The natural history of *Chlamydia trachomatis* infection in women: a multi-parameter evidence synthesis

Malcolm J Price,[1] AE Ades,[2*] Kate Soldan,[3] Nicky J Welton,[2] John Macleod,[2] Ian Simms,[3] Daniela DeAngelis,[3,4] Katherine ME Turner[2] and Paddy J Horner[2,5]

[1]Institute of Applied Health Research, University of Birmingham, Birmingham, UK
[2]School of Social and Community Medicine, University of Bristol, Bristol, UK
[3]Public Health England (formerly Health Protection Agency), Colindale, London, UK
[4]Medical Research Council Biostatistics Unit, Cambridge, UK
[5]Bristol Sexual Health Centre, University Hospital Bristol NHS Foundation Trust, Bristol, UK

*Corresponding author

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Scientific summary

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Scientific summary

Background and objectives

The National Chlamydia Screening Programme (NCSP) was initiated in 2003 and was operational throughout England by 2008. It offers screening for *Chlamydia trachomatis* (CT) infection annually, and on partner change, to sexually active men and women under 25 years attending general practitioner (GP) surgeries and other services. In 2012, over 1.7 million chlamydia tests were carried out in England among young people aged 15–24 years old. Assuming one test per person, this approximates to 35% of young women and 16% of young men being tested for chlamydia. The objectives of the programme (see www.chlamydiascreening.nhs.uk/ps/overview.asp) are to:

- prevent and control CT through early detection and treatment of infection
- reduce onward transmission to sexual partners
- prevent the consequences of untreated infection, principally pelvic inflammatory disease (PID), which can result in ectopic pregnancy (EP) and tubal factor infertility (TFI).

The effectiveness and cost-effectiveness of the programme has yet to be clearly established.

Treatment of current CT infection is considered to be both safe and effective, and screening has been proposed because the majority of incident CT remains asymptomatic. However, the cost-effectiveness and clinical effectiveness of screening depends primarily on the precise extent of reproductive morbidity caused by untreated CT, chiefly PID, EP and TFI, and on the proportion that can be prevented by screening.

The work reported here was funded by the Medical Research Council. The premise for the project was that there was no consensus on the quantitative risks of PID, EP and TFI following a CT infection, or on how to derive estimates from the evidence available, or even on what kind of evidence should be used. The objective, therefore, was to comprehensively assemble all the available evidence on the incidence and prevalence of CT in the UK, and the evidence from the various prospective and retrospective study designs from which quantitative relationships between CT, PID, EP and TFI can be derived, as well as routine sources of evidence on PID, EP and TFI in the UK, in order to assess the consistency of the different types of evidence, and, if possible, to provide a coherent, unified account of the clinical and population epidemiology of CT in the UK and its reproductive consequences in women.

Methods

Evidence sources were identified using 'high-yield' strategies, based on citations in recent cost-effectiveness analyses, reviews and research papers, and on the advice of the multidisciplinary group of investigators. New formal systematic reviews were not undertaken. Where routine UK data were used, this was from 2002, prior to the introduction of the NCSP.

In the interests of transparency and simplicity, the problem was broken down into separate but interlinked subproblems. These were: duration of asymptomatic CT; incidence, prevalence and duration of CT considered together; the risk of PID following CT infection; the incidence of PID and the proportion of PID attributable to CT; the cumulative incidence of PID, of repeat episodes and the prevalence of previous salpingitis; the relation between salpingitis and EP; the relation between salpingitis and TFI; and the relation between CT and TFI from serological case–control studies. Under each of these headings, multiple sources of evidence were assembled and their interpretation was reviewed. Models were estimated from the assembled data following a Multi-parameter Evidence Synthesis (MPES) approach, using Bayesian Markov chain Monte Carlo.

Where appropriate, we combined the evidence from multiple sources to form a single coherent set of estimates for multiple parameters (such as incidence, prevalence and duration). Wherever possible, we assessed the consistency of estimates derived from alternative evidence sources. Where evidence sources were in conflict, we attempted to identify alternative sets of assumptions, or alternative interpretations of the data sources, under which the different sources of data could be regarded as making consistent predictions for the model parameters. In such cases, where models and interpretations were based on post-hoc reasoning, this was highlighted, and any conclusions were considered as tentative and requiring further confirmation.

Results

The key results from each of the analyses are as follows.

Duration of asymptomatic Chlamydia trachomatis *infection in women (see* Chapter 4*)*

Evidence on CT duration in women was extraordinarily heterogeneous. However, the heterogeneity can be explained if studies of incident and prevalent infection are distinguished, and if one assumes that 'passive' infections clear over approximately 1 week. A model including such passive and 'real' infections gave an adequate fit. The evidence was also compatible with a three-rate model which includes fast clearing real infection as a result of a protective immune response in addition to passive infection and slow clearing real infection.

