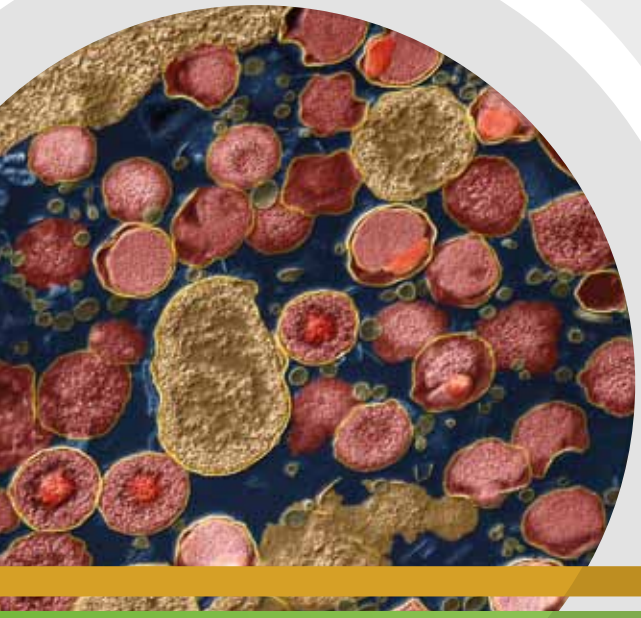

TECHNICAL REPORT

Chlamydia control in Europe: literature review

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ECDC TECHNICAL REPORT

Chlamydia control in Europe: literature review

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Abbreviations

CI	Confidence interval
DEGS	German Health Interview and Examination Survey for Adults
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EU	European Union
GP	General practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
MOA	Major outcome averted
NAAT	Nucleic acid amplification test
PHSSP	Philadelphia High Schools Screening Program, USA
PID	Pelvic inflammatory disease
PN	Partner notification
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SIRS	Susceptible-Infected-Recovered-Susceptible
SIS	Susceptible-Infected-Susceptible
STI	Sexually transmitted infection
UK	United Kingdom
USA	United States of America

Glossary

Cross-sectional survey	A survey done in a defined population at a specific point or period in time.
Effectiveness	The degree to which a healthcare intervention can be shown to accomplish what it set out to achieve in practice. Evidence of effectiveness of screening programmes should come from high quality randomised trials (www.nsc.org.uk).
Efficacy	Efficacy is defined as the extent to which a specific intervention, procedure, regimen or service produces a beneficial result under ideal conditions.
High income country	World Bank classification, 2012; gross national income >US$12,475 per capita. Includes all EU/EEA Member States except Bulgaria ($6,530), Latvia ($12,350), Lithuania ($12,280), Romania ($7,910) (http://data.worldbank.org/income-level/OEC).
Military recruits	Military recruits could be defined as the general population in member states where there is conscription for military service and the study was performed at stages of conscription when there are no exclusions from participation.
Narrative review	A descriptive review of a body of evidence that uses expert opinion and non-systematic search methods to select literature for inclusion.
Population-based survey	A cross-sectional survey in which the source population is intended to be representative of all of the general population of a country, or a defined part of the population, such as those in certain sex or age groups.
Positivity rate	Chlamydia positivity rate is the total number of individuals with a positive chlamydia test divided by the number of chlamydia tests. In some studies, the denominator might include multiple tests from the same individual.
Prevalence	Chlamydia prevalence is defined as the total number of all individuals who have a disease at a particular time divided by the population at risk of having the disease. In this report, the disease is infection with *C. trachomatis* and the population at risk is the sexually experienced general population of each study country. Findings are reported for the whole study population and, if available, those sexually experienced.
School students	School students aged 15 and over were defined as general population if participants were sampled from all schools in a defined area or region without exclusion criteria.
Sequelae	Pathological conditions resulting from a previous disease. Reproductive tract sequelae of chlamydia include pelvic inflammatory disease, ectopic pregnancy, tubal infertility and chronic pelvic pain in women and epididymo-orchitis in men.
Source population	The population from whom eligible subjects for the study are drawn. The source population is comprised of persons eligible for the study, persons assessed and found not to be eligible, those who were assessed but could not be classified and those who could not be assessed.
Systematic review	A review of evidence that applies strategies that limit bias in the assembly, critical appraisal, and synthesis of all relevant studies on a specific topic.
Target population	The population to whom the researchers wish to generalise the results of the study.

Executive summary

The literature reviews in this report bring together published evidence about the prevalence and reproductive tract complications of chlamydia infection, and about the effectiveness and cost-effectiveness of chlamydia screening interventions.

Population prevalence of chlamydia in EU/EEA Member States

- Ten EU/EEA Member States have conducted population-based cross-sectional surveys to measure the prevalence of chlamydia infection in a nationally representative sample of the population or in a sub-national sample of the population. Fourteen EU/EEA Member States have conducted cross-sectional surveys using non-population-based sampling methods. Three EU/EEA Member States have no studies estimating chlamydia positivity or prevalence.
- Estimates of chlamydia prevalence in population-based studies varied by country, sex, age group, national or sub-national coverage and inclusion of all or only sexually experienced participants.
- Four EU/EEA Member States (France, Germany, Slovenia, UK) have reported findings from nationally representative surveys of sexually experienced adults ≤25 years, with response rates from 46 to 71%. Chlamydia point prevalence estimates in women aged 15–24 years ranged from 3.0% (18–24 year olds in UK) to 4.7% (18–24 year olds in Slovenia). Point prevalence estimates in men aged 15–24 years ranged from 0.4% (16–17 year olds in Germany) to 4.7% (18–24 year olds in Slovenia). Estimates of chlamydia prevalence in EU/EEA Member States were statistically consistent with those in other high income countries.
- Selection bias in chlamydia prevalence surveys is likely, with over-estimation of prevalence being more likely than under-estimation. Cross-sectional surveys with lower response rates are associated with higher estimates of chlamydia prevalence. Estimates of chlamydia positivity in surveys with low response rates should not be interpreted as estimates of population prevalence. Only two population-based surveys in EU/EEA Member States in this review had a response rate of >70%. The highest response rates were seen when specimens for chlamydia testing were taken as part of general health surveys.
- Reporting standards for prevalence surveys in epidemiological research might help to improve consistency in future.

Reproductive tract complications of chlamydia infection

- The probability of pelvic inflammatory disease from any cause in asymptomatic women in the community with untreated chlamydia infection was estimated to be 9% (95% CI 4, 19%) after 12 months of follow up in one prospective study. This is lower than estimates from studies conducted in clinic settings.
- There is a strong association in prospective studies between chlamydia infection and pelvic inflammatory disease from any cause in women with both symptomatic and asymptomatic infection.
- The incidence of pelvic inflammatory disease cases from all causes has fallen in many high income countries over time, from as early as 1975. The contribution of chlamydia control activities cannot be disentangled from other factors including antibiotic use, health promotion activities and other changes in sexual health status. The incidence of primary and secondary infertility in high income countries has remained stable since 1990.
- Chronic pelvic pain lasting >6 months has been reported in 18% to 75% of women with pelvic inflammatory disease compared with 5% to 25% of unaffected women. In one prospective study with up to seven years follow up after treatment for PID, 42% (95% CI 38, 45%) women reported chronic pelvic pain.
- Most women with chlamydial pelvic inflammatory disease have mild or moderate clinical disease. When estimating the probability of tubal factor infertility following chlamydial pelvic inflammatory disease, an average estimate should be weighted towards the probability following mild pelvic inflammatory disease. A low overall probability of tubal factor infertility might explain in part the lack of association observed in the few studies that have examined long term reproductive tract outcomes in women with chlamydia or pelvic inflammatory disease.

Efficacy and effectiveness of chlamydia screening interventions

- The pooled risk ratio for all cause pelvic inflammatory disease after one year of follow up, in women invited to have a chlamydia screening test in four randomised controlled trials was 0.64 (95% CI 0.45, 0.90, I^2=20%). This is moderate quality evidence of the efficacy of chlamydia screening using the Grading of Recommendations Assessment, Development and Evaluation tool.
- The results from randomised controlled trials suggest that there is a window of opportunity in which treatment for screen-detected chlamydia can interrupt tubal pathology. These findings are consistent with the hypothesis, derived mainly from studies in animal models, that *C. trachomatis* provokes persisting cellular immune responses that can cause tubal damage throughout the course of infection. Knowledge about the timing of chlamydial disease progression and pathogenesis remains limited, however.
- It is unclear whether the size of the effect on pelvic inflammatory disease incidence that is observed in randomised controlled trials is all attributable to specific effects on chlamydia. If 30% of pelvic inflammatory disease episodes are caused by *C. trachomatis*, the pooled risk ratio from the review in this report suggests that the intervention prevented all chlamydia-associated pelvic inflammatory disease. This is unlikely because screening and treatment would have been too late to prevent ascending infection in many cases. It is possible that the antibiotics used to treat chlamydia also treated some other pelvic inflammatory disease - causing bacteria, or had non-specific anti-inflammatory effects.
- Two non-randomised cluster controlled trials have examined the effectiveness of chlamydia screening on chlamydia positivity over time in pragmatic settings. In the Netherlands, three yearly screening invitations with uptake of 16% at the first round did not result in lower chlamydia positivity (4.1%) compared with control clusters at the first screening round (4.3%, risk ratio 0.96, 95% CI 0.84, 1.09). In an earlier study in three US high schools, overall chlamydia positivity (6.7%) after five screening rounds with uptake >50% was lower than in five control schools tested for the first time (9.3%, risk ratio 0.72, 95% CI 0.56, 0.92).
- Repeated chlamydia infection in screen-detected and treated individuals can limit the long-term impact of chlamydia screening on levels of circulating infection. The effectiveness of partner notification remains sub-optimal and untreated, or inadequately treated partners can re-introduce infection into an ongoing sexual partnership, or can leave other partners in a sexual network untreated. The long-term impact of repeated chlamydia infections remains unknown but higher levels of chlamydia screening uptake will result in higher levels of repeated infections from any cause.

Cost-effectiveness of chlamydia screening

- Cost-effectiveness studies of chlamydia screening rely on accurate estimates of the incidence of chlamydia-associated pelvic inflammatory disease and its sequelae, and of assessments about their impact on quality of life because chlamydia and its complications are rarely fatal.
- Ten studies in high income countries have reported on the cost-effectiveness of chlamydia screening interventions with the outcome expressed as incremental cost effectiveness ratios of the cost per quality-adjusted life year gained in comparison with an alternative strategy.
- Although most studies concluded that at least one strategy for chlamydia screening was cost-effective at nationally accepted thresholds, these conclusions were often based on assumptions about the probability and valuation of utilities for complications of chlamydia that favour screening.
- High estimates of the probability of complications result from extrapolation from clinical studies to asymptomatic women in the community, or by applying probabilities of the consequences of pelvic inflammatory disease to all women with chlamydia. High estimates of impact on quality of life result from the application of poorly estimated utilities for a prolonged period of time.
- The number of cost-effectiveness studies using dynamic models to represent chlamydia transmission has increased in the last decade. The advantage of these models is that the impact of screening on chlamydia prevalence can be taken into account. The disadvantages are that most compartmental models cannot take into account the effects of unsuccessful partner notification and re-infection within sexual partnerships and that published model descriptions do not give enough information to understand the reasons for discrepancies between studies.

Implications for future research and practice

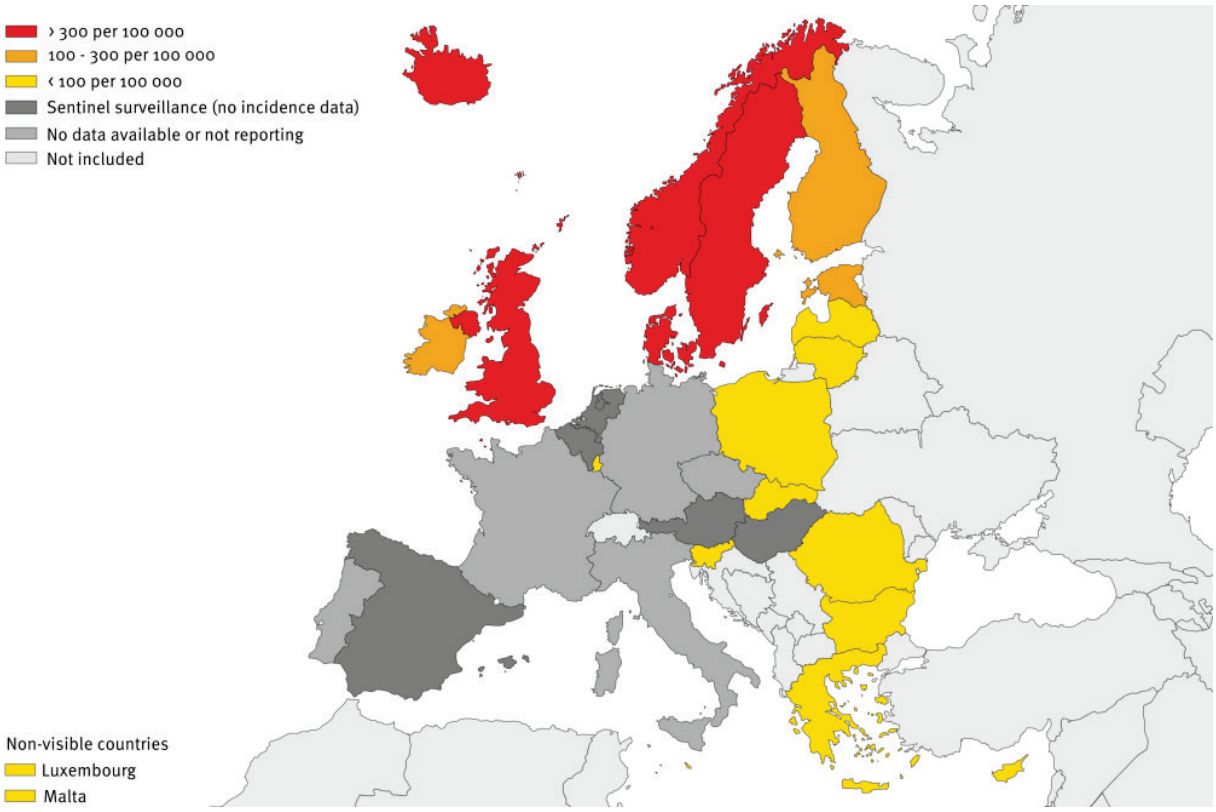
- The literature reviews in this report provide information that allows the role of chlamydia control activities and screening as a public health intervention with both benefits and harms to be assessed. The potential benefits of preventing chlamydia transmission and its complications need to be accurately determined and need to be balanced against the potential harmful effects on relationships, repeated infections and increasing antibiotic use.
- The ascertainment of chlamydia infection prevalence in a wide range of EU/EEA Member States would be valuable, particularly in Southern and Eastern Europe. Measuring chlamydia prevalence as part of a more general health survey is a potential strategy for achieving a high response rate.
- There is a need for improved methods of diagnosis of pelvic inflammatory disease and for markers of chlamydial infection that predict women at high risk of tubal damage. Statistical modelling methods to synthesise evidence from different sources of existing studies of chlamydia infection, progression and complications would help to overcome some of the ethical problems of clinical epidemiological studies.
- There is still a need for well-designed and well-conducted randomised controlled trials of the longer term effects of chlamydia screening on objective biological outcomes, including repeated infection and tubal damage. Mathematical modelling studies could also help to determine the relative contributions to the reduction in chlamydia transmission from shorter duration by picking up infection earlier and from reducing incidence.
- Epidemiological and economic research studies would improve the assessment of the impact on quality of life of symptomatic chlamydia infection and its complications. This would help to provide more accurate data for cost-effectiveness studies.

