apply to all STIs in the same way, people with one STI may have a second one simultaneously.

There is also biological evidence that the presence of one STI can harm the tissue integrity and therefore make a patient more susceptible of catching another infection at the same time [12, 13].

Disease Modelling and STIs

Disease models for STIs have been used since the mid-80s. Systematics reviews of single STI models, e.g. for chlamydia and gonorrhoea, have already been undertaken [14, 15]. Some of these single STI models have informed government policy like the National Chlamydia Screening Programme in the UK [16].

Rationale and research aims

Many disease models exist which examine single STIs, which is why there is good evidence on the methods to develop such a model [1, 3]. However, some STI interventions may impact on several STIs at once. For example, interventions to increase condom use have shown to decrease the prevalence of STIs [17, 18], whereas a Cochrane did not find significant evidence that increased condom use will result in decreased transmission rates for STIs [19]. This ambiguous situation underlines the importance to include more than one infection in an STI model to further examine potential effects of interventions targeting more than one STI at the same time. We aim to summarise the literature on the simultaneous modelling of at least two different STIs and report on the methodology and quality of these multi STI models.

Registration

This review is registered with the international database of Prospectively Registers Systematic Reviews in health and social care (PROSPERO) under the registration number: CRD42017076837 (available at https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=76837).

Methods and analysis

Eligibility Criteria

Inclusion Criteria

Articles will be included if they:

- Report on a disease model as one of the main aims of the paper
- Examine STIs at a population or cohort level to describe the spreading of the disease.
- Cover two or more different STIs.
- Contain an English title and abstract.

Other inclusion criteria by characteristic

- **Type of study:** governmental documents, journal articles, clinical trials with modelling component, theses
- **Populations:** sexually active population (or subgroups of it), examining at least horizontal STI transmission
- **Interventions:** Any kind of intervention

Exclusion Criteria

Articles will be excluded if they:

- Do not provide enough detail to extract the relevant output (see Appendix A) to reproduce the modelling approach.
- Focus on conditions other than STIs, e.g. cancer, diabetes or tuberculosis.
- Examine the interaction of a STI with a non-STI.
- Examine only one STI, even if the model covers different strains of the same STI.
- Examine the connection of a STI and its sequelae, e.g., the progression from human immunodeficiency virus (HIV) infection to acquired immunodeficiency syndrome, without taking other STIs into account.

Other exclusion criteria by characteristic

- **Type of study:** qualitative work, case reports
- **Populations:** solely regarding vertical transmission

Type of study

The search focusses on modelling studies, which also includes health economic analyses. As we want to extract much information, only articles which aim to report in a detailed way on the disease model and its development can be included. At least one of the objectives of the studies to be examined should be the detailed description of the model or the model development process.

The references of any review looking at multi-STI modelling studies will be included. We will add the mentioned modelling studies into the set of articles to be screened.

Clinical trials which have a modelling component and report on this with sufficient detail will be included.

Governmental documents and theses will be included.

Any other type of publication, for example, case reports or qualitative work, will be excluded.

Populations

Models have to look at the sexually active part of a population. Models which only look at subgroups of the sexually active part of the population, such as homosexual men, sex workers or young people will be included as well.

The review focusses on articles which examine horizontal transmission, e.g. through sexual contact. If an article only simulates vertical transmission, i.e. mother to child transmission (congenital transmission), it will not be included in the study. If an article considers horizontal and vertical transmission it will be included in the review. We will include studies looking at any kind of horizontal transmission. This could also be non-sexual transmission of STIs, e.g. through needle sharing.

Interventions

Relevant modelling studies could examine a variety of different interventions, for example screening, treatment or behaviour change approaches. This review does not aim to examine a certain type of intervention. This review will look at models which are able to simulate interventions for at least two STIs at the same time. Therefore articles reporting on models covering any intervention will be included.

If studies do not look at any specific intervention, but only introduce a model generally with the ability to examine several STIs at the same time, these studies will be included.

Outcomes

Outcomes

We want to get an overview over multi-STI disease models as well as the methodology used to implement these models. Therefore we will extract the following information:

- Modelling approach,
  - Entity level,
  - Open cohort vs closed cohort,
  - Interacting vs. 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 data item "output" will capture the different outputs model can calculate. These can be economic outcomes, like "cost per infection prevented" or "costs per QALY gained" or other numeric outcomes such as the "total number of infections". All parameters which can be inputted in the model or have been used by the researchers are captured using the data item "input". We will also capture the degree to which "input" parameters can be modified if/when additional evidence becomes available or to modify the model to ask a different research question. This will be captured in the "customisability" data item. All data items and the reasons for including them are reported more detailed in Appendix A. Additionally data identifying the study as year of publication, authors, title, and journal are captured.