Incidence, prevalence, and duration of Chlamydia trachomatis *in the UK (see* Chapter 5*)*

It was shown that available evidence on CT incidence in the UK (infection rates and re-infection rates), appropriately calibrated to apply to the general population, was consistent with evidence on duration and prevalence. Key findings were:

- Approximately 77% [95% credible interval (CrI) 68% to 84%] of incident CT in women is asymptomatic.
- An asymptomatic CT infection has an average duration of 1.31 years (95% CrI 1.06 to 1.56 years).
- A CT infection (symptomatic and asymptomatic) has an average duration of 1.03 years (95% CrI 0.82 to 1.25 years).
- CT prevalence in women ranges from 8.4% per year in 16- to 17-year-olds to 0.8% in 30- to 44-year-olds. It was 5.2% (95% CrI 3.8% to 6.9%) in 16- to 24-year-olds and 2.1% (95% CrI 1.6% to 2.7%) in 16- to 44-year-olds.
- CT incidence ranges from 8.2 per 100 person-years in 16- to 18-year-olds to 0.8 in 30- to 44-year-olds. It was 5.0 per 100 person-years (95 CrI 3.5 to 7.1) in 16- to 24-year-olds and 2.1 per 100 person-years (95% CrI 1.5 to 2.8) in 16- to 44-year-olds.

Risk of pelvic inflammatory disease following Chlamydia trachomatis *infection (see* Chapter 6*)*

A Markov model was constructed which allowed for CT clearance as a 'competing risk' alongside the development of PID. Estimates of the proportion of incident CT that progresses to PID were generated, based on synthesised data from three trials, as well as estimates of the proportion of CT-related PID that could be prevented by screening on an annual basis. We explored the possibility that rates of progression to PID could be higher in the 3 months following infection, but the data available could not distinguish between one- and two-rate models:

- 14.9% (95% CrI 4.8% to 24.8%) of incident CT infections progress to symptomatic PID
- 17.1% (95% CrI 5.6% to 28.9%) of incident CT infections progress to PID (symptomatic and asymptomatic)
- 7.3% (95% CrI 2.3% to 14%) of incident CT infections progress to salpingitis
- In women aged 16–24 years who undergo screening at annual intervals, at best, 61% (95% CrI 55% to 67%) of CT-related PID and 22% (95% CrI 7% to 43%) of all-cause PID can be directly prevented.

Incidence of pelvic inflammatory disease and proportion of pelvic inflammatory disease attributable to chlamydia (see Chapter 7*)*

We established that the all-cause PID incidence as observed in the Prevention of Pelvic Infection (POPI) trial, taking account of the proportion that is asymptomatic (13%), is consistent with routinely collected data on PID from hospital, GP and genitourinary medicine clinic returns, taking account of the overlap between these data sets and the proportion of PID that is undiagnosed (64%).

- A pooled estimate of PID incidence in 16- to 24-year-olds, including diagnosed and undiagnosed PID, is 2.5 per 100 person-years (95% CrI 1.8 to 3.4), and in 16- to 44-year-olds is 1.8 per 100 person-years (95% CrI 1.3 to 2.5).
- 62.9% (95% CrI 57.8% to 67.4%) of PID episodes are in women aged > 24 years.

Several estimates of the proportion of PID due to CT, the Population Excess Fraction (PEF) (see *Chapter 3*), were compared:

- the PEF is four to six times higher in 16- to 19-year-olds than in 35- to 44-year-olds
- the preferred estimate of the PEF was 35.3% (95% CrI 10.5% to 68.5%) in 16- to 24-year-olds, and 19.7% (95% CrI 5.9% to 38.1%) in 16- to 44-year-olds, based on estimates of CT incidence, CT-related PID incidence and the CT-to-PID progression risk
- this is consistent with estimates derived from case–control studies, adjusted for under-ascertainment of CT infection, and with estimates of relative risk reduction from the POPI trial although uncertainty is high.

Cumulative incidence of Chlamydia trachomatis*-related and non-*Chlamydia trachomatis*-related pelvic inflammatory disease and salpingitis (see* Chapter 8*)*

Based on a Markov model of PID and salpingitis incidence and repeat episodes:

- A total of 42.9% (95% CrI 25.5% to 61.2%) of incident PID would be confirmed as salpingitis on laparoscopy.
- In women aged 35–44 years, 33.6% (95% CrI 25.4% to 43.1%) have experienced at least one episode of PID (all causes, diagnosed and undiagnosed), and 16.1% (95% CrI 9.0% to 24.7%) have experienced at least one episode of salpingitis (all causes, diagnosed and undiagnosed).