1. Introduction

Chlamydia trachomatis is the most commonly reported sexually transmitted infection (STI) in Europe [1]. In the EU/EEA and the USA, chlamydia is also the most common of all notifiable infections, and the rate of reported diagnoses continues to increase [2]. *C. trachomatis* is an infection of the lower genital tract in women and men, which is known to cause a number of complications resulting from spread to the upper genital tract, transmission of infection during labour, or as a result of immunological mechanisms [3]. In addition, *C. trachomatis* is a co-factor for HIV infection, increasing both susceptibility and infectiousness [4]. Despite a large body of research into basic science, clinical epidemiology, social science and prevention and control, there remain many uncertainties about how best to control chlamydia transmission and prevent complications. There are many challenges to studying the epidemiology and natural history of chlamydia. In part, these relate to the pathogen and its clinical manifestations; *C. trachomatis* is intracellular and fastidious, re-infection after treatment is common, infections and their complications are in inaccessible physical locations and there are long delays until some reproductive tract complications in women become apparent [3]. Furthermore, the stigma attached to STI and the behaviour that transmit them, compound these by making it difficult for people to speak about chlamydia, risky sexual behaviour and sometimes access to treatment and care.

Information about *C. trachomatis* infection and its sequelae in Europe is a prerequisite for assessing the needs of European Union (EU) Member States for prevention and control measures. Since 2009, the European Centre for Disease Prevention and Control (ECDC) has coordinated the surveillance of STI in Europe [1], and surveillance reports are published every year. The rate of diagnosed chlamydia cases reported to ECDC from EU Member States in 2011 was 175 per 100 000 population (346 911 cases) [1]. There is substantial variation across the EU/EEA in reported chlamydia cases, with rates ranging from below 1 to more than 500 reported cases per 100 000 population. Rates above the EU/EEA average were reported by Denmark (479 per 100 000), Finland (254 per 100 000), Iceland (657 per 100 000), Norway (458 per 100 000), Sweden (396 per 100 000) and the UK (341 per 100 000). The UK continues to contribute a large proportion of reported cases, with 62% of all cases reported in 2011. Rates below 10 per 100 000 were reported by seven countries (Bulgaria, Cyprus, Greece, Luxembourg, Poland, Romania and Slovakia) (Figure 1). Comparison between countries is challenged by differences in the surveillance systems, the diagnostic methods used, the amount of testing and screening for chlamydia, and the proportion of underreporting. The availability of a screening programme in dedicated STI services or targeted at (sub)groups of the population may significantly affect the reported number of *C. trachomatis* infections. The true incidence and prevalence of chlamydia are likely to be higher than suggested by rates of reported infection. Additional information from cross-sectional surveys is therefore needed to obtain a more complete picture of the distribution of chlamydia in Europe.

Figure 1. Number of reported chlamydia cases per 100 000 population, EU/EEA, 2011



Source: European Centre for Disease Prevention and Control. Sexually transmitted infections in Europe 2011. [1].

Cross-sectional surveys of a representative sample of the general population (population-based surveys) should provide the least biased estimate of the level of a condition in a country at a particular time [5]. The epidemiology of chlamydia infection according to demographic characteristics such as sex, age and ethnic group can then be compared between countries. Population-based surveys of chlamydia prevalence however are logistically complex. The availability of nucleic acid amplification tests, which can be used to diagnose *C. trachomatis* in urine specimens and vulval or vaginal swabs has made it more feasible to carry out cross-sectional surveys in the last decade. Cross-sectional studies in sample populations attending healthcare settings are conducted more often. Such studies measure the percentage of samples tested with a positive chlamydia test result in the target population. These surveys can be used to provide preliminary data about the epidemiology of chlamydia in such countries. Studies in healthcare settings can also give insights about small or hard to reach populations that might not be well-represented in population-based surveys. It is not clear, however, how valid it is to extrapolate such estimates to the general population because of differences in clinical, demographic and behavioural factors.

The need for better information about the complications of chlamydia infection to plan control strategies is well-recognised, as *C. trachomatis* infections that ascend to cause pelvic inflammatory disease (PID) can go on to cause infertility, ectopic pregnancy and chronic pelvic pain [3], which have severe economic [6] and psychological consequences [7,8].

Control of *C. trachomatis* transmission is a public health responsibility of national communicable disease control programmes. In 2009, ECDC published a guidance document with a framework for developing, implementing or improving national strategies to prevent and control chlamydia for Member States [9], based on a survey conducted in 29 European countries in 2007 [10,11]. The ECDC Guidance document sets out a step-by-step approach that emphasises the importance of primary prevention activities (Level A) and clinical case management of diagnosed cases (Level B), including partner notification [9]. Organised screening programmes are described in Level D, but limited evidence of effectiveness is noted [9]. The effectiveness and cost-effectiveness of chlamydia screening programmes remain controversial [12]. Widespread screening of asymptomatic sexually active women, or women and men, up to the age of 25 years is however widely recommended [13–16]. The rationale for screening is that detection of asymptomatic infections will allow early treatment and prevention of complications. Annual testing of those in target age groups, as well as older adults with risk factors such as multiple partners or a new sex partner, is often recommended [13]. Regular testing should help to identify repeated chlamydia infections in those tested and treated and infections acquired from new partners. Widespread chlamydia screening on a regular basis requires the infrastructure, monitoring and evaluation that are typical of other organised screening programmes [12].

This report critically reviews the scientific evidence for the epidemiology and natural history of chlamydia infection, in order to better evaluate and estimate the impact and cost-effectiveness of public health interventions targeted at chlamydia. This technical report includes results from reviews of chlamydia epidemiology in Europe, of the reproductive tract complications of chlamydia in women, and on the effectiveness and cost-effectiveness of chlamydia control interventions. In the next chapter the general review methods and objectives for each individual review are described. Section 3 describes the population prevalence of chlamydia in Europe and the association between chlamydia infection and pelvic inflammatory disease (PID), ectopic pregnancy, tubal infertility and chronic pelvic pain. Section 4 presents the evidence for the effectiveness and cost-effectiveness of chlamydia control interventions. Section 5 discusses and synthesises the findings of Sections 3 and 4 and end with a discussion about the implications of the report's findings for practice and research.

2. Methods

The evidence was reviewed using both systematic reviews and narrative reviews. Features of the systematic reviews that are common to all are reported first. Methods specific to each individual review are then reported. Details of the search strategies and flow charts of included and excluded studies for each review are presented in the Appendices.

Systematic reviews followed protocols that were written in advance. The protocols describe the review questions, criteria for considering studies for the review, search methods for identifying relevant studies, and methods for data collection. Details of search strategies are in the Appendices.

References were retrieved, de-duplicated and then catalogued in a bibliographic database (Endnote); one per review. Two suitably qualified reviewers screened the titles and abstracts of all articles identified by the search strategy. The full text of potentially eligible studies was retrieved and studies fulfilling the inclusion criteria were included for data extraction. Studies were translated where necessary. Flow charts showing the numbers of included and excluded studies are in the Appendices.

Two independent reviewers extracted data in duplicate onto pre-defined piloted forms in EpiData (EpiData Association, Odense, Denmark), or into spreadsheets (Microsoft Excel) with pre-defined fields. If there was more than one publication per study, data were first extracted from the primary publication. Associated publications were used if the data item was not reported in the primary publication. In case of conflicts information, the report in the primary publication was used. The two reviewers compared the extracted data and resolved discrepancies by discussion. If there was still a discrepancy, a third reviewer adjudicated. The final consensus datasets were imported into Stata statistical software (StataCorp, Austin, TX). Tables summarising the characteristics of included studies for each review are in the Appendices.

Two independent reviewers assessed the risk of bias related to methodological aspects of included studies using the Cochrane Collaboration tool for randomised controlled trials (RCT)[17], and published guidelines for cross-sectional prevalence studies [18]. Discrepancies were resolved by discussion.

Where appropriate, we pooled data using random effects meta-analysis to estimate the average effect across studies. Estimates from comparable studies were first examined in forest plots. Evidence of between study heterogeneity was described using the I^2 statistic, which gives the percentage of the variability of results between studies due to factors other than random variation [19]. As a guide, I^2 values above 25%, 50% and 75% have been suggested as evidence of mild, moderate and severe between study heterogeneity.

Where there was evidence of moderate or severe heterogeneity, we explored reasons for this by stratifying studies by age group, sex and geographic coverage (national vs. sub-national). We estimated prediction intervals, in addition to confidence intervals. The prediction intervals suggests the range of possible values across all studies [20].

Systematic review of the prevalence of chlamydia infection

Objectives

- To collate published literature about the population prevalence of *C. trachomatis* infection in the general populations of EU/EEA Member States;
- To examine the association between study design features and estimated chlamydia prevalence in population-based studies;
- To document studies of chlamydia infection in non-population based settings in EU/EEA Member States.

Population

Eligible studies included women or men aged 13 years and over from whom specimens from the urogenital tract were analysed for evidence of *C. trachomatis* infection. Eligible populations were EU/EEA Member State populations.

For the investigation of the association between study design features and estimated chlamydia prevalence, we also included studies in representative samples of the general adult population (>13 years) of non-EEA countries in high income countries. This allowed the inclusion of a larger number of similar studies in countries sharing geographical or economic characteristics with EU/EEA member states.

Inclusion criteria

Eligible study designs were: cross-sectional population-based studies; baseline surveys in randomised controlled trials or cohort studies; and systematic reviews containing original data from population-based surveys.

All population-based studies from EU/EEA Member States were eligible for inclusion. For EU/EEA Member States where no population-based study was identified, we recorded details of non-population based studies and extracted information about the country, year of publication, setting and population studied.

Exclusion criteria

Studies with any of the following characteristics were excluded: studies in countries other than those mentioned above; serological studies and studies sampling only from extra-genital sites; narrative reviews that did not contain original data; age below 13 years; studies from USA, Canada, Australia or New Zealand that were not done in a representative sample of the general population; data published in letters, commentaries and editorials.

Study selection

Studies were triaged to document available data from EU/EEA Member States first. Data from population-based studies were then extracted and gaps in evidence about general population chlamydia epidemiology documented. Studies from countries with no population-based survey were read in detail. A hierarchy of study methods based on study population, setting, and method of enrolment was developed, based on criteria for evaluating cross-sectional prevalence studies [18]. For each Member State, the study judged to be the least biased was selected and the estimate of chlamydia positivity was used to provide an estimate of chlamydia prevalence.

Data extraction

The following information was collected from population-based studies: study design, country, study population and setting, demographic characteristics, numbers eligible, invited and participating, numbers excluded with reasons, numbers infected with *C. trachomatis*, authors' estimated prevalence and 95% confidence intervals (CI), comparison between responders and non-responders, methodological and reporting quality. For Member States with no population-based survey, the country, study population and study setting only were recorded.

Risk of bias assessment

The items assessed included [18]: if the target population was representative of the study country and clearly defined, if the source population was representative of the target population, similarity of responders and non-responders, if a sample size calculation had been described and was reached, if standardised data collection methods were used, if chlamydia infection was detected using a nucleic acid amplification test (NAAT), if appropriate statistical methods were used (e.g. weighting) to account for the sampling design. Criteria were developed to determine whether each feature had been adequately addressed, not adequately addressed, or if there was insufficient information to decide. An adequate response rate was defined by Boyle as >80% [18]. There were no studies in this review with such a high response rate so we reported those with a response rate of >60% and >70%.

Statistical analysis

Chlamydia prevalence was estimated from data for different sex, age and, where available, ethnic groups. Where there were enough studies, results were stratified according to whether the study population was sampled from the whole national population or from a sub-national region or regions. Where complex sampling methods were reported we used the 95% CI presented in published papers. Where simple random sampling was done and data were available, we calculated chlamydia prevalence (with 95% CI) for available sex, age and ethnic groups. We tried to calculate a consistently defined response rate for all studies. Where available, the numerator was the number of people providing a sample for chlamydia testing and the denominator was the number of eligible subjects asked to participate, provide a sample, or sent an invitation for testing. This followed the definitions of the Council of American Survey Research Organizations (CASRO) and excluded people who were not reachable, had moved away, or were ill. If these numbers were not available we used the number of samples tested, followed by the number of test results used in the analysis as the numerator, and the number of eligible people as the denominator. The calculated response rate did not always correspond to the response rates given by the study authors. If no numbers were available we used the response rate as given by the study authors. Meta-regression was used to examine the relationship between the estimate of chlamydia prevalence and the response rate. Meta-regression results were expressed in 'bubble plots' in which each study is represented by a circle whose size corresponds to the precision of the estimate. Larger circles are from larger studies with greater precision. The regression line predicted from the data is shown and the I^2 value shows the amount of heterogeneity between study results after taking into account the association between prevalence and response rate.

Narrative review of the female reproductive tract complications of chlamydia

Objectives

The objectives of this review were to summarise evidence about the association between chlamydia and PID, ectopic pregnancy, tubal infertility and chronic pelvic pain and to determine whether the strength of association has changed over time.

Search strategy and study selection

Published narrative and systematic reviews about the female reproductive tract complications of chlamydia were used to identify relevant studies. Studies were selected for data extraction if they were prospective studies that assessed chlamydia status at baseline, and examined the risk of complications in untreated chlamydia positive and in chlamydia negative women. Studies with other designs were included if they were deemed to be useful. Systematic records of retrieved studies and reasons for inclusion or exclusion were not kept.

Data synthesis

Studies that reported on the incidence of PID, ectopic pregnancy, tubal infertility or chronic pelvic pain were summarised. Where possible the relative risk of specific complications in women with and without chlamydia was calculated (with 95% CI). The results were described narratively, in chronological order.

Systematic review of the effects of chlamydia screening interventions

Objectives

To determine the effect of chlamydia screening on the incidence of PID and other reproductive tract complications of chlamydia in women, the effect of screening on chlamydia incidence and prevalence, and the adverse effects of chlamydia screening for participants.

Inclusion criteria

Eligible study designs were: randomised controlled trials, quasi-randomised controlled trials, and non-randomised controlled trials with a parallel control group.

Exclusion criteria

Non-randomised comparative studies without a concurrent control group and data published in letters, commentaries and editorials were excluded.

Population

Sexually active women or men under 30 years in any country and setting.

Intervention

Any activity described as screening, or in which testing for chlamydia was offered to asymptomatic sexually active adults. We considered studies reporting entire screening programmes (for example, including treatment and partner notification), and studies that only described the results of offering screening tests, providing the primary outcome was also reported.

Comparison groups

We considered studies that reported comparisons of any screening intervention with no intervention or with another intervention.

Outcome

Primary outcomes

There were two primary outcomes, which were considered to be equally important: 1) complications of chlamydia, measured as incidence of PID; 2) transmission of chlamydia, measured as chlamydia incidence, prevalence or positivity.

Secondary outcomes

There were six secondary outcomes: adverse effects of screening on the participant (psychological distress, partner violence, relationship breakdown); ectopic pregnancy, female infertility; adverse pregnancy outcomes; neonatal morbidity or mortality; and male reproductive tract morbidity.

Data extraction

The following items were extracted: citation, source of funding, study design and measures taken to reduce the risk of bias, population, intervention, comparison groups, outcomes.

Risk of bias assessment

The Cochrane Collaboration tool for assessing the risk of bias in randomised controlled trials was used [17]. The tool assesses the risk of selection, detection, performance and attrition biases based on the authors' description of the trial methods. The assessors judged whether the methods described were adequate or inadequate to minimise bias, or unclear if there was insufficient information.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool [21] was used to assess the quality of evidence for all trials measuring each primary outcome using GradePro software [22]. In the GRADE process, the quality of evidence addressing a question about a healthcare decision is distinguished from the risk of bias assessment, which is applied to an individual trial to assess the quality of study design and methods. In the GRADE process, evidence from RCTs begins as high quality evidence, but can be downgraded. Evidence from observational studies begins as low quality evidence, but can be upgraded [21]. The GRADEPro software assigns a category of high, moderate, low or very low quality evidence depending on assessments about items such as study characteristics, consistency of results, directness of evidence, precision and dose-response effects.

