Describing the Progression from *Chlamydia trachomatis* and *Neisseria gonorrhoeae* to Pelvic Inflammatory Disease: Systematic Review of Mathematical Modeling Studies

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Supplemental Digital Content 1

Protocol used for the systemic review of mathematical modeling studies

Protocol for the systematic review of mathematical modelling studies describing the progression from *Chlamydia trachomatis* and *Neisseria gonorrhoeae to* Pelvic inflammatory Disease

1. Background

Pelvic inflammatory disease (PID) is the most common direct complication of sexually transmitted *Chlamydia trachomatis* (chlamydia) and *Neisseria gonorrhoeae* (gonorrhoea) infections in women.[1] PID occurs when microorganisms ascend from the vagina and/or endocervix to the upper genital tract, including endometrium, fallopian tubes and contiguous structures.[2] Inflammation and scarring in the fallopian tubes is a strong risk factor for subsequent ectopic pregnancy and tubal infertility.[3] The link between 'latent gonorrhoea', pelvic inflammation and infertility was first suggested in the late 19th century[4] and gonorrhoea was the subject of the first mathematical modelling studies examining the impact of sexually transmitted infections on fertility.[5] Screening to detect and treat asymptomatic chlamydia, which is now the most common notifiable sexually transmitted infection in the U.S.,[2] is recommended to prevent PID.[6,7]

Screening programmes could work either by identifying and treating infections before they progress to PID and/or reducing transmission and hence exposure to the causative agent.[8] The timing of progression from infection to PID could influence the potential impact of a screening programme but there is no agreement on when sexually transmitted infections ascend to the upper genital tract.

Mathematical modelling can be used to investigate processes and mechanisms that are difficult to observe in practice.[9] Publications using models to investigate the potential impact of screening strategies on PID incidence should provide a source of information about assumptions about the timing of progression from infection to PID.

A systematic review will be beneficial to understand how other researchers have conceptualised progression from chlamydia or gonorrhoea to PID, especially the timing of progression. We are interested in what kinds of models have described both chlamydia or gonorrhoea infection dynamics and progression to PID. This will help us to improve our own modelling work and to gives us an overview which parameters have been used.

2. Objective

To conduct a systematic review to determine how the natural history of *C. trachomatis* or *N. gonorrhoeae* infection and progression to PID have been described in mathematical modelling studies

3. Methods

In this section we set out the research questions and the methods for preparing the systematic review.

3.1. Questions

Questions to be answered by the systematic review:

- How is the natural history of chlamydia and gonorrhoea described in reports of modelling studies?
- What are the estimates used about progression from chlamydia/gonorrhoea to PID and its consequences (rates or probabilities) and their range?
- How is the timing of progression from chlamydia/gonorrhoea to PID described?

- How are the consequences of PID, such as ectopic pregnancy and infertility, described?

3.2. Inclusion criteria

We will search for publications in which *C. trachomatis* or *N. gonorrhoeae* are modelled (compartments/individual based) and PID is included in the model or the progression probability is described in a decision tree.

3.2.1. Study types

We will consider the following study types for inclusion:

- Mathematical models
- Economic evaluations

3.2.2. Population

We will consider following populations:

- Women or men

3.2.3. Intervention

Not essential for inclusion, but if included we will extract information about following interventions in the model:

- Screening
- Partner notification
- Treatment of chlamydia

3.2.4. Outcomes reported

One or more of the following:

- Progression to PID
- PID is included directly in the model of the infection (as a compartment or a status in an individual based model) or has a decision tree attached to the model

3.3. Exclusion criteria

We will exclude publications if one or more of the following is applicable:

- Models with only men as a population that do not consider complications in women
- Animal models
- No progression to PID considered, e.g. cost of illness studies
- Studies reporting on PID as a complication of contraceptive methods such as intrauterine device (IUD)
- If progression to PID is described with probabilities in a decision tree but no graphical illustration of the decision tree is shown

3.4. Search strategy

3.4.1. Electronic databases

The following databases will be searched from the earliest date of the databank to 19. October 2009 without language restrictions:

- Ovid Medline
- Embase
- Popline

- The Cochrane Library

3.4.1.1. Search terms

There is no single Medical Subject Heading search term in Medline for mathematical modelling studies. Search strategies will use subject headings specific to each database and free text search that combine terms for

- Mathematical models
- Pelvic inflammatory disease

For details see appendix (Appendix 1: Search strategies).