Information Sources

The following databases will be used to search for disease models: Cochrane, Embase, PLOS, ProQuest, Medline, and Web of Science. Grey literature will be searched to find additional material using OpenGrey and New York Academy of Medicine Grey Literature Report. Conference Proceedings will be found using Web of Science and EMBASE. PhD theses will be searched using ProQuest, Web of Science, OpenGrey and the DART-Europe portal.

We will not contact authors to understand papers with incomplete information, as we regard the completeness of information given in an article as a quality indicator. The details provided in an article should be sufficient to understand and evaluate the described model.

Before starting the title and abstract screening pilot searches will be carried out to see whether the search terms yields all known key articles. If the potentially relevant articles are not found we will amend the search terms.

Search strategy

The search terms will be adapted for different search engines and database to fit their syntax. The Medline (via Ovid) version of the search term can be found in appendix B. The general search strategy is split into three main fields; "disease models", "sexually transmitted infections" and "the interacting feature". For each field an individual search term was developed. These search terms were combined using "AND".

The search terms are set up to have a high sensitivity to avoid missing potentially important articles. On the other hand the search term has a lower specificity, which will be compensated by manually sieving out the irrelevant search results.

The search was carried out on 27. November 2017.

Selection Process

All researchers involved in article screening and data extraction will attend a meeting before starting the screening/ data extraction to develop a common understanding of the inclusion and exclusion criteria and to harmonise their understanding of the matter.

Two reviewers will independently do the title and abstract screening, with FS screening all articles and another reviewer screening 20%. During the title and abstract screening the reviewers will not know the year of the study, the authors, and the journal the study was published in. Arising conflicts will be solved by RH. If the second and third reviewer find, that the first reviewer is over exclusive and has missed some papers we will increase the percentage of papers reviewed by two reviewers

by 10% and repeat the process.

All articles eligible for full text screening will be independently screened by two reviewers, with FS screening all articles and another reviewer screening 20%. RH will solve any conflicts.

The data extraction will be done independently by two researchers. If any conflicts arise, a meeting will be set up to find consensus, if necessary this will be moderated by RH.

The PRISMA framework will be used to systematically report the results [20].

Quality Assessment

We will examine the quality of the included disease models. The quality will be assessed using a percentage scale [21]. In this percentage scale the quality of the model is examined in 17 dimensions, which are in grouped in five categories:

- Conceptual model,
- Parameters,
- Computer implementation,
- Evidence from examining model performance, and
- Evidence from examining the consequences of model-based decisions.

Each Dimension can be scored as “none” (= 0 points), “partial” (= 1 point) or “complete” (= 2 points). If some of the dimensions of the score are not applicable this particular dimension will not be included in the calculation. The sum of all points over all applicable dimensions for a model are divided by the total points a model could have reached to calculate the percentage as a quality indicator.

Bias Assessment

We will examine, using standard statistical methods, whether published models tend to report a positive effect of the examined intervention, so that we can uncover a potential publication bias.

Analyses

All reviewed studies will be reported in the final report, including their calculated percentage scale of the quality assessment value.

We will report how often each modelling approach has been used and how high the average percentage scale for each modelling approach was. We will report on the distribution of years in which the study has been conducted to understand potential trends in multi STI modelling.

To understand which STI interaction have been the most relevant, we will set up a graph to show which STIs have been modelled together most frequently.

Subgroup analysis

We will use the percentage scale of the quality assessment to differentiate between models with higher and lower quality. We will compare these subgroups individually to examine the differences between those.

We will examine whether articles obtained through grey literature searches differ from articles obtained through searches in published literature databases.

To examine trends in the usage and variations in quality of modelling approaches we will examine all

modelling approaches separately.

It might be possible to use the same methodology to model STIs in a low-income country and in a high income country or in a low prevalence vs high prevalence setting. Whereas the input of these models might and most certainly will differ, the technological approach in both settings could be the same. This is why we do not focus the search on a particular setting, but examine the different income subgroups separately later on.

Study records and data management

The result list from different search engines and databases will be downloaded. We will import these search results into a new and empty Endnote database. To guarantee the reproducibility of results a backup of this database will be saved.

Endnote [22] will be used to remove duplicates. An automated check for duplicate titles and year of publication will be applied. Each possible duplicate will be deleted manually to prevent deleting non-duplicates. Another backup after the duplicate elimination will be stored.

All articles will be imported into a Microsoft Access database [23]. After title and abstract screening and after full text screening copies of the database will be saved.