Statistical analysis

The risk ratio was used as the measure of effect and calculated from raw data where appropriate. Effect estimates derived from trials that had been analysed to take clustering into account were not analysed further.

Systematic review of the cost-effectiveness of chlamydia screening programmes

Objectives

To describe the findings of cost-effectiveness studies of chlamydia screening interventions in women and men under 30 years.

Inclusion criteria

This was a systematic review to update the findings of an earlier review [23,24]. Studies were included if they measured incremental cost-effectiveness ratios and expressed the results in terms of cost per quality-adjusted life years.

Data extraction

The following items were extracted: citation, source of funding, study design, model parameters, outcomes.

Data synthesis

Study findings were described narratively. No statistical analyses were done.

3. Epidemiology of chlamydia infection and long term sequelae in Europe

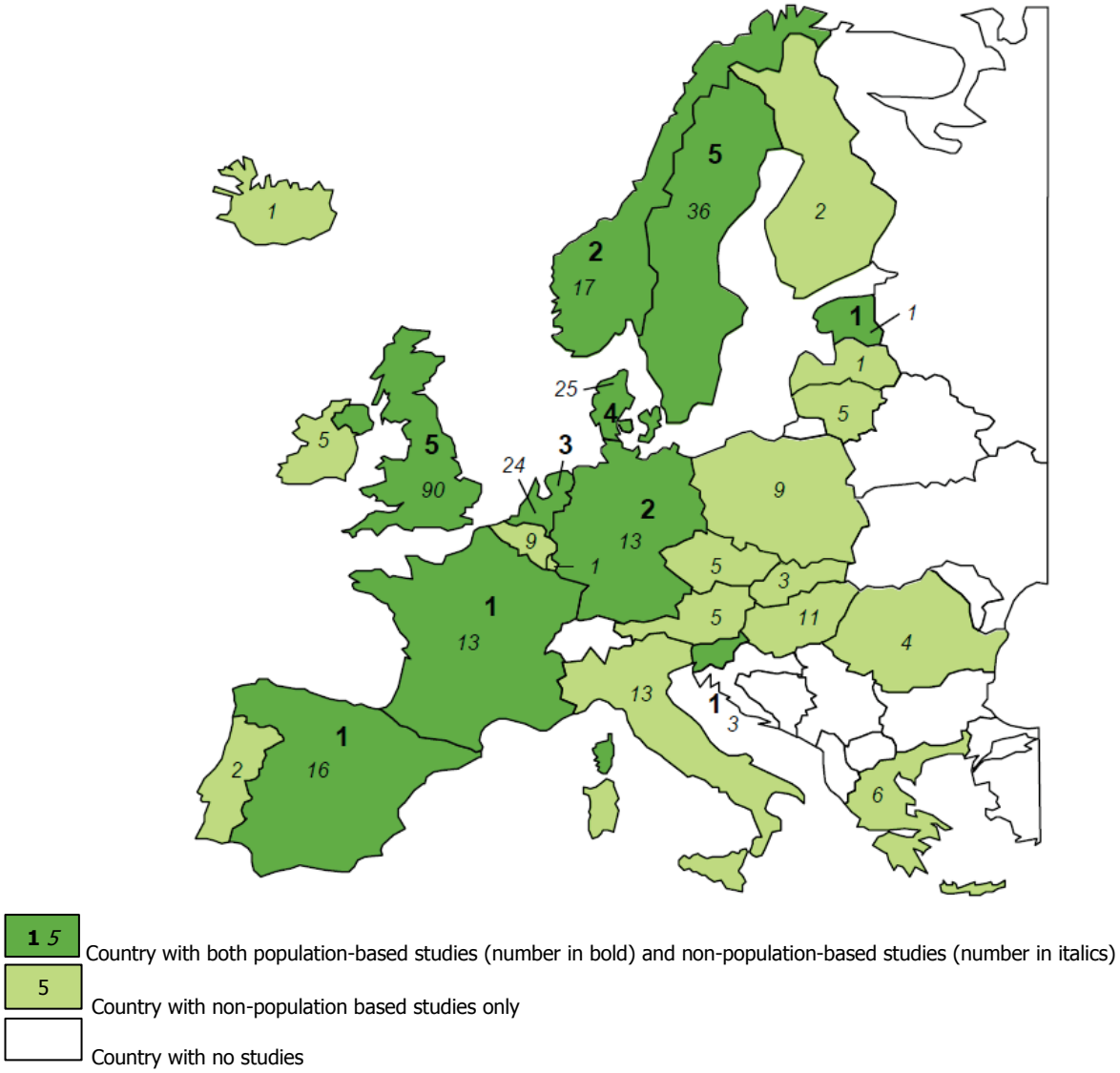
This section presents the findings from a systematic review of published literature about the prevalence of *C. trachomatis* infection in the general populations of EU/EEA countries and from a narrative review of evidence about the reproductive tract complications of chlamydia infection in women.

Prevalence of chlamydia infection

Description of included studies

The search strategy identified 39 separate studies (25 studies in 10 EU/EEA and 14 studies in 6 non-EU/EEA countries) reported in 90 publications that used methods that attempted to enrol a representative sample of the general population. References to all publications from included EU/EEA population based studies are listed in Appendix 1 (Table 11). In the 10 EU/EEA countries with a population-based study, there were another 233 publications of studies that were not done in the general population. In 17 EU/EEA countries with no study in the general population, there were 81 publications from studies conducted in other settings. The flow of included and excluded studies in population based and non-population based settings is shown in Appendix 1 (Figure 20). Figure 2 summarises the number and type of studies from each EU/EEA Member State. The population-based studies were published between 1992 and 2012.

Figure 2. Surveys of chlamydia infection in EU/EEA countries



Most population-based studies were done in the Netherlands (3 studies, 17 publications [25–40]), Denmark (4 studies, 7 publications [41–47]), Sweden (5 studies, 7 publications [48–54]) and UK (5 studies, 9 publications [24,55–62]). The remaining countries had two studies each: Germany (5 publications, 2 personal communications [63–69]), Norway (2 publications [70,71]) or only one study: Estonia (2 publications [72,73]), France (3 publications [74–76]), Slovenia (2 publications [77,78]) and Spain (2 publications [79,80]). Half of the studies in non-population-based settings were from Italy (13), Hungary (11), Poland (9) and Belgium (9). There were no publications identified from Cyprus, Malta or Liechtenstein. We identified population-based studies from two non-EU/EEA countries in Europe (Croatia [81], Switzerland [82]). At the time the searches were performed, and this technical report was prepared Croatia was an EU acceding country (one of the EU enlargement countries) and thus treated as a non-EU/EEA country.

Characteristics of included studies from EU/EEA Member States are summarised in Table 1 and presented in more detail in Appendix 1, Table 13.

Table 1. Summary of characteristics of population-based studies in EU/EEA Member States reporting estimates of chlamydia prevalence

Characteristic		Number of studies, N=25	Countries
Geographic coverage	National	6	France [74], Germany [63,68] , the Netherlands [28], Slovenia [77], UK [57]
	Sub-national, stratified random sample	2	Estonia [72], Spain [79]
	Sub-national, simple random sample	17	Denmark [41,42,44,45], the Netherlands [25,36], Norway [70,71], Sweden [48,49,52,53,54], UK [24,55,56,62]
Population	Sexually experienced only	9	Denmark [44,45], France[74], the Netherlands [36], Norway [71], Spain [79], Sweden[48], UK [55,57]
	Whole population only	12	Denmark [41,42], Germany [68], the Netherlands[25], Norway [70], Sweden [49,52,53,54], UK [24,56,62]
	Both	4	Estonia [72], Germany [63], the Netherlands [28], Slovenia [77]
Sex	Women only	4	Denmark [42], Spain [79], Sweden [48,49]
	Men only	4	Denmark [41], Sweden [52,54], UK [56]
	Both	17	Denmark [44, 45], Estonia [72], France[74], Germany, the Netherlands [25, 28, 36], Norway [70,71], Slovenia [77], Sweden [53], UK [24,55,57,62]
Age groups	Adolescent only	2	Denmark [45], Germany [63]
	<29 only	11	Denmark [42,45], the Netherlands [25, 28, 36], Norway [70,71], Sweden [49,52,53,54], UK [62]
	both <29 and >29	12	Denmark [41, 45], Estonia [72], France[74], Germany [68], Slovenia [77], Spain[79], Sweden[48], UK [24,55,56,57]

In terms of geographic coverage, five population-based studies included a nationally representative sample of the general adult population (France [74], Germany [68,69], the Netherlands [28], Slovenia [77], UK [57]), and one a similar sample of the child and adolescent population (Germany [63]). All surveys used stratified random sampling methods to select a study sample that represented the national population. In France, Germany, Slovenia and the UK, random samples were selected from all geographic regions. In the Netherlands, geographic areas were non-randomly selected but municipalities within selected regions and individuals within municipalities were randomly sampled. The final sample was weighted to reflect the entire population of the Netherlands.

In Slovenia and the UK, interviews were done in the homes of participants and urine specimens were collected at the same time as the interview. In both studies in Germany, participants made an appointment with the examination centre in their sample point, where they (or their parents) filled out a questionnaire, gave a computer assisted personal interview administered by a physician, underwent physical examinations and tests, and gave urine samples. In France, participants were interviewed by telephone and, if they agreed, they were sent a home sampling kit (urine for men and self-taken vaginal swab for women), which they returned to a laboratory by mail. In the Netherlands all invitations were mailed and all samples (urine for men, vaginal swab or urine for women) were home-collected and returned to laboratories by mail. In Slovenia all those interviewed were asked to provide a specimen for chlamydia testing, in Germany a urine specimen was obtained from all participants wherever possible, and used for multiple assays including chlamydia testing. In France and the UK, specimens were obtained from a random sample of sexually experienced participants who were taking part in national surveys of sexual attitudes and behaviours. More details on the samples taken and the methods used for chlamydia testing, for all studies, are described in Appendix 1 (Table 13).

The remaining studies enrolled participants from the general population in one or more regions of a country (Denmark [42,45], Estonia [72], the Netherlands [25,36,40], Norway [71], Spain [79], Sweden [48,49,52,53], UK [56,62]) or from a specific group within the general population (e.g. school students or men presenting for military service in Denmark [41,44]). Both stratified random sampling methods (Estonia, Spain) and simple random samples (Denmark, the Netherlands, Norway, Sweden, UK) were used. The number of people invited for testing ranged from 200 (a simple random sample of people aged 20–24 living in Umeå, Sweden [53]) to 261 025 (all 16 to 29–year-old residents of Amsterdam, Rotterdam, and selected municipalities of South Limburg, the Netherlands [36]).

The characteristics of 14 population-based studies from non-EU/EEA European countries, EU applicant countries and non-EU high income countries are shown in Appendix 1 (Table 13). There were four population-based studies that included a nationally representative sample of the general adult or adolescent population in Croatia (1 study, 1 publication [81]) and the USA (3 studies, 15 publications [83–97]). The remaining studies enrolled participants from the general population in one or more regions of a country (four studies in Australia, 6 publications [98–103], two studies in Canada, two publications [104,105], two studies in the USA, three publications [106–108]), or from a specific group within the general population (e.g. low income women in the USA [109,110], school students in New Zealand [111,112] or men presenting for military service in Switzerland [82]).

Results are presented separately for EU/EEA and non-EU/EEA countries and, within each group of countries, results are presented separately for the whole study population and for those reported to be sexually experienced. We also calculated response rates to each survey, based on the number of people tested and the number of people invited from the eligible population. Where complex sampling methods were used we used the published response rates.

Risk of bias in included studies

There was a risk of bias in the methods of all included studies (Appendix 1, Figure 22 and Figure 23). There were eight studies where the target population was assessed as being truly representative of the general population of the country concerned (five in EU/EEA and three in non-EU/EEA studies). In EU/EEA Member States these were sexually active people in the general population in France [74] and the UK [57], adults and adolescents in Germany [63,68] and the general population of Slovenia [77]. In non-EU countries these were the general population of Croatia [81] and two studies in the US [84,92]. The rest of the studies did not adequately describe their target population, or gave a narrow description which was identical to their source population. More than half of EU/EEA studies (14/25) did not give enough information about the source population to determine whether this was representative of the target population. Most studies did not include a sample size calculation. All the EU/EEA studies had standardised data collection methods and all but two older studies [50, 51] used NAAT to detect chlamydia.

The authors did not use a common method of calculating response rates. The reported data differed for the denominators- the number of people who were eligible and invited to participate and the numerator- the number of people who responded, returned specimens or had valid results. No EU/EEA study had a response rate of over 80%, which has been applied as a criterion for a low risk of bias in other reviews [18]; only two had a response rate of over 70% [49,57] and six over 60% [48,49,53,57,63,79]. The response rate reported by the authors ranged from 12% to 71%. The lowest response rates tended to be in studies where entire populations of a certain age group in large geographic areas were invited by post (13% East Anglia, UK [62]; 16% three regions in the Netherlands [36]). The highest response rates were achieved in small studies (e.g. 69% of women living in a single primary health care area in Sweden [48]) or in those where people were already taking part in a face-to-face survey and were asked for a urine specimen (71% UK Natsal[1] [57]). In surveys of this kind, the responders are those who have already agreed to participate in the original study. In non-EU countries, three studies reported response rates above 80% [84,105,111], five studies above 70% [84, 92, 105, 108, 111] and six above 60% [84, 92, 105, 108, 109, 111]. As with EU/EEA Member States, high response rates were obtained in studies of people who were already taking part in another study or survey.

Only two EU/EEA studies did not perform appropriate analyses [56] or provide confidence intervals [55] for the chlamydia prevalence or positivity estimates (or raw numbers so that confidence intervals could be calculated). All non-EU studies performed appropriate analyses and five did not provide confidence intervals or raw numbers to calculate them from [87, 104, 105, 106, 107].

Chlamydia prevalence estimates from population-based studies

The estimates of chlamydia prevalence extracted from each study, according to the data available, are shown in forest plots in Figures 3–10.