3.4.2. Additional searches

The following additional searches will be done:

- Reference lists of included publications will be screened
- For included publications where a reference is given for the used model we will retrieve the original
- Experts in the field will be contacted for publications that might fit our inclusion criteria

3.5. Selection of eligible studies

Two suitably qualified reviewers will review the lists of articles identified by the search strategy independently using the inclusion and exclusion criteria listed in paragraphs 3.2. and 3.3. Any study selected as being potentially eligible by either reviewer, will be retained for review of the full text.

3.6. Potentially eligible studies

The reviewers will read the abstract of each identified article if fewer than 500 articles are returned in total. If the searches identify 500 or more articles, the reviewers will select potentially eligible titles first and will then read the abstracts of titles that potentially fit the inclusion criteria. If no abstract is available electronically, the full text of the article will be requested. The abstracts of articles identified through additional searches (paragraph Additional searches) will be reviewed in the same manner as for studies identified through database searches.

3.7. Retrieval of full-text articles

We will obtain the full text of articles or other documents reporting studies identified as being potentially eligible for inclusion. We will make every effort to locate documents through internet downloads, inter-library loans and contacting authors of reviews citing potentially eligible documents. We will request translation if necessary to confirm or refute eligibility.

3.8. Selection of studies for inclusion

The two independent reviewers will examine full text articles and compare their lists of studies eligible for inclusion. Studies identified by both reviewers as being eligible for inclusion and having adequate data for extraction will be included in the review. Where there are discrepancies, the reasons for these will be discussed and a decision about inclusion reached by consensus. If there is no agreement, a third independent reviewer will adjudicate to make a final decision about eligibility.

3.9. Data extraction forms

We will develop forms for extracting consistent data about:

- Description of the natural history of chlamydia and gonorrhoea in models
- Type of model for the infection and for PID
- Is symptomatic and asymptomatic PID considered
- Rate or probability of progression from infection to PID and the considered range (e.g. confidence interval, range used in sensitivity analysis)
- When during infection progression to PID happens and how is this implemented in the model
- Duration of PID status and considered range if applicable
- What are the references for parameters about PID: modelling paper or clinical data
- Which complications are considered and how are they implemented (chronic pelvic pain, ectopic pregnancy, infertility, neonatal pneumonia, neonatal conjunctivitis, epididymitis)
- Methodological and reporting quality (see paragraph 3.12.)

Data extraction forms will be designed to capture any information for the outcomes listed in paragraph 3.2.4. as well as any specific data for more restricted forms of outcome definitions which may be used in analysis.

We will pilot test the forms to ensure ease of use and capture of all relevant data. The forms will be developed using Epidata (Epidata version 3.1, EpiData Association, Odense, Denmark).

3.10. Data extraction

Two appropriately qualified people will extract and enter data independently from each included study into Epidata. Articles in languages other than English will either be translated first and then duplicate data extraction conducted as above or, if there are two reviewers who understand the language of publication, they will extract the data directly.

The two files will be compared using the validation function available in this program. Discrepancies in data extraction or data entry will be resolved by consensus. If there is no agreement a third independent reviewer will adjudicate to make a final decision.

Studies might be excluded at the data entry stage if it becomes apparent that inclusion criteria are not met or there is not enough information in the documents to extract the required data.

3.11. Data analysis

The data analysis will be descriptive including:

- A flow chart describing included and excluded publications
- A table with the characteristics of the included publications
- For the publications with a decision tree an overview of the used probabilities of progression
- For the publications with models other than decision trees an overview about the model characteristics, specially the parameters about PID
- A table with an overview about the conceptualised progression from chlamydia or gonorrhoea to PID

3.12. Assessment of quality of reporting

We will search for checklists of items associated with methodological and reporting quality that are specific to modelling papers – if not, define our own:

- Is a flow diagram of model shown?
- Are values for all parameters used in the model stated and referenced?
- Is the unit of each parameter clearly stated (e.g. rate or probability)?
- Is it stated in which languages/programme the model is implemented?
- Does each branch in a decision tree some up to 1 if probabilities are used?
- Has a sensitivity analysis be done?

4. Write report

Reports will be written following the appropriate guidelines (e.g. PRISMA Guidelines for reporting of meta-analyses and systematic reviews) and will clearly present the methods used as well as findings.