Electronical input forms to capture the information retrieved from the title and abstract screening, the full text screening, and data extraction will be developed. These forms will be used by all researcher (FS, AH, RH) involved in article screening and data extraction. The forms will be developed in Microsoft Excel and VBA programming. The information extracted with the help of these forms are also stored in Excel workbooks, one for each researcher. These workbooks will then be imported into the Microsoft Access database for further processing, quality assessment, bias assessment and analyses.

Patient and Public Involvement

This review did not and will not involve patients or any other member of the public. No patients or members of the public were involved in the development of the research question and outcome measures, the design of the study, and the conduct of the study.

Ethics and dissemination

No patient level data is included or used in this systematic review. Therefore ethical approval is not necessary as no privacy concerns can arise.

The aim of this review is to describe the quantity and quality of published multi STI models. A limitation of this is that we will not be able to conduct a meta-analysis of the findings. We will summarise all results, but we will not be able to produce aggregate figures such as funnel plots as it is likely that the models included in the review will report a range of outcomes with no single identifiable outcome to evaluate.

We will summarise the methodology which has been used to model STIs and assess the quality of existing multi STI models. We will not assess whether the most suitable approach to answer the research question of interest has been chosen by the authors of those disease models.

The modelling of STIs interacting with non-STIs, e.g. HIV and tuberculosis, although being clinically important [24], will not be examined in this review, as it will not answer our research question and is beyond the remit of the review.

We will publish the results in a peer-reviewed journal and present them at a suitable conference. The findings of this review will be used to inform the development of a multi STI disease model, incorporating the most important STIs in an UK setting.

Contributors

FS is the guarantor. FS developed and refined the study protocol with comments from JS, RH, and GR. FS will be responsible for the literature search. FS and AH will carry out the data extraction. FS will do the analysis, interpretation and report writing in cooperation with RH, JS, and GR. All authors read and approved the final manuscript.

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Amendments

This is the first version of the protocol. No amendments have been made to this version so far. If the protocol has to be amended, all amendments will be listed in a table in the final report on the results of the review.

Competing Interests

None declared

Provenance and peer review

Not commissioned. Externally peer reviewed.

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Appendix A

We will extract the following information from all eligible article. Each data item and a short explanation are given in a separate paragraph. We will also store information which identifies the study, which is: year of publication, authors, title, abstract, and publishing journal.

Modelling approach

We will extract the general approach the modellers used. This can be for example “Discrete Event Simulation” or “Markov Microsimulation”. This approach will be described in more detailed by the following items.

Entity level

This item will be used to describe whether an individual-based or a compartment-based approach is used, which means whether the model simulates each simulated patient individually or whether they are put into subgroups of the population, for example “infected” and “non-infected”.

Open cohort vs closed cohort

We will extract 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).

Interacting vs. non interacting population

We will extract information on whether the individuals in a model can interact in some form with each other or whether they are mostly independent from each other.

If they can interact with each other we will look whether a sexual contact network is used to describe this model and how this network is described.

Time handling

We will look at how time is simulated in a model. Does it proceed in slices of fixed length or does the model jump from one event to the next.

Data origin

We will look at the inputted cohort of the model. Is it based on a real life cohort or is generated hypothetical data used. If hypothetical data is used we will look at the origin for the authors’ assumptions.

Cohort Size

We will look 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.

Time horizon

We will extract data on the time horizon of the model which can be useful to understand the purpose of the model.

Modelling software

We will extract the data on the modelling software which was used to set up the model. This could be either specialised modelling software or more general tools like spreadsheet tools.

List of included STIs

We will list all STIs which were examined in this model.

Interaction

We will extract data on whether the simulated STIs are modelled in parallel or whether they interact in some form. If possible we will describe how the interaction affects the STIs.

List of sequelae of STIs

Additionally to the STIs, we will look at (long-term and short-term) sequelae which are included in the model.

Interventions

We will look at the intervention which were simulated by the model and whether the model recommends the implementation of this intervention.

Economic component

We will extract information on the economic component of the model, if there is any. We will extract the type (or types) of analysis this model is able to perform.

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 store the year in which the study actually has been conducted. If this year is not reported in the article we will assume that the study has been conducted in the year of the publication.

Input

We will collect all parameters which can be inputted by a user.

Country

We will extract information on the country (or countries) of the modelling study. The Region will be mapped to a high-, middle- or low-income region based on the World Bank definition of July 2017 [1], see also Table 1.

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

Table 1 Mapping of average gross national income per capita to income group by World Bank definition

Output

We will collect all output parameters which can be calculated by a model.

Customisability

Based on the possibility to generalise a model we will try to extract information on the generalisability. This means whether the model can be used by other researcher for other research questions.