Overall estimates, all EU/EEA studies

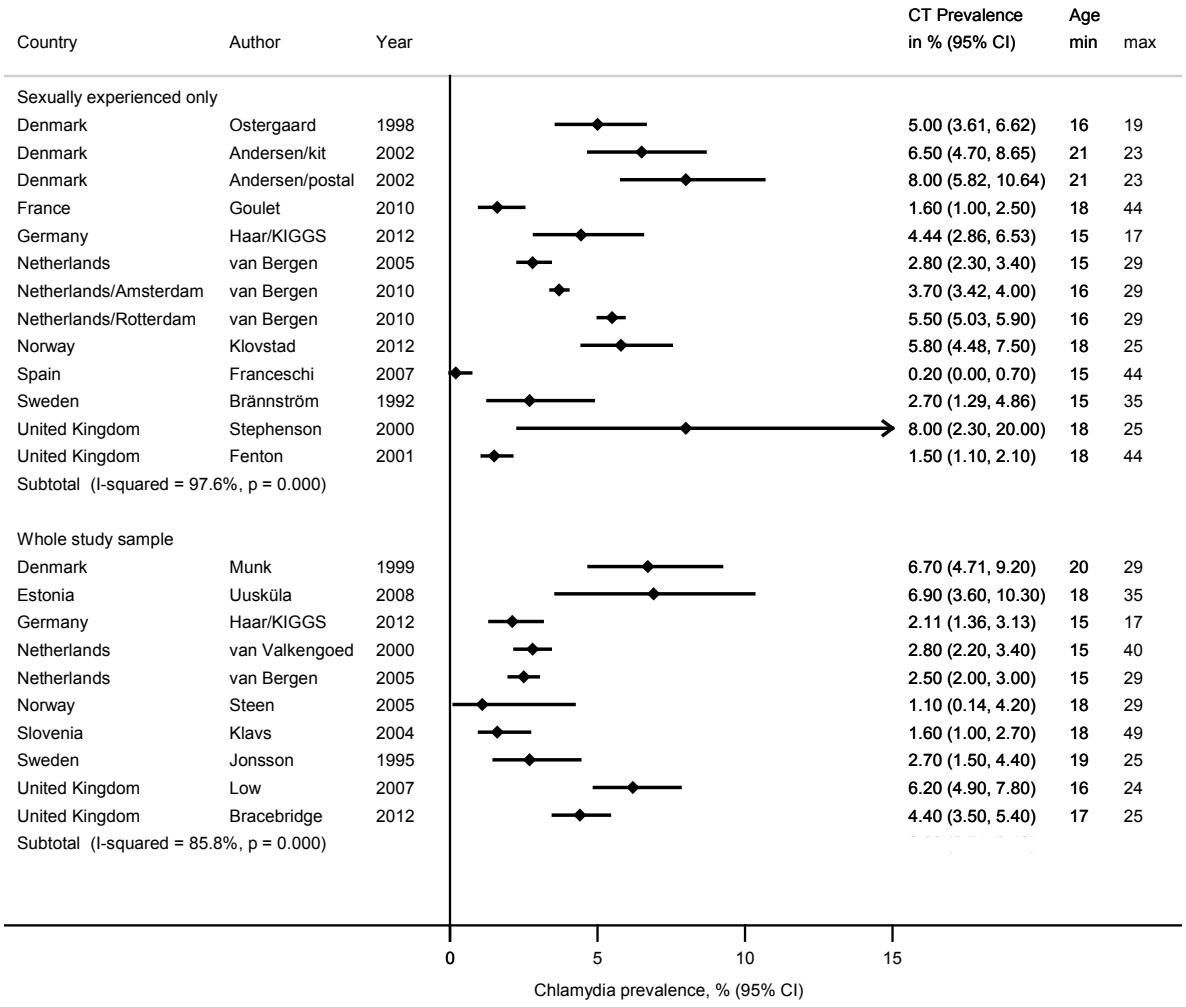
Figures 3 and 4 summarise overall results from all included population-based studies in EU/EEA Member States in any age group and in both nationally representative and sub-national studies. Data are presented, separately for women and men and estimates stratified into those from the whole study population and those restricted to the sexually experienced population. The age groups included in individual studies ranged from 15–17 years in Germany to 18–49 years in Slovenia.

Chlamydia prevalence point estimates for women of any age in the whole study sample in EU/EEA countries ranged between 1.1% (Norway) and 6.9% (Estonia) (Figure 3). Amongst sexually experienced women, point estimates ranged from 0.2% in Spanish women aged 15–44 years taking part in a multinational study of human papilloma virus infection (Spain) and 8.0% (Denmark and UK) (Figure 3). For men the prevalence point estimates ranged from 0.4% amongst 16–17 year old males in Germany (KIGGS study[2]) to 6.2% (Norway) for the whole study sample and 0.8% (KIGGS, Germany) to 6.9% (Denmark) for the sexually experienced population(Figure 4).

[1] National Survey of Sexual Attitudes and Lifestyles, UK

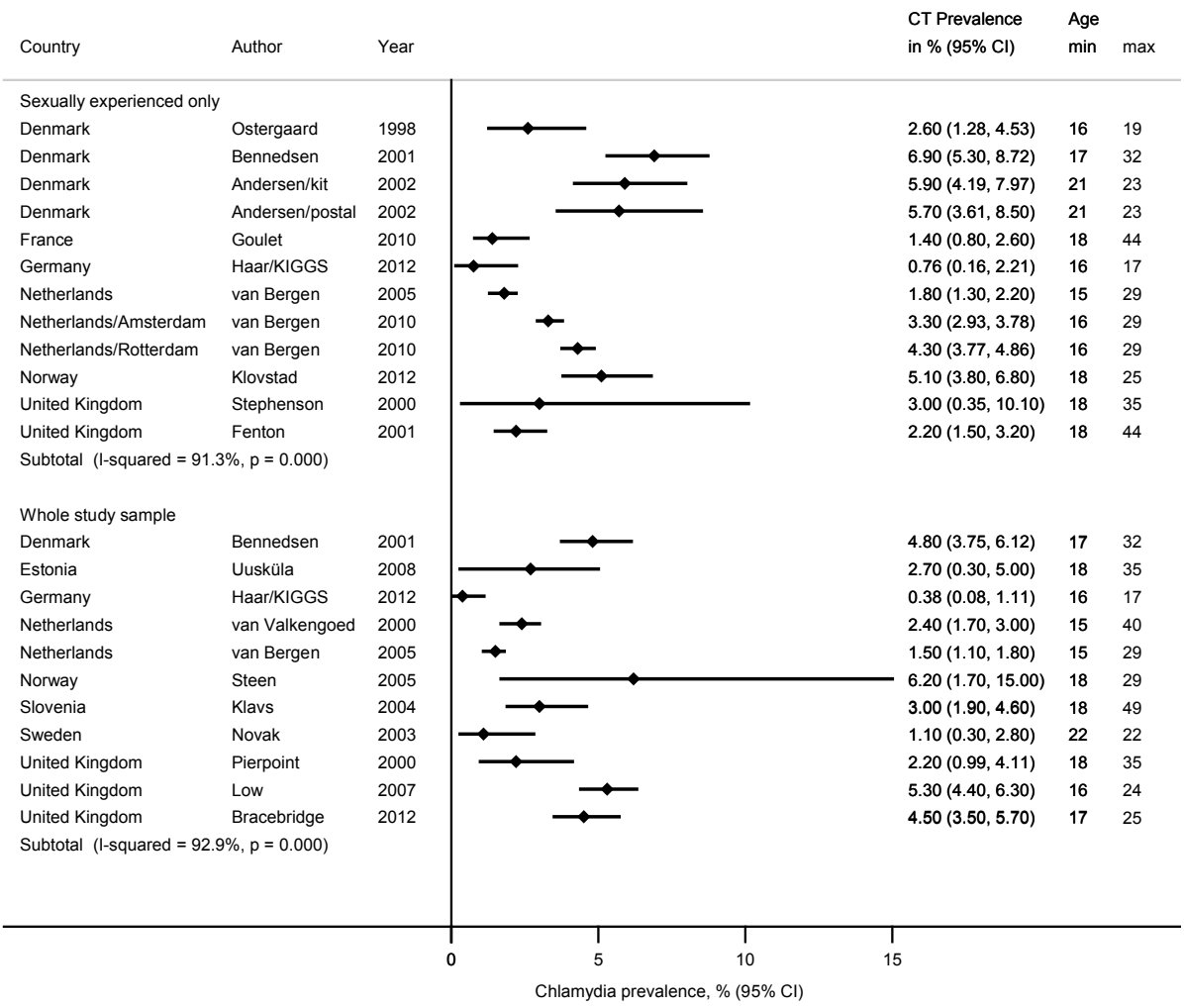
[2] German Health Interview and Examination Survey for Children and Adolescents

Figure 3. Estimates of chlamydia prevalence, EU/EEA Member States, all studies in women of any age group



CT, Chlamydia trachomatis; CI, confidence interval; min, minimum age in years; max, maximum age in years. Forest plot shows each row as a study or separate age group in the same study. The diamond shows the point estimate of prevalence, the lines either side are the 95% CI. Estimates are shown separately for sexually experienced participants only or for the whole sample; the studies in each group are not necessarily the same because comparable data are not available for all studies.

Figure 4. Estimates of chlamydia prevalence, EU/EEA Member States, all studies in men of any age group



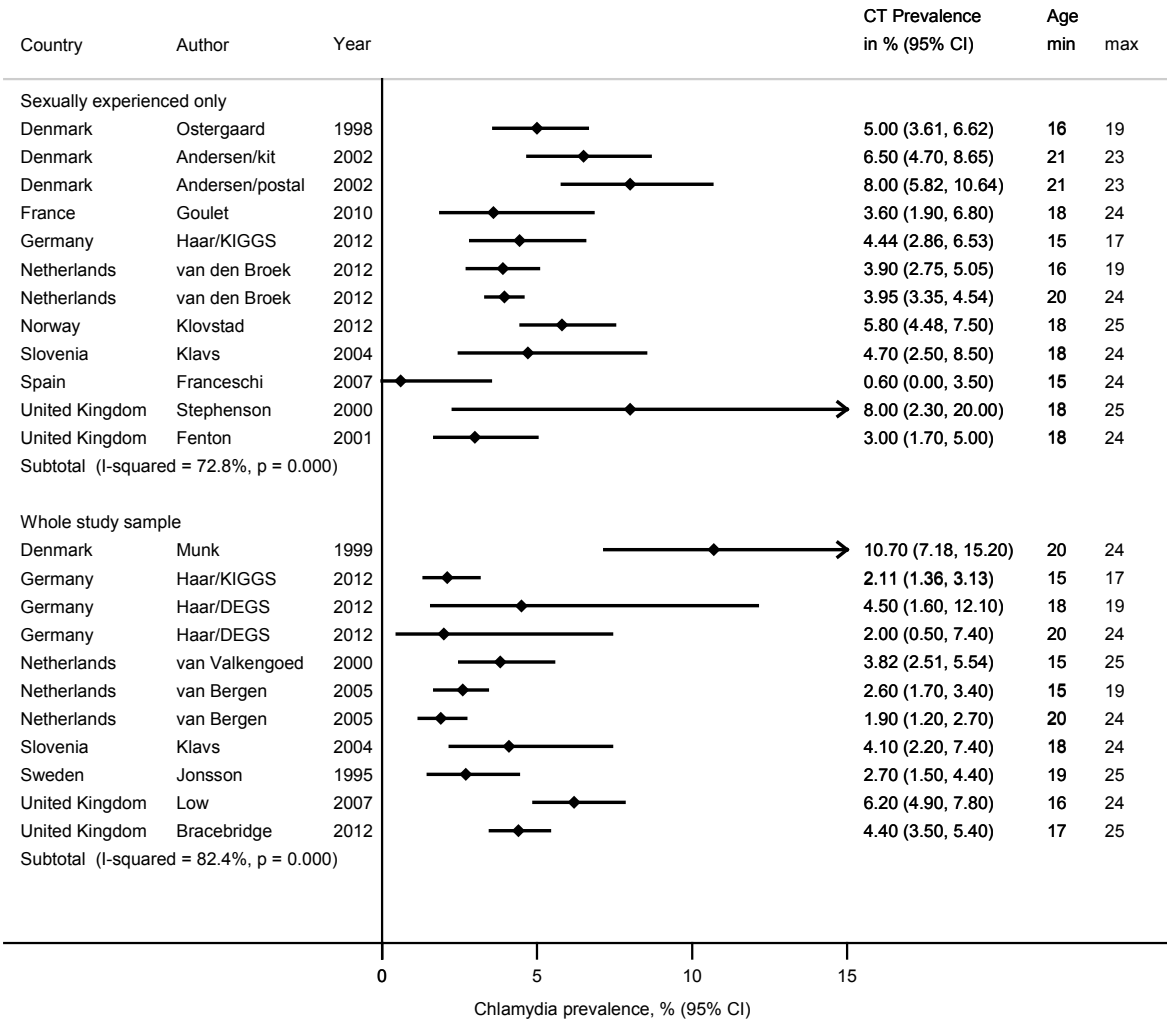
CT, Chlamydia trachomatis; CI, confidence interval; min, minimum age in years; max, maximum age in years. Forest plot shows each row as a study or separate age group in the same study. The diamond shows the point estimate of prevalence, the lines either side are the 95% CI. Estimates are shown separately for sexually experienced participants only or for the whole sample; the studies in each group are not necessarily the same because comparable data are not available for all studies.

Meta-analysis was not conducted because of the high levels of between study heterogeneity, which are shown in the forest plots (Appendix 1, Table 11).

Estimates for young population ≤25 years, all EU/EEA studies

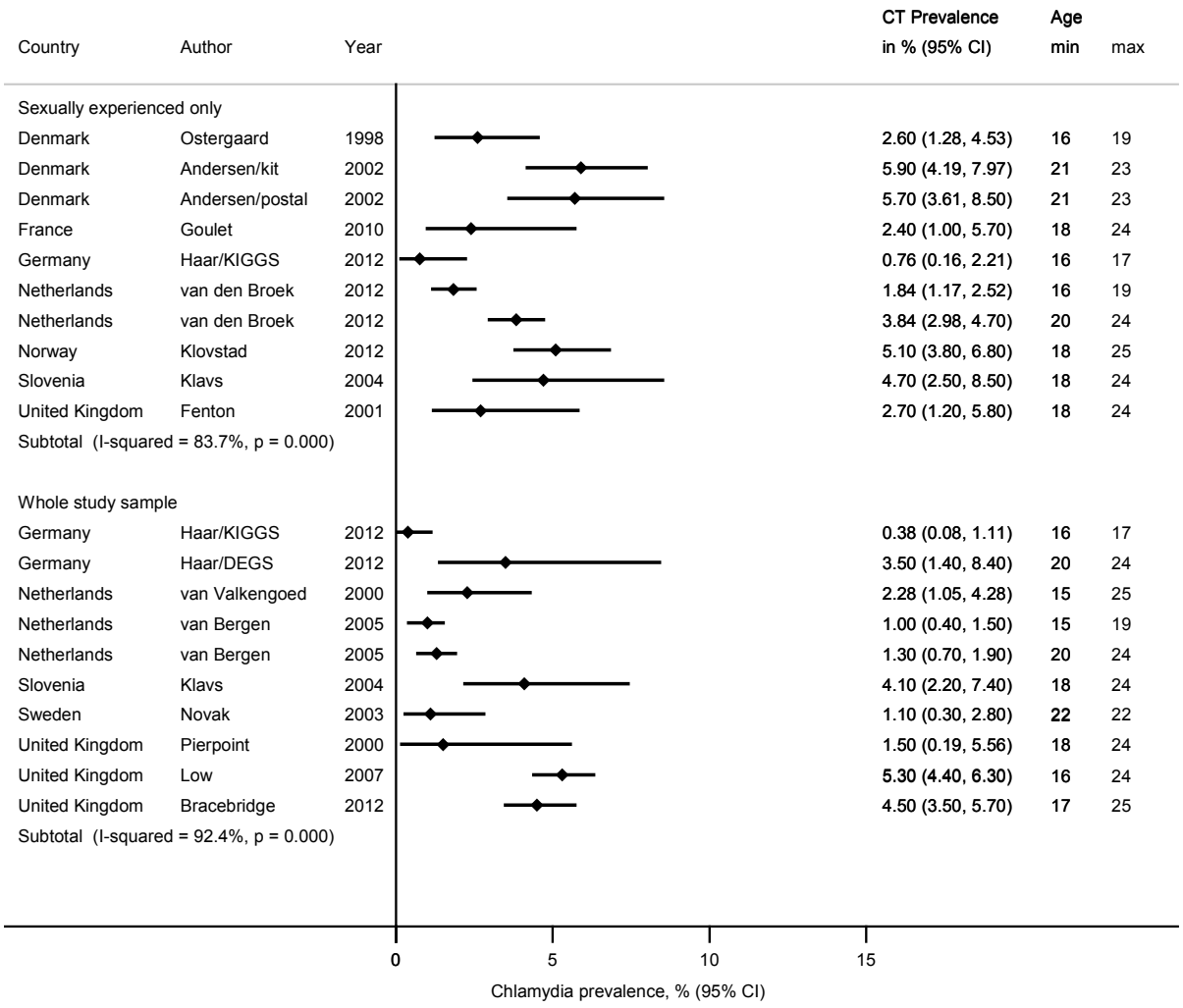
In young women aged up to 25 years the point estimates of chlamydia prevalence ranged from 1.9% (Netherlands) to 10.7% (Denmark) for the whole study sample (Figure 5), to between 0.6% (Spain) and 8.0% (Denmark, UK) for sexually experienced women. In young men aged up to 25 years the prevalence point estimates ranged from 0.4% (Germany) to 5.3% (UK) in the whole study sample, to between 0.8% (Germany) and 5.9% (Denmark) in sexually experienced men (Figure 6). Meta-analysis was not conducted, owing to heterogeneity.