Comparison of ectopic pregnancy rates predicted from the Lund study with UK data on ectopic pregnancy incidence (see Chapter 9*)*

Although conception rates peak between the ages of 20 and 30 years, the proportion of conceptions that are EPs rises sharply with age, indicating its sensitivity to cumulative exposure to risk factors. The proportion of EP that is due to salpingitis was derived from two French case–control studies.

- 1.13% of all pregnancies in the UK are EPs
- an estimated 27% (95% CrI 11% to 46%) of EPs are due to salpingitis
- an estimated 4.9% (95% CrI 1.2% to 12.1%) of EPs are due to CT.

We derived predictions for UK EP conception rates based on the salpingitis-to-EP risks observed in the Lund study, and a parallel set of predictions were made for TFI. It was concluded, however, that the salpingitis-to-EP risks observed in the Lund study were too high to be consistent with UK data on EP, possibly because of changes in interuterine device use.

Comparison of tubal factor infertility rates predicted from the Lund study with UK infertility surveys (see Chapter 10*)*

- Prevalence of primary and secondary TFI in women aged 44 years was 1.08% (95% CrI 0.79% to 1.54%), based on UK infertility surveys.
- This is consistent with the salpingitis-to-TFI risks observed in the Lund study, if it is assumed that the TFI risks associated with *all* salpingitis, whether diagnosed or not, is the same as, or slightly lower than, the salpingitis-to-TFI risk observed in the Lund study.
- An estimated 29% (95% CrI 9% to 56%) of TFI is attributable to CT.

Proportion of tubal factor infertility attributable to Chlamydia trachomatis*, based on serological case–control studies (see* Chapter 11*)*

We developed a method for estimating the proportion of TFI cases due to CT from serological studies, with adjustment for the sensitivity and specificity of the serological assays. This was applied to a case–control study from the Netherlands. It was estimated that 45% (95% CrI 28% to 62%) of TFI was attributable to CT in this study, but this is likely to be an overestimate. There is a large body of evidence clearly demonstrating that CT is a significant cause of TFI.

Conclusions

The study has generated a set of estimates on chlamydia epidemiology, from its incidence, prevalence and duration of infection, all the way through to its role in PID, EP and TFI. These estimates are not only consistent with an extensive body of literature, and with fertility surveys and routine statistics on PID and EP, but they are also internally coherent. To achieve this, the study has produced a coherent set of interpretations of the key study designs.

Public health significance

- Our findings confirm that CT is an important cause of PID and TFI.
- The findings support the view that screening of prevalent cases prevents PID, but suggest that a greater emphasis should be placed on detection and treatment of incident CT infection, as part of an integrated programme for sexually transmitted infection treatment and control.
- Current guidance on PID management, regarding a low threshold for presumptive treatment with broad-spectrum antibiotics, should not be changed.
- Women with lower abdominal pain require advice on when to seek early medical attention to avoid risk of reproductive damage.
- Every 1000 CT infections in women aged 16–44 years, on average, gives rise to approximately 171 episodes of PID and 73 of salpingitis, 2.0 EPs and 5.1 women with TFI at age 44 years.

Limitations

The study has a limited scope: it has not covered dynamic models of CT transmission, and therefore cannot by itself fully inform cost-effectiveness analyses of screening. Neither costs nor impact on quality of life have been addressed. Chronic pelvic pain, CT infection in pregnancy, and the role of CT in neonatal pneumonia and conjunctivitis have not been covered.

Within its scope, the main limitations relate to the large number of assumptions that have been made, although these are assumptions that have been commonly made in the previous literature, in particular:

- the proportion of PID that is undiagnosed is the same, regardless of age and whether or not the PID is CT related
- the proportion of PID that would be confirmed as salpingitis on laparoscopy is the same, whether or not it is CT related
- the proportion of PID that would be confirmed as salpingitis on laparoscopy is the same, whether or not it is diagnosed
- the reproductive damage caused by salpingitis is the same whether it is CT related or not.

Recommendations for further research

Further research is recommended as follows:

- A suite of serological studies, based on routine health service activity, should be undertaken to estimate the causal role of CT in PID, EP and TFI, and how this might vary with age.
- Such studies would also offer the opportunity to gain up-to-date information on: PID referral patterns, leading to better estimates of PID incidence; the proportion of PID causing reproductive damage that is diagnosed, and the proportion that is silent; whether or not the CT-related PID is more or less likely to be associated with reproductive damage, and is more or less likely to diagnosed. Microbiological studies of the aetiology of reproductive damage following salpingitis could also be undertaken.
- Further dynamic modelling, within a MPES framework, so that *all* sources of evidence can be incorporated and checked for consistency, with appropriate uncertainty propagation. Further research may be required to develop methods of Bayesian computation capable of incorporating sexual network dynamics in disease transmission models.

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