References

1. World Bank, *World Bank list of economies*, World Bank, Editor. 2017: Washington, D.C., United States.

Appendix B

Basically, we used the same search strategy for all databases. But due to different thesauri and syntaxes the search strategy had to be amended to fit with the requirements of each database. Within this appendix the search strategies for all databases are listed.

Medline and Embase

This was the baseline search strategy. This strategy was used to derive the search strategies for all other databases.

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

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

Dart Europe

Dart Europe is, compared with Embase and Medline, a fairly 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

OpenGrey

Preiliminary 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 diseases”

PLOS and ProQuest

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, we decided to search for all terms in the title and abstract only.

ProQuest does not support thesaurus search or advanced syntax, which is why we had to simplify the search strategy as well. We decided to search anywhere but in the full text. We searched for scholary articles, dissertations, theses, working papers, reports, conference papers, and conference proceedings. We did not search for wire feeds, newspapers, trade journals, magazines, blogs, podcassts, and websites.

Due to the similar requirements we 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

Web of Science

Web of Science does not use a thesaurus. The database does not have a limited suffix search, which is why we replaced those with unlimited suffix searches. The adjacent operator is the same as of the Cochrane search tool. As Web of Science access also non medicinal journals, we decided to not use any abbreviations to decrease the possibility of picking up 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

Checklist PRISMA-P

For submission: Methods and Quality of disease models incorporating more than two sexually transmitted infections: A protocol for a systematic review of the evidence

Checklist filled by Fabian Sailer

Item No	Section and Topic	Checklist item	Addressed where
Administrative Information			
1a	Title: Identification	Identify the report as a protocol of a systematic review	Page 1, Line 3-12: Title
1b	Title: Update	If the protocol is for an update of a previous systematic review, identify as such	N/A in this submission
2	Registration	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 1, Line 53-54: Abstract: last paragraph; Page 3, Line 29-32: Introduction: registration
3a	Authors: Contact	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1, Line 14-23 & Page 8, Line 27-44: Authors & Author affiliations
3b	Authors: Contributions	Describe contributions of protocol authors and identify the guarantor of the review	Page 8, Line 46-50: Contributors
4	Amendments	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Page 9, Line 5-9: Amendments
5a	Support: Sources	Indicate sources of financial or other support for the review	Page 8, Line 52 - page 9, Line 4: Funding
5b	Support: Sponsor	Provide name for the review funder and/or sponsor	Page 8, Line 52 - page 9, Line 4: Funding
5c	Support: Role of sponsor or funder	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Page 8, Line 52 - page 9, Line 4: Funding
Introduction			
6	Rationale	Describe the rationale for the review in the context of what is already known	Page 3, Line 17-27: Introduction: Rationale and research aims
7	Objectives	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 3, Line 17-27: Introduction: Rationale and research aims
Methods			
8	Eligibility Criteria	Specify the study characteristics (such as PICO, study design, setting,	Page 3, Line 36 - Page 4, Line 56: Methods

		time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	and analysis: Eligibility Criteria
9	Information sources	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 1, Line 40: Abstract: Methods and analysis; Page 5, Line 43-53: Methods and analysis: Information Sources
10	Search strategy	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 6, Line 5-18: Methods and Analysis: Search strategy; Page 14-21: Appendix B
11a	Study Records: Data Management	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 7, Line 35-56: Methods and analysis: Study records and data management
11b	Study Records: Selection Process	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 6, Line 18-38: Methods and analysis: Selection Process
11c	Study Records: Data Collection Process	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 6, Line 34-36: Methods and analysis: Selection Process & Page 7, Line 48-56: Methods and analysis: study records and data management, last paragraph
12	Data Items	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 5, Line 3-42: Methods and analysis: Outcomes; Page 11-14: Appendix A
13	Outcomes and Prioritization	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 5, Line 9-30: Methods and analysis: Outcomes
14	Risk of bias in individual studies	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 6, Line 39-56: Methods and analysis: Quality Assessment & Page 7, Line 3-6: Methods and analysis: Bias assessment
15a	Data synthesis	Describe criteria under which study data will be quantitatively synthesised	N/A in this review
15b		If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I_2, Kendall's τ)	N/A in this review
15c		Describe any proposed additional analyses (such as sensitivity or subgroup	Page 7, Line 19-35: Methods and analysis:

		analyses, meta-regression)	Subgroup Analysis
15d		If quantitative synthesis is not appropriate, describe the type of summary planned	Page 6, Line 50-56: Methods and analysis: Quality Assessment, last paragraph
16	Meta-bias(es)	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 7, Line 3-7: Methods and analysis: Bias Assessment
17	Confidence in cumulative evidence	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 6, Line 39-56: Methods and analysis: Quality Assessment

We are confident that we addressed all of the above mentioned items of the PRISMA-P checklist in a sufficient manner.