Figure 5. Estimates of chlamydia prevalence, EU/EEA Member States, women aged ≤25 years



CT, Chlamydia trachomatis; CI, confidence interval; min, minimum age in years; max, maximum age in years. Forest plot shows each row as a study or separate age group in the same study. The diamond shows the point estimate of prevalence, the lines either side are the 95% CI. Estimates are shown separately for sexually experienced participants only or for the whole sample; the studies in each group are not necessarily the same because comparable data are not available for all studies.

Figure 6. Estimates of chlamydia prevalence, EU/EEA Member States, men aged ≤25 years

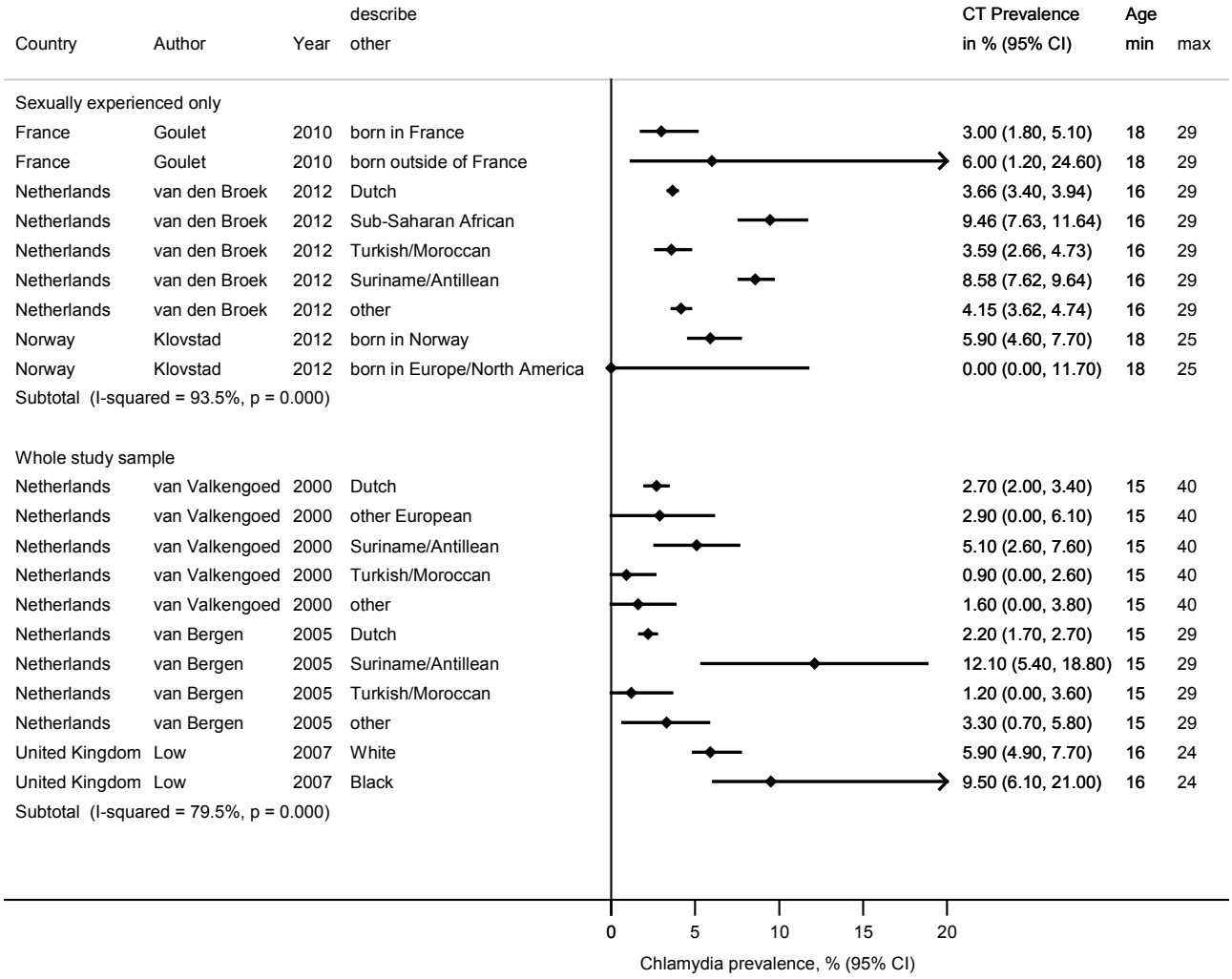


CT, Chlamydia trachomatis; CI, confidence interval; min, minimum age in years; max, maximum age in years. Forest plot shows each row as a study or separate age group in the same study. The diamond shows the point estimate of prevalence, the lines either side are the 95% CI. Estimates are shown separately for sexually experienced participants only or for the whole sample; the studies in each group are not necessarily the same because comparable data are not available for all studies.

Estimates for different national or ethnic groups, EU/EEA studies

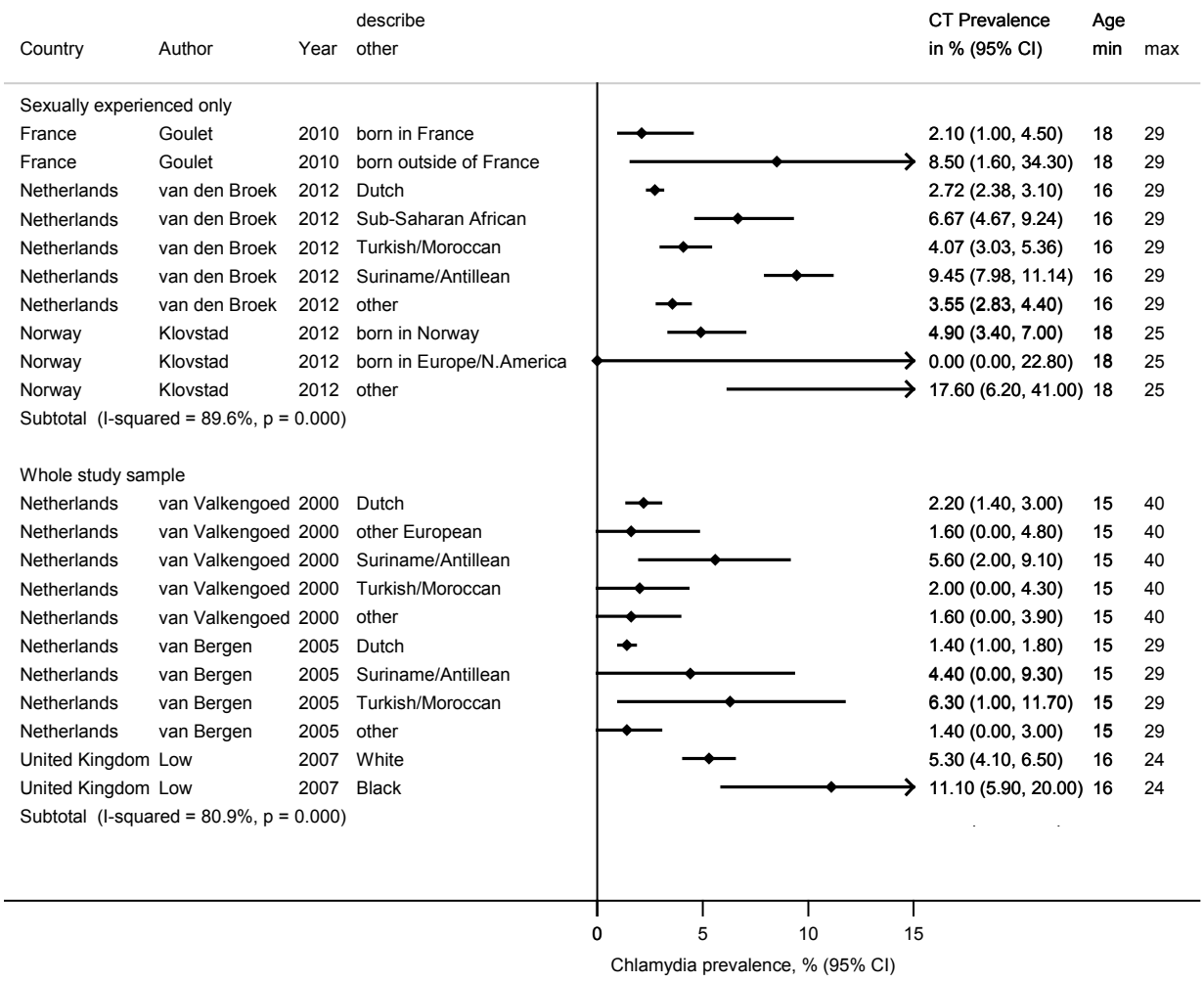
Where studies gave results for different ethnic or racial groups or nationalities each used its own categories and chlamydia prevalence estimates were not pooled. The lowest values in women in the whole study sample were seen for Turkish/Moroccan (0.9%) or Dutch (2.2%) women and the highest in black women in the UK (9.5%) or those from Surinam or the Dutch Antilles (12.1%) (Figure 7). In men the lowest values in the whole study sample were 1.4% for Dutch men or 1.6% for 'other European' and the highest values were 6.3% in Turkish/Moroccan men (all three in the same study set in the Netherlands) and 11.1% in black men in the UK (Figure 8). Confidence intervals for many estimates were very wide owing to small numbers of cases in each group.

Figure 7. Estimates of chlamydia prevalence, EU/EEA, women all ages, by reported national or ethnic group



CT, Chlamydia trachomatis; CI, confidence interval; min, minimum age in years; max, maximum age in years. Forest plot shows each row as a study or separate age group in the same study. The diamond shows the point estimate of prevalence, the lines either side are the 95% CI. Estimates are shown separately for sexually experienced participants only or for the whole sample; the studies in each group are not necessarily the same because comparable data are not available for all studies.

Figure 8. Estimates of chlamydia prevalence, EU/EEA, men all ages, by reported national or ethnic group



CT, Chlamydia trachomatis; CI, confidence interval; min, minimum age in years; max, maximum age in years. Forest plot shows each row as a study or separate age group in the same study. The diamond shows the point estimate of prevalence, the lines either side are the 95% CI. Estimates are shown separately for sexually experienced participants only or for the whole sample; the studies in each group are not necessarily the same because comparable data are not available for all studies.

Association between study design features of surveys and estimated chlamydia prevalence

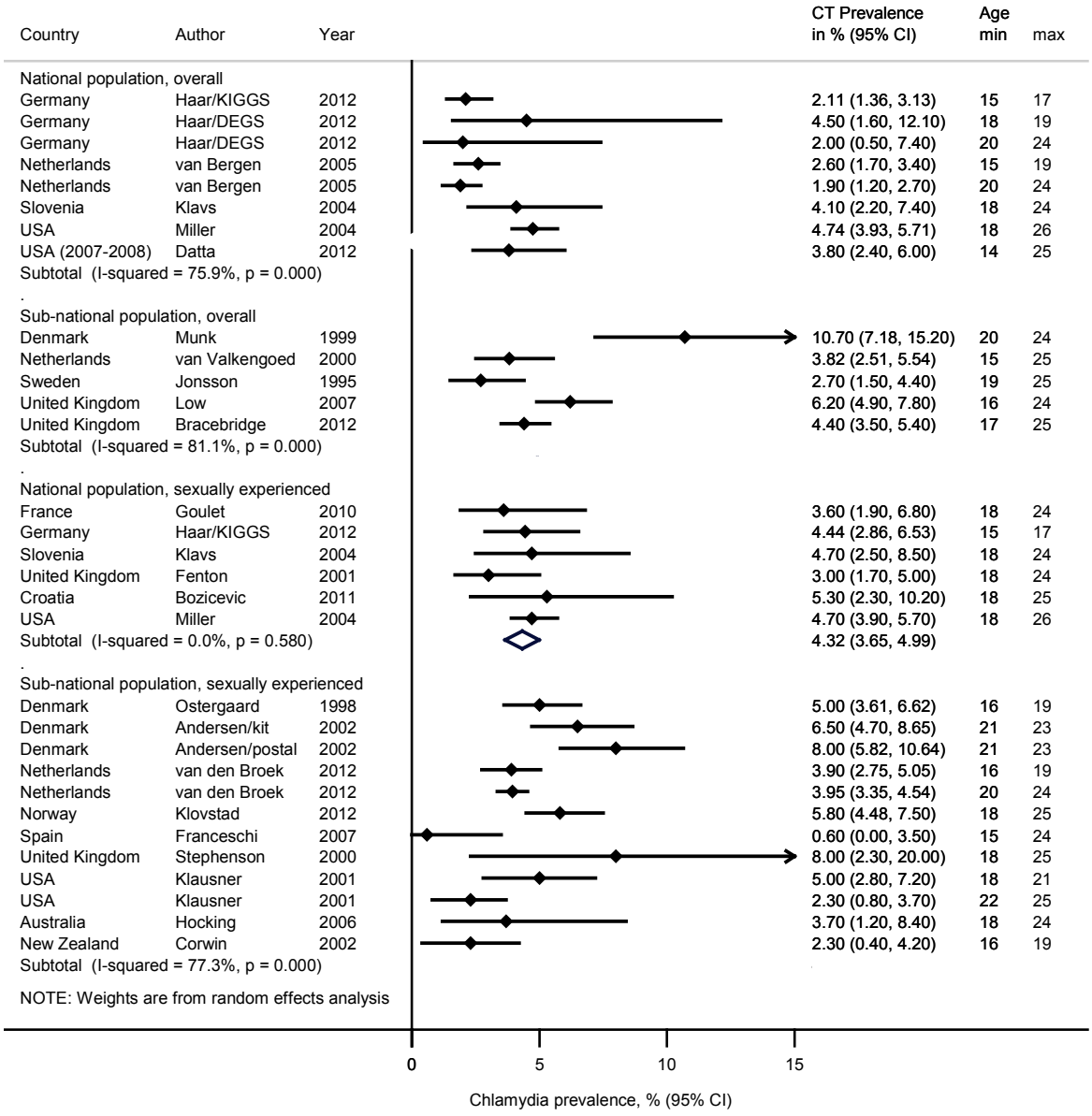
We examined differences between estimates of prevalence and two features of study design: whether the study population was representative of the whole country or was selected from a limited geographical region of the country; and the response rate to the survey. Analyses of these two features include studies done in non-EEA high income countries.

Estimates from nationally and sub-nationally representative studies, EU/EEA and other high income countries

Figure 9 and Figure 10 include results of studies conducted in all European countries or other high income countries among younger men and women, defined as aged ≤26 years (one study in the US had an upper age limit of 26 years [84]). Studies were categorised into those that used methods to achieve a sample representative of the whole national population and those restricted to one or more regions within a country.

Estimates of chlamydia prevalence in different countries were heterogeneous in studies that were not restricted to sexually active participants and in studies conducted in specific regions of a country; results from these studies were not pooled (Figure 9).

Figure 9. Estimates of chlamydia prevalence, all high income countries, women aged ≤26 years, national or sub-national study design.

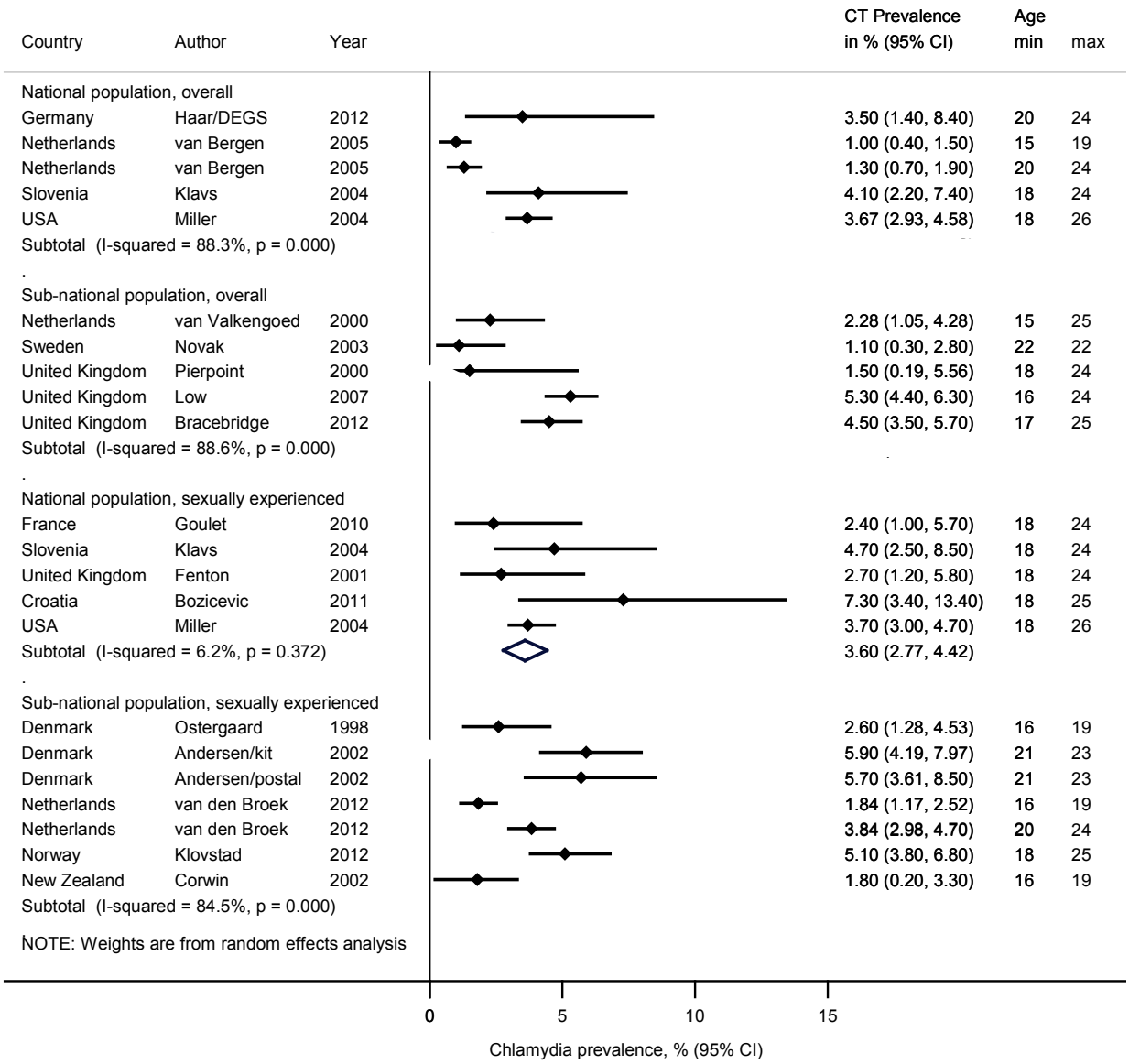


CT, Chlamydia trachomatis; CI, confidence interval; min, minimum age in years; max, maximum age in years. Forest plot shows each row as a study or separate age group in the same study. The solid diamond shows the point estimate of prevalence, the lines either side are the 95% CI. The open diamond shows the pooled estimate from a random effects model. Estimates are shown separately for sexually experienced participants only or for the whole sample; the studies in each group are not necessarily the same because comparable data are not available for all studies.

For nationally representative studies of sexually experienced women ≤26 years (six studies), point estimates of chlamydia prevalence ranged from 3.0% (18–24 year olds in the UK) to 5.3% (18–25 year olds in Croatia). The forest plot includes one row per study for women with a minimum age of 18 years, except for the KIGGS study in Germany, which included only women aged 15–17 years (Figure 9). This estimate was, however, compatible with those from the other studies (I^2=0%). The pooled average estimate of chlamydia prevalence in all six studies in this group was 4.3% (95% CI 3.7, 5.0%).

For men (Figure 10), there was strong evidence of heterogeneity between estimates in all studies from nationally representative samples in high income countries (I^2=90.2%). When excluding the KIGGS study population (point estimate 0.4% in 16–17 year olds) from the estimate for the overall population, statistical evidence of heterogeneity was only slightly reduced (to I^2=88.3%). Amongst sexually experienced young men aged 18–26 years in nationally representative studies, there was high heterogeneity (I^2=79.2%) but after excluding the KIGGS study population this was reduced greatly (I^2=6.2%) and the pooled average estimated chlamydia prevalence was 3.6%, 95% CI 2.9, 4.3%. Chlamydia prevalence estimates from sub-national populations were heterogeneous and results were not pooled.

Figure 10. Estimates of chlamydia prevalence, all high income countries, men aged ≤26 years, by national or sub-national study design.

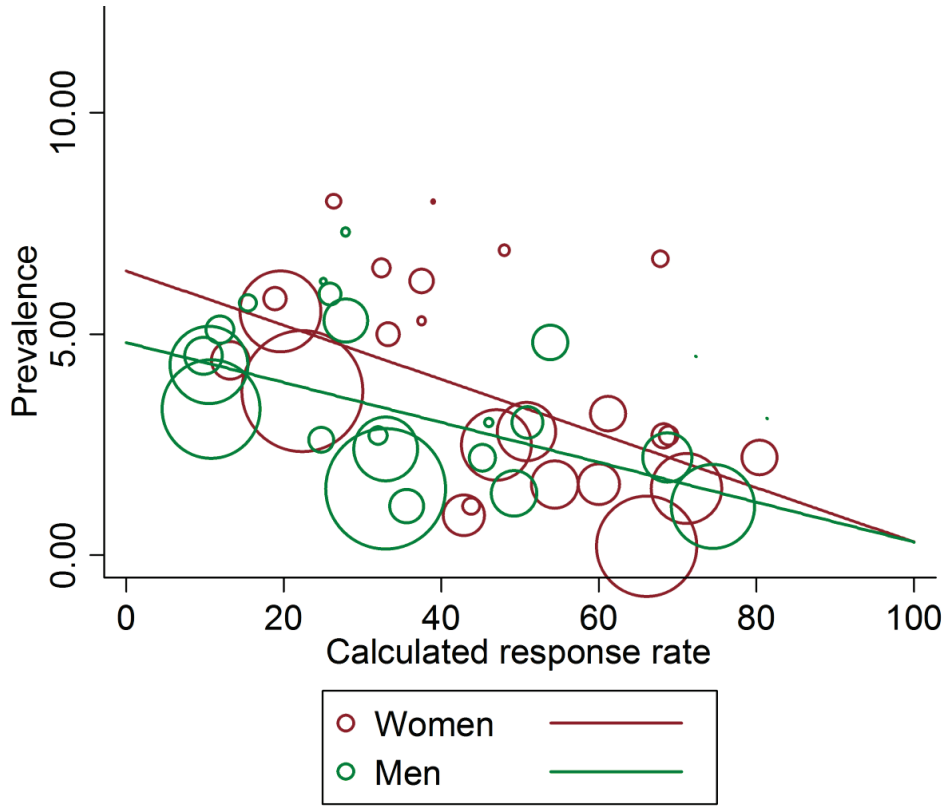


CT, Chlamydia trachomatis; CI, confidence interval; min, minimum age in years; max, maximum age in years. Forest plot shows each row as a study or separate age group in the same study. The solid diamond shows the point estimate of prevalence, the lines either side are the 95% CI. The open diamond shows the pooled estimate from a random effects model. Estimates are shown separately for sexually experienced participants only or for the whole sample; the studies in each group are not necessarily the same because comparable data are not available for all studies.

Association between response rate and estimated prevalence

There was evidence of an association between estimated chlamydia prevalence and the study response rate. Figure 11 shows all studies from high income countries, stratified by sex. The bubble plot shows an inverse relationship, with higher point estimates of chlamydia prevalence in studies with lower response rates. There was still a high level of heterogeneity between studies after taking account differences in response rates.

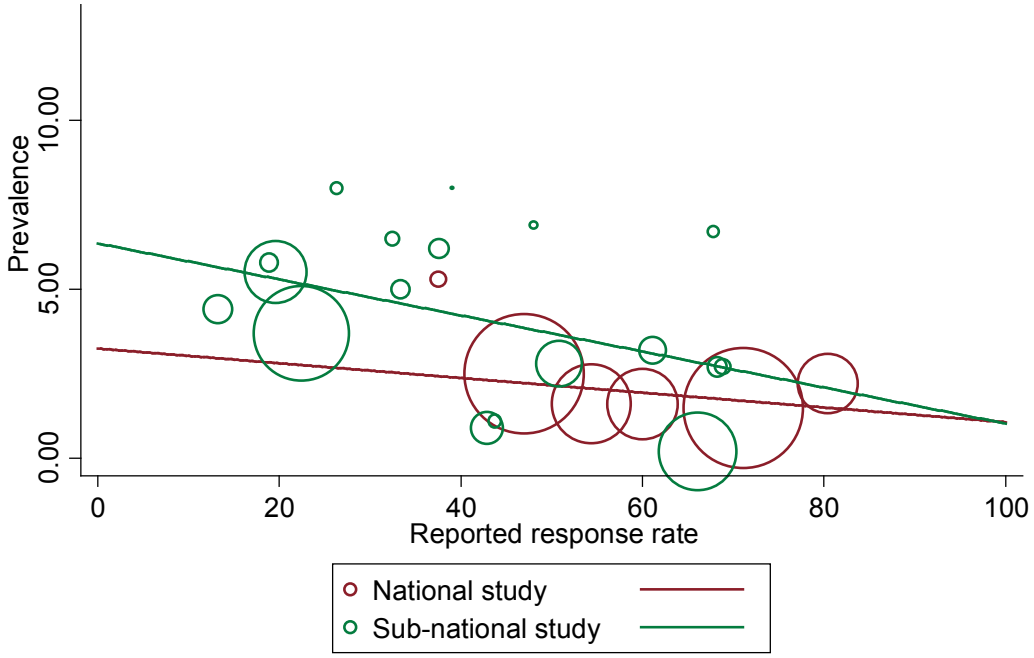
Figure 11. Meta-regression of estimated chlamydia prevalence against calculated response rate, whole study population and sexually experienced women and men of all ages, all studies in high income countries.



Plot includes 1 estimate per study. The size of the open circle corresponds to the precision of the prevalence estimate (1/standard error squared). Women, n=24 studies, P=0.005, I^2=89.6%; men, n=21 studies, P=0.012, I^2=86.3%.

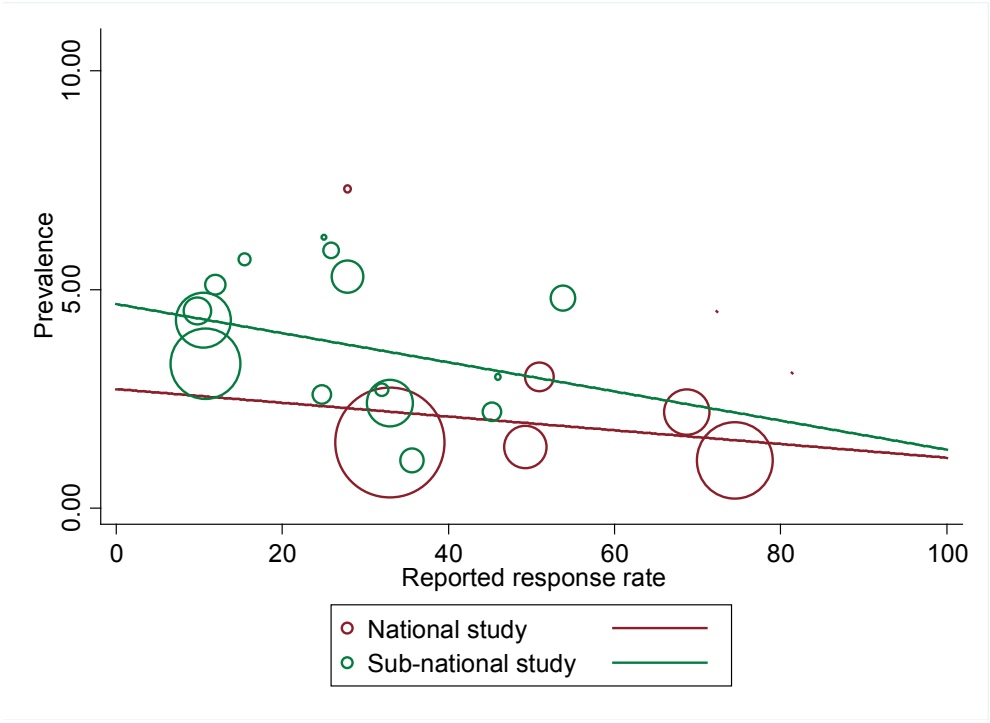
Figures 12 and 13 show the association between response rate and estimated prevalence in nationally representative and sub-national studies. In meta-regression analysis, there was no strong relationship between estimated chlamydia prevalence and response rate in national studies but moderate heterogeneity. There was stronger statistical evidence of an association with response rate in studies done in subnational regions of a country in women but not men, and substantial residual heterogeneity between prevalence estimates.

Figure 12. Meta-regression analysis of chlamydia prevalence estimates against response rate for all studies in women of all ages, by national or sub-national study design.



Plot includes 1 estimate per study or study region. The size of the open circle corresponds to the precision of the prevalence estimate (1/standard error squared). (National studies, n=6 studies, P=0.350, I^2=47.5%; sub-national studies, n=18 studies, P=0.063, I^2=91.23%)

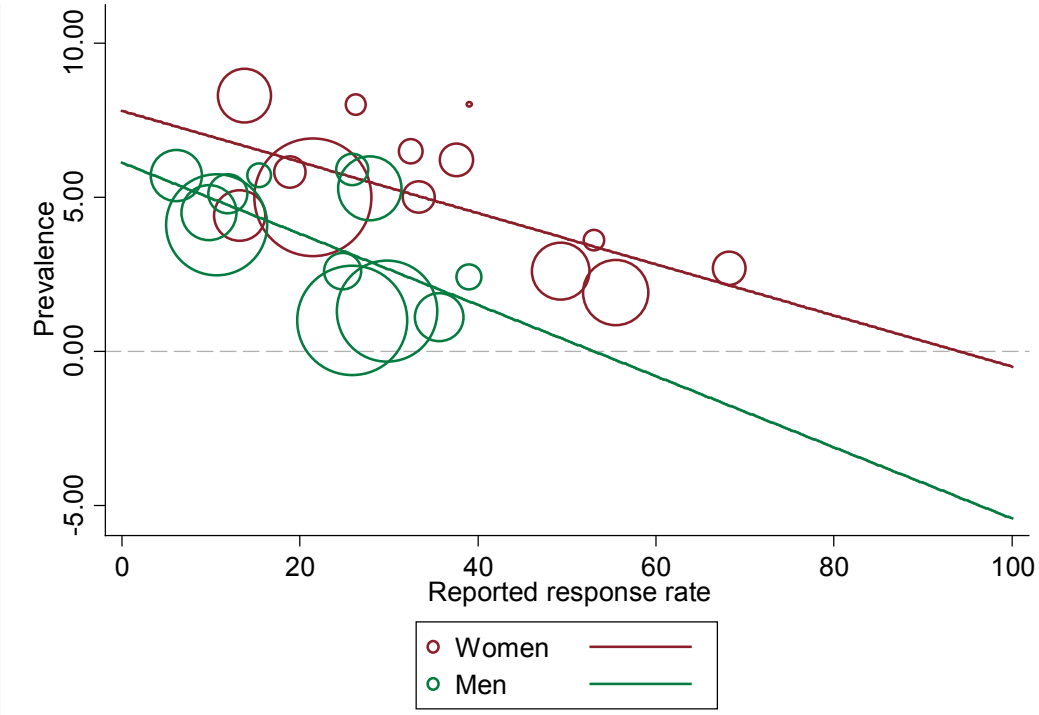
Figure 13. Meta-regression analysis of chlamydia prevalence estimates against response rate for all studies in men of all ages, by national or sub-national study design.



Plot includes 1 estimate per study or study region. The size of the open circle corresponds to the precision of the prevalence estimate (1/standard error squared). (National studies, n=6 studies, P=0.561, I^2=58.7%; sub-national studies, n=15 studies, P=0.267, I^2=81.3%).

Figure 14 shows the association between estimated response rates in women and men aged ≤25 years in studies done in EU/EEA Member States. There is a difference in response rates between women and men, with a tendency towards lower response rates in men and a stronger association between response rate and estimated prevalence in men than women.

Figure 14. Meta-regression analysis of chlamydia prevalence estimates against reported response rate for women and men aged 15–25 years, EU/EEA Member States only.



The size of the open circle corresponds to the precision of the prevalence estimate (1/standard error squared). (Women n=13 P=0.007, I^2=83.4%; Men n=12 P=0.029, I^2=89.1%)

Studies of chlamydia infection in non-population-based settings

Table 2 shows the numbers of studies and settings of non-population-based studies of chlamydia in EU/EEA Member States in countries with no general population studies. We found 80 publications from 73 different studies, 20 studies included both women and men, with a median sample size of 707 (range 130–38 265), 48 studies included women only (median sample size 558 women, range 50–31 419), and five studies included men only (median sample size 410 men, range 121–705). There were 14 studies in nine countries (Austria, Belgium, Bulgaria, Czech Republic, Ireland, Italy, Lithuania and Slovakia) in non-healthcare settings. The study populations included army recruits, school and college students, and women responding to newspaper advertisements. There were 45 studies in 16 countries (Austria, Belgium, Bulgaria, Czech Republic, Finland, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Poland, Portugal, Romania, and Slovakia) and one study in 13 countries from general healthcare settings such as general practice, student healthcare, orthopaedic clinics, routine gynaecology clinics, or specialist clinics for women's health including family planning clinics, antenatal clinics, women attending for routine cervical smears, asymptomatic women attending for termination of pregnancy. In populations at increased risk for chlamydia infection such as asymptomatic people attending STD or GUM clinics there were 14 studies in countries (Austria, Bulgaria, Czech Republic, Finland, Greece, Iceland, Italy, Poland and Slovakia).

Table 2. Summary of characteristics of studies from EU/EEA Member States in non-population-based samples

		Number of studies, by setting							
Country	Sex	Total	Students recruits, other non-healthcare	Healthcare settings e.g. GP, gynae, FPC, TOP	GUM or STD clinic	Population at high risk e.g. FSW, MSM	People with comorbidity e.g. infertility	Other	Summary of settings
Austria	F&M	5	2	3	1	1	1	2	Army recruits, STD or infertility clinic, FSW
Belgium	F&M	8 (9)	2	3	0	3	1	0	School medical, students, GP, FSW, MSW, HIV+ women
Bulgaria	F&M	4	4	1	2	1	0	0	Gynaecology clinic, STD clinic, symptomatic and asymptomatic
Czech Republic	F&M	4 (5)	2	1	2	1	0	0	Schools, students, prenatal clinic, STD clinic, FSW
Finland	F&M	3	0	1	1	0	1	0	FPC and STD clinics, HIV+ women
Greece	F&M	6	0	3	1	1	2	1	GP, FPC, gynaecology, dermatology; STD clinic; infertile women; FSW, HIV+ women
Hungary	F&M	6 (11)	0	5	0	1	2	4	Pregnant women; infertile women; symptomatic men and women, FSW
Iceland	F&M	1	0	0	1	0	1	0	Symptomatic STD clinic attendees, and partners of chlamydia infected people
Ireland	F&M	5	2	4	0	0	1	0	Students; student healthcare, orthopaedic clinics; routine gynaecology; antenatal, FPC, infertility clinics.
Italy	F&M	13	1	7	4	2	4	2	FPC; gynaecology; routine smears; STI screening programme; STD; infertile couples; partners of chlamydia+; FSW, HIV infected women
Latvia	F	1	0	1	0	0	0	0	Low risk pregnant women
Lithuania	F&M	5	3	2	0	0	0	3	Women responding to newspaper invitation; students; military recruits; healthcare attendees; symptomatic patients
Luxembourg	F&M	1	1	1	0	0	0	0	Schools, FPC, occupational health centre
Poland	F&M	9	0	6	1	0	5	2	Outpatient clinic; pregnant women; women having miscarriage; aborted tissue; cervical cancer patients; partners of chlamydia+ women
Portugal	F	2	0	1	0	0	1	0	Systematic sample from GP, FPC and teenager clinics, HIV infected women
Romania	F	2	0	2	0	0	2	0	Women with gynaecological diseases
Slovakia	F&M	3	1	2	1	0	1	0	Roma; gynaecology and/or urology clinics; symptomatic women; asymptomatic women before TOP
13 countries	F	1	0	13	0	0	0	0	FPC
12 countries	F	1	0	0	0	0	12	0	STI in HIV+ women: Belgium, Denmark, Finland, France, Greece, Italy, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland

Total number of studies (total number of publications if different) FPC, family planning clinic; GP, general practice; FSW, female sex worker; GP, general practice; GUM, genitourinary medicine clinic; MSM, men who have sex with men; TOP, termination of pregnancy

[†] Additional publications are those that use data from the same study but report subsidiary findings, or report on methodological aspects

For high risk populations such as female sex workers or MSM there were studies in seven countries (Austria, Belgium, Bulgaria, Czech Republic, Greece, Hungary and Italy). In people with a co-morbidity such as infertility, HIV infection, and those at highest risk of chlamydia infection such as partners of chlamydia infected persons or people with genital symptoms attending, there were 20 studies in 12 countries (Austria, Belgium, Finland, Greece, Hungary, Iceland, Ireland, Italy, Poland, Portugal, Romania and Slovakia) and one study in 12 countries investigating chlamydia co-infection in HIV-infected women. Many studies included multiple settings.

In Cyprus, Malta and Liechtenstein there were no studies identified, and only one per country for Iceland, Latvia, and Luxembourg, the highest number of studies were found in Italy (13), Poland (9) Hungary and Greece (6 each).

Reproductive tract complications of chlamydia infection in women

This review summarises evidence about the association between *C. trachomatis* infection in women and PID, ectopic pregnancy, tubal factor infertility and chronic pelvic pain. The rationale for chlamydia screening is that early detection and treatment will prevent or interrupt reproductive tract morbidity, particularly in women. The reported incidence of PID has fallen in several countries over the last decades [2,113–116], and the risk of complications is reported to be lower than previously estimated [117–119]. It is therefore important to determine whether the association between chlamydia infection and associated complications has changed over time.

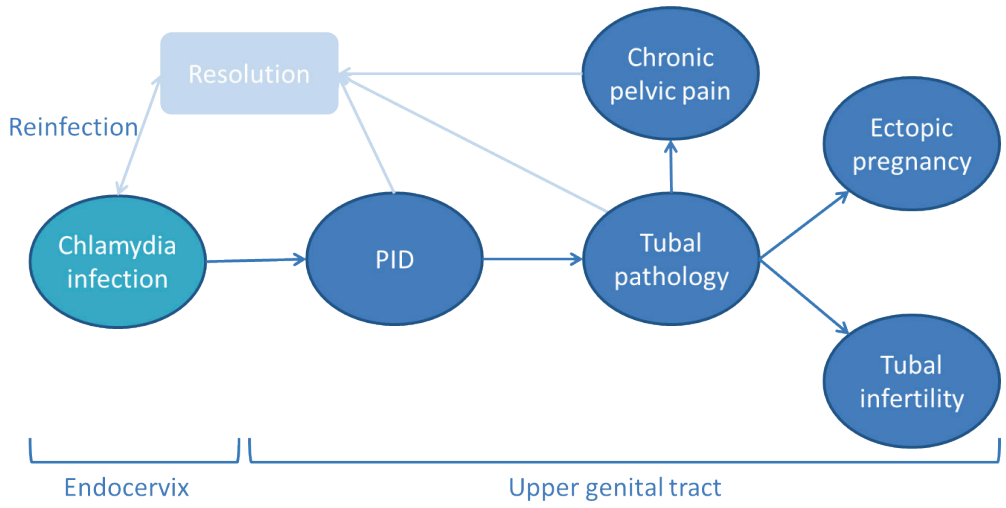
Several reviews have summarised studies that have investigated the risk of pelvic inflammatory disease, ectopic pregnancy and infertility following chlamydia infection [118–123]. These reviews provide comprehensive overviews of the published literature but leave ongoing uncertainty about absolute values for the incidence of the complications of chlamydia and of the fraction attributable to chlamydia. The authors of previous reviews note the methodological and ethical challenges of investigating the natural history of untreated genital tract infections. Some also describe situations in which extrapolation or generalisation might result in misinterpretation of study findings [118,119,123]. New reviews that simply update the same evidence base will not be able to overcome these challenges. It is therefore important to interpret the existing evidence in the context of strengths, limitations and changes over time.

This review begins with a description of a conceptual model for the natural history and pathogenesis of chlamydial disease. Methodological issues affecting the measurement and interpretation of natural history studies are then described, followed by a chronological overview of the findings of previous reviews and more recent individual studies .

Conceptual model of the natural history of chlamydia infection

Figure 15 shows the relationships that are assumed to exist between chlamydial infection in the endocervix and complications in the upper genital tract.

Figure 15. Natural history and sequelae of chlamydia infection in non-pregnant women.



Length of arrows is not proportional to time. Pale blue arrows point from conditions that can resolve spontaneously or with treatment. The double-headed pale arrow from resolution to chlamydia infection indicates that reinfection can occur after spontaneous clearance or treatment.

The progression of genital chlamydial disease can be conceptualised as a process with a 'two-phase temporal lag' [124], first from chlamydia to PID and then from PID to reproductive complications or chronic pelvic pain. Infection and pathological processes in fallopian tube cells are assumed to be necessary for progression to infertility and ectopic pregnancy [125]. PID is the clinical syndrome that results from a vaginal or endocervical infection that ascends through the cervical canal to the endometrium, fallopian tubes and contiguous structures and usually presents with lower abdominal pain [13,126]. PID can resolve spontaneously or after treatment without any pathological consequences. Inflammatory processes in the pelvic organs can, however, cause scarring and fibrosis, which result in further reproductive tract sequelae. Tubal damage can result in infertility, subfertility or ectopic implantation if pregnancy occurs.

Pathogenesis and timing of PID and tubal pathology

The exact mechanism by which *C. trachomatis* ascends through the endocervical canal to the endometrium, fallopian tubes and contiguous structures remains unclear. Smooth muscle contraction during sexual intercourse, retrograde menstruation and haematogenous spread have all been suggested [124,127].

There are two main hypotheses for explaining the immunological and pathological processes that result in tubal damage; the cellular and immunological paradigms [125]. The cellular paradigm is based on the assumption that actively infected epithelial cells are the key players. Chemokines secreted by these cells, which recruit leucocytes or induce cellular inflammatory responses cause tissue damage directly [128]. Thus, both innate immune cells (neutrophils and monocytes) and adaptive cells (lymphocytes) contribute to pathogenesis. The long duration of chlamydial infection means that cytokine release can continue to cause tubal damage, which resolves with scarring and fibrosis [125]. Women with genetic polymorphisms that increase innate inflammatory responses might be at high risk of PID [125]. The main premise of the immunological paradigm is that tissue damage is a result of T cell responses that are involved in clearing chlamydial infection after repeated infections [129]. Differences in the responses to chlamydial infection in different animal models, and difficulty in extrapolation of results to humans, contribute to the ongoing debate about the most appropriate model for the pathogenesis of chlamydial disease.

The pathogenetic mechanisms are relevant to chlamydia screening and prevention strategies [125]. Under the cellular paradigm, infection in the fallopian tube is a prerequisite for disease. Tissue damaging responses in mouse and guinea pig models begin as soon as the bacterium infects the oviduct epithelium and continue as long as the pathogen remains. This implies that identifying and treating chlamydia infection before it ascends, or shortening duration of infection in the fallopian tube, should be the focus of chlamydia control programmes in humans. Under the immunological paradigm, tissue damage results from repeated infection and even a small insult could trigger T cell responses. Prevention of re-infection or repeated infection would then be a more important focus for a chlamydia control programme. Darville and Hiltke conclude that there is strong evidence to support the cellular hypothesis but that T cell responses must also play a role because of the intracellular habitat of *C. trachomatis* [125].

The timing of progression from endocervical chlamydia infection can affect the impact of a chlamydia control programme. If chlamydia ascends to infect fallopian tube cells immediately after endocervical infection and inflammation follows soon after, opportunistic screening and treatment would, in most cases, be too late to prevent tubal pathology [130]. The reduction in the incidence of PID in RCTs comparing women receiving chlamydia screening interventions with control groups [131–133] suggests that there must be an interval between endocervical and tubal infection during which screening can prevent or limit tubal damage and clinical PID.

Methodological issues in measuring female reproductive tract outcomes of *C. trachomatis infection*

The pathological processes involved in the evolution of chlamydial infection and disease take place in internal organs (endocervix, cervical canal and pelvic organs) and cannot be observed directly. The timepoint from the start of the pathological processes is also an unobserved event (infection in the endocervix resulting from an episode of sexual intercourse). In practice, progression is measured from the point at which *C. trachomatis* is detected. Specific factors affecting the measurement and interpretation of the association between chlamydia and reproductive tract complications in women have been described [123] and are outlined below. The interpretation of studies of the association between chlamydia infection and its complications is confounded by the introduction of increasingly sensitive diagnostic tests and the increasing use of chlamydia testing. Many of the factors involved in determining the natural history of chlamydial disease also affect the study of other chronic diseases.

Studying the natural history from untreated chlamydia infection to fertility outcomes

It is not possible to study the effects of untreated chlamydia infection in detail over a prolonged period of time. In theory, the risk of complications of chlamydia infection would be studied in a cohort of women in the general population who are followed untreated over time. Chlamydia infection status would be measured regularly, together with information about sexual partners and practices, contraception, other STI, etc. Outcomes of PID, pregnancies and pregnancy outcomes would also be reliably ascertained at regular intervals. The absolute incidence rate of PID and other complications in women with chlamydia would be measured and the relative rate compared to women without chlamydia. In practice, such detailed studies are rarely conducted for any condition, including chlamydia.

Early studies to establish associations between chlamydia and reproductive tract morbidity were case-control studies. Exposure to *C. trachomatis* was measured as the presence of serum antibodies in women with ectopic pregnancy [134,135] or tubal infertility [135,136]. Biases inherent to case-control studies [137] and the limited sensitivity and specificity of chlamydia antibody assays [138,139] are well-documented. By the time an association had been established, it was widely regarded as unethical to withhold treatment from people with positive test results who might be at risk of the complications of chlamydia. Studies of untreated chlamydial infection are described below.

Changes in diagnostic test technology and performance

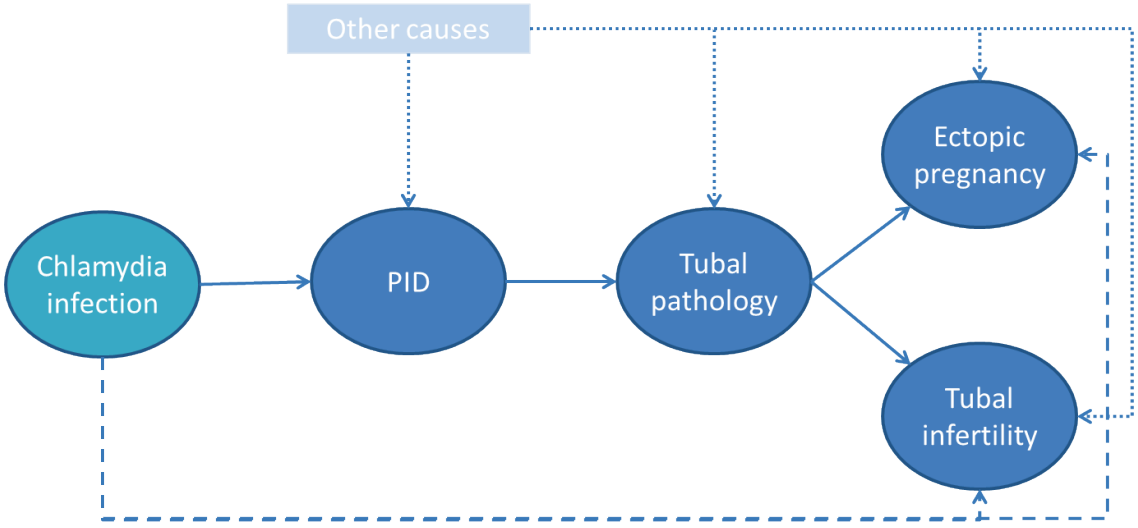
Technologies for detecting *C. trachomatis* have developed from culture of inclusion bodies from infected cells, through enzyme-linked assays for antigen detection, to the use of methods that amplify small amounts of DNA from urine specimens [140]. Tissue culture was the first established method for detecting *C. trachomatis* in specimens of patients with trachoma [141] and then from women with PID [142]. A positive culture result demonstrates the presence of active infection. A negative culture result does not necessarily exclude infection, however, as there might have been insufficient numbers of inclusion bodies to grow. The first clinical studies examining the association between chlamydia and sequelae used culture for diagnosis amongst women in hospital or attending STI clinics.

The sensitivity of culture tests depends on the laboratory and method used [140,143]. NAAT detect 10–30% more chlamydia positive specimens than culture in studies comparing the two methods [144,145]. It is not known whether the natural history of NAAT positive chlamydia infections in people without symptoms and at low chlamydia organism loads, is the same as that of culture positive chlamydia infections [146].

Diagnosis of chlamydial PID

PID is assumed to be the necessary intermediate condition between lower genital tract chlamydia infection and late sequelae (Figure 15). PID is a clinical condition in itself but is also used as a surrogate marker for ectopic pregnancy and tubal infertility. It is therefore important to understand the role of PID as a surrogate marker Figure 16.

Figure 16. Factors affecting the relationship between PID and ectopic pregnancy and tubal infertility.



Dashed line represents causal effects of chlamydia on ectopic pregnancy and infertility that are not mediated by PID. Dotted line represents other causes of PID, tubal pathology, ectopic pregnancy and tubal infertility.

PID is a clinical syndrome, which results from ascending infection from the vagina and endocervix [13]. Criteria for PID diagnosis are neither sensitive nor specific [147]. Lower abdominal pain and adnexal tenderness, which form the basis of the clinical diagnosis of PID, are non-specific [148]. Laparoscopy is considered the gold standard diagnostic tool but this is an invasive investigation which requires a general anaesthetic. Although its use has been encouraged [126], it is rarely used for routine diagnosis of mild or moderate symptoms and signs. In addition, laparoscopy will not detect isolated intratubal pathology and will miss some cases of salpingitis. The performance of clinical findings of adnexal tenderness can be improved by the addition of fever and raised erythrocyte sedimentation rate [148]. This triad correctly identified 65% (95% CI 61, 69%) of laparoscopically diagnosed PID cases in one study in Sweden [148]. The data were, however, collected from 1960–1969, when the main cause of PID was *N. gonorrhoeae*, rather than chlamydia.

C. trachomatis is only one of the causal organisms in PID and polymicrobial infections can occur [149] (Figure 16). A diagnosis of chlamydial PID is usually inferred from the findings of a positive chlamydia test result in the lower genital tract in the presence of a compatible clinical picture. This is also suboptimal [123]; *C. trachomatis* might be detected but might not be responsible for symptoms, which would overestimate the incidence of PID. Alternatively, *C. trachomatis* might have been eradicated from the endocervix by the host immune response, which might also have triggered pathological processes in the fallopian tubes [125], which would underestimate the incidence.

Asymptomatic infection with *C.* trachomatis

Several features of chlamydia make it difficult to link infection episodes to ectopic pregnancy and tubal infertility, although these conditions are consistently associated with evidence of past chlamydial infection at the population level [124]. Register-based studies allow linkages between individuals and their histories of chlamydia testing and hospitalisation for reproductive tract events. Several of these studies have been done in Scandinavian countries [150–153]. Asymptomatic chlamydia infections remain undiagnosed unless levels of regular screening are high, so many women who have been infected will be misclassified. Most cases of ectopic pregnancy and infertility occur in the absence of a diagnosed chlamydia infection [150], which underestimates the strength of association. On the other hand, there are many causes of ectopic pregnancy and infertility and a past chlamydia infection might not have been responsible for the outcome.

The use of contraception to delay pregnancy means that long-term studies are needed to examine the final endpoints of chlamydial disease. In an ecological study in Malmö, Sweden, the incidence of ectopic pregnancy in women aged 20 to 39 years peaked in 1989, about 15 years after a peak in the incidence of PID in the early 1970s [116]. PID cases in the 1970s were caused by both *Neisseria gonorrhoeae* and *C. trachomatis*. The trend in PID closely followed the trend in gonorrhoea diagnoses in the same year. One possible explanation for the delay in the trend for ectopic pregnancy is women's use of contraception to postpone childbearing. There is also ecological evidence that ectopic pregnancy might occur in association with current chlamydia infection. In younger women aged 20 to 24 years in Uppsala, Sweden, an association was observed between declining incidence of ectopic pregnancy and levels of chlamydia diagnosis in the same calendar year [154].

Risk of female reproductive tract morbidity resulting from chlamydia

Pelvic inflammatory disease

The incidence of PID in women with diagnosed chlamydia infection can be measured if they are followed over time. The relative risk of PID in women treated and untreated for chlamydia can be calculated in studies with a control group in whom chlamydia test status has been measured at baseline. In such studies, it is assumed that chlamydial PID is present in women with a clinical diagnosis of PID and a positive lower genital tract chlamydia result. In reviews of different studies of women with diagnosed PID, in which chlamydia test results are available, approximately 30% of women with PID have chlamydia detected in the lower genital tract [155]. It is not known if this has changed over time.

The first prospective studies comparing the risk of PID in women with and without chlamydia infection were done in the 1980s when the importance of *C. trachomatis* as a pathogen was being investigated (Table 3). *C. trachomatis* was diagnosed by culture from endocervical swabs. All were conducted in sexually transmitted diseases clinics amongst women at high risk of PID with short follow up periods. In two studies, women were co-infected with gonorrhoea and chlamydia [156,157] and in one study they were partners of men with non-gonococcal urethritis [158]. PID was ascertained in women treated with antibiotics that were active against gonorrhoea but not chlamydia, or received placebo.

In all studies PID was diagnosed in >10% of women with positive chlamydia culture results at their baseline visit. In the study by Rees [156], the relative risk of PID in gonorrhoea-treated women with chlamydia compared to those without chlamydia at baseline was 2.5 (95% CI 0.7, 8.9). Thus, the risk of PID is higher in chlamydia positive than chlamydia negative women but the confidence intervals are wide because of the small study size. Four of the eight women diagnosed with PID appeared to have cleared the chlamydia infection from the endocervix between the baseline visit and the date of PID diagnosis. It is not known whether *C. trachomatis* was present in the upper genital tract. The interval between chlamydia diagnosis and PID diagnosis was not reported in any study and the small study sizes means that the precision of the estimates is limited.

In studies done in the 2000s, study populations were larger and mostly asymptomatic, follow up was longer and chlamydia was detected using NAAT rather than tissue culture (Table 3). Ness and colleagues did a prospective study, the Gynaecological Infections Follow Through (GIFT) study, to predict the future risk of PID amongst US women at high risk of chlamydia [159]. They tested women for chlamydia at baseline and treated those with positive results. This study therefore differs from the others, in which women were untreated or received only antibiotics without activity against *C. trachomatis.* The study population of women attending outpatient clinics with known risk factors for STI was, however, similar to those of the studies from the 1980s. The point estimate for the relative risk of PID in women who had chlamydia at baseline compared with those who did not (2.5, 95% CI 1.6, 4.1) is similar to that obtained from the study by Rees [156].

Two studies were conducted in women enrolled in community settings [133,146]. Morré et al. followed women who were tested for chlamydia during pre-employment medical examinations and had follow up tests at 1, 6 and 12 months without receiving results or treatment. The study measured clearance of infection amongst those who were chlamydia positive and the incidence of infection amongst those chlamydia negative at baseline. PID was only assessed in those who were chlamydia positive at baseline and none of 30 women reported clinical symptoms or treatment during the follow up period. In the control group, 5/186 women acquired chlamydia during the follow-up period and three women consulted their GP and received antibiotics for supposed chlamydia infection, but without prior positive testing.

Table 3. Prospective comparative studies of PID incidence in women with and without chlamydia infection, by publication date

First author, date [ref]	Study population	Study design	PID incidence
Paavonen, 1980 [158]	Study dates 1978. Finland. 75 female partners of men with non-gonococcal urethritis (age not reported). Symptom status not reported. 41 couples received placebo, in whom 15 (37%) women and 21 (51%) men had chlamydia at baseline.	RCT of TMP-SMX or placebo for non-gonococcal urethritis. Couples treated together at day 0, follow up at 4 weeks. Chlamydia diagnosed by culture. PID diagnosed clinically.	PID in 3/15 (20%, 95% CI 4, 48%) chlamydia +ve women in placebo group at 4 weeks. Number in TMP-SMX group not reported, so relative risk cannot be calculated.
Rees, 1980 [156]	Date unknown. UK. 262 women with gonorrhoea 15-52 years, of whom 139 (53%) also had chlamydia at baseline. Symptom status not reported. 129 received penicillin (67 with chlamydia); 133 received oxytetracycline (72 with chlamydia).	Non-randomised controlled trial. Women followed at 6, 9, 12 weeks for chlamydia tests. Follow up 29-90 days in 38% of women treated with penicillin, 50% of women treated with oxytetracycline. Chlamydia diagnosed by culture. PID diagnosed clinically.	PID in 8/67 (12%, 95% CI 5, 22%) chlamydia +ve treated with penicillin at baseline. PID in 3/62 (5%, 95% CI 1, 13%) of oxytetracycline treated); chlamydia in 4/67 (6%, 95% CI 2, 15%) at time of PID diagnosis; Relative risk of PID in chlamydia +ve vs. chlamydia –ve treated with penicillin 2.5 (95% CI 0.7, 8.9).
Stamm, 1984 [157]	Date unknown. US 3 cities. 246 women with gonorrhoea 14-47 years, of whom 64 (26%) also had chlamydia at baseline. 68 received penicillin, 89 received TMP-SMX, 89 received tetracycline.	RCT of penicillin, TMP-SMX, tetracycline. Follow up 7, 21, 42 days. Chlamydia diagnosed by culture. PID diagnosed clinically.	PID in 6/20 (30%, 95% CI 12, 54%) chlamydia +ve in Seattle treated with penicillin at baseline (follow up time not reported). PID in 0/37 chlamydia –ve. Relative risk of PID in chlamydia +ve vs. chlamydia –ve treated with penicillin ∞.
Morré, 2003 [146]	Study dates 1995-1997. The Netherlands. 744 women, 18-40 years, tested in pre-employment medical checks. 30 (4%) chlamydia +ve at baseline and 186 randomly selected controls.	Nested case-control study. Follow up 1, 6, 12 months. Chlamydia diagnosed by NAAT. PID diagnosed by self-reported symptoms, GP visits or antibiotics.	PID in 0/30 (95% CI 0, 12%) chlamydia +ve by 12 months. PID in chlamydia –ve not reported, so relative risk cannot be calculated.
Ness, 2006 [159]	Study dates 1999-2001. 5 US sites. 1170 women, 13-36 years at high risk of chlamydia at health clinics. 122 (10%) chlamydia +ve at baseline.	Prospective cohort study. Tested for chlamydia and gonorrhoea at baseline and treated if +ve. Chlamydia diagnosed by NAAT. Tests at 6, 12 months. PID diagnosed on clinical signs or histological endometritis. Follow up median 3 years.	PID in 19/106 (18%, 95% CI 11, 27%) of chlamydia +ve, gonorrhoea –ve at baseline. 69/979 (7%, 95% CI 6, 9%) of chlamydia & gonorrhoea -ve. Relative risk of PID in chlamydia +ve vs. chlamydia –ve 2.5 (95% CI 1.6, 4.1).
Oakeshott, 2010 [133]	Study dates 2004-2006. UK universities and colleges. 2563 women 16-24 years, 150 (6%) with chlamydia at baseline. 1270 (80 with chlamydia) received screening after 12 months; 1259 (70 with chlamydia) received immediate screening. Most asymptomatic.	RCT of immediate vs. deferred screening and treatment. Chlamydia diagnosed by NAAT. PID diagnosed by self-report and notes review. Follow up of 94% at 12 months.	PID in 7/74 (9%, 95% CI 4, 19%) of chlamydia +ve at baseline in deferred screening group (5/7 chlamydia +ve at time of PID diagnosis). 14/1112 (1%, 95% CI 0.7, 2%) of chlamydia –ve at baseline. Relative risk of PID in chlamydia +ve vs. chlamydia –ve 6.6 (95% CI 2.8, 15.5).

PID, pelvic inflammatory disease; RCT, randomised controlled trial; TMP-SMX, trimethoprim-sulphamethoxazole;

The study by Oakeshott et al. is the largest to date [133]. Asymptomatic young women were enrolled from universities and further education colleges into an RCT comparing the effect of immediate screening and treatment with screening but with testing and treatment deferred for one year. The level of chlamydia test positivity (6%) was lower than in all clinic-based studies. The incidence of PID in women with chlamydia (9% after 12 months) was lower than in the studies from the 1980s. An earlier study from the Netherlands, which followed 30 chlamydia positive women who were identified during pre-employment medical examinations, did not receive any reports from the women about clinical diagnoses or treatment for PID.

Oakeshott et al. report that 62% (16/26) of women tested for chlamydia at the time of PID diagnosis had positive results (numbers not reported separately for immediate and deferred screening groups), suggesting that most of these cases resulted from chlamydia infections acquired during follow up. Amongst untreated women in the deferred screening group, the relative risk of PID in chlamydia positive compared with chlamydia negative women was 6.6 (95% CI 2.8, 15.5). The association between chlamydia and PID therefore appears stronger in the asymptomatic population than in women at higher risk of STI, but confidence intervals for all estimates are wide and a formal test of interaction has not been done.

Tubo-ovarian abscess

An abscess can form in the fallopian tube and present as a surgical emergency. In the PID Evaluation and Clinical Health (PEACH) trial of PID treatment strategies, 0.8% (7/808) women with PID developed a tubo-ovarian abscess [160].

Ectopic pregnancy and tubal infertility

Ectopic pregnancy and tubal infertility or subfertility are the pathological reproductive endpoints of chlamydial disease. Starting from these endpoints, the fraction of ectopic pregnancy and tubal factor infertility cases that is attributable to chlamydia infection (population attributable fraction or aetiologic fraction) can be estimated. Price et al. used a statistical modelling approach to estimate that 45% (credible interval 28%, 62%) of tubal infertility cases are caused by chlamydia [138]. This estimate is similar to some obtained directly from case-control studies but has the advantage that the method takes into account uncertainty about the sensitivity and specificity of chlamydia antibody tests [139] and the likelihood that chlamydia antibody levels are higher in women with tubal factor infertility that was caused by chlamydia that in women with tubal factor infertility caused by another organism or condition in women with coincidental exposure to chlamydia [161]. The attributable fraction could change over time if either prevalence or the strength of association change. There were insufficient data to assess this.

It is more difficult to find direct evidence to