5. References

1. Paavonen J, Westrom L, Eschenbach D. Pelvic Inflammatory Disease, In: Holmes KK, Sparling PF, Stamm W et al., eds. Sexually transmitted diseases. 4th Edition. New York: McGraw-Hill Medical; 2008:1017–50
2. Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2009. Atlanta, GA; 2010
3. Westrom L, Joesoef R, Reynolds G et al. Pelvic inflammatory disease and fertility. A cohort study of 1, 844 women with laparoscopically verified disease and 657 control women with normal laparoscopic results. Sex Transm Dis 1992; 19:185–92
4. Oriel JD. The scars of Venus: A History of Venereology. London: Springer; 1994
5. Brunham RC, Garnett GP, Swinton J et al. Gonococcal infection and human fertility in sub-Saharan Africa. Proc. Biol. Sci 1991; 246:173–77
6. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2010. MMWR Recomm Rep 2010; 59:1–110
7. Department of Health. Chlamydia screening programme roll out. Core requirements. London; 2003. Available at: http://www.doh.gov.uk/sexualhealthandhiv/pdfs/corereq.pdf
8. Gottlieb SL, Martin DH, Xu F, Byrne GI, Brunham RC: Summary: The Natural History and Immunobiology of Chlamydia trachomatis Genital Infection and Implications for Chlamydia Control. J Infect Dis 2010, 201:190-204.
9. Garnett GP, Cousens S, Hallett TB et al. Mathematical models in the evaluation of health programmes. The Lancet 2011; 378:515–25

6. Appendix 1: Search strategies

6.1. Medline: Mathematical models of PID (19.10.2009)

#	Searches	Results
1.	exp Pelvic Inflammatory Disease/	8’742
2.	exp Models, Biological/	461’551
3.	exp Models,Theoretical/	905’200
4.	exp Computer,Simulation/	91’237
5.	model*.mp.	1’596’934
6.	exp Markov Chains/	5’971
7.	exp Decision Support Techniques/	43’326
8.	exp Decision Trees/	7’076
9.	exp Decision Making/	87’136
10.	Animals/	4’526’199
11.	(2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10) not 11	1’014’586
12.	1 and 12	**181**

Database: Ovid MEDLINE(R) 1950 to September 2009
Homepage: http://ovidsp.tx.ovid.com/

6.2. Embase: Mathematical models of PID (19.10.2009)

#	Searches	Results
1.	'pelvic inflammatory disease'/exp AND [embase]/lim	6’951
2.	'mathematical model'/exp AND [embase]/lim	94’310
3.	'computer model'/exp AND [embase]/lim	15’043
4.	'decision tree'/exp AND [embase]/lim	327
5.	'decision support system'/exp AND [embase]/lim	1’724
6.	'decision making'/exp AND [embase]/lim	45’020
7.	markov AND chain AND [embase]/lim	1’689
8.	'health economics'/exp AND model* AND [embase]/lim	24’037
9.	'animal model'/exp AND [embase]/lim	511’365
9.	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 NOT #9	171’906
10.	#1 AND #9	**65**

Database: Embase
Homepage: http://www.embase.com

6.3. Popline: Mathematical models of PID (19.10.2009)

KEYWORDS: =”Pelvic Inflammatory Disease”
ABSTRACT: model*
With AND
Results: **31**

Database: Popline
Homepage: http://db.jhuccp.org/ics-wpd/popweb/expert.html

6.4. The Cochrane Library: Mathematical models of PID (19.10.2009)

#	Searches	Results
1.	MeSH descriptor Pelvic Inflammatory Disease explode all trees	423
2.	MeSH descriptor Models, Theoretical explode all trees	13’481
3.	MeSH descriptor Models, Biological explode all trees	1’754
4.	MeSH descriptor Computer Simulation explode all trees	940
5.	MeSH descriptor Models, Economic explode all trees	2’126
6.	MeSH descriptor Decision Trees explode all trees	762
7.	MeSH descriptor Decision Support Techniques explode all trees	2’573
8.	MeSH descriptor Decision Making, Computer-Assisted explode all trees	2’354
9.	MeSH descriptor Markov Chains explode all trees	1’070
10.	pelvic inflammatory disease	485
11.	MeSH descriptor Animals explode all trees	5’425
12.	#1 OR #10	705
13.	((#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9) AND NOT #11)	18’771
14.	#12 AND #13	**49**

Database: Cochrane Library (all Cochrane products)
Homepage: http://www.mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html

6.5. Deduplication

Total number of hits from all databases: 326

Deduplication is done in Reference Manager 11 keeping the record with more information and added additional information from other records

First deduplication:

- Search criteria: start page; volume; date, primary
- Suspected items: 143
- Duplicates: 62
- Total included items: 264

Second deduplication:

- Search criteria: authors, primary*: check last name only; title,primary*: 80%
- Suspected items: 20
- Duplicates: 9
- Total included items: 255

Third deduplication:

- Search criteria: title,primary*: 50%
- Suspected items: 243
- Duplicates: 2
- Total included items: 253

After deduplication 253 publications from all databases (19.10.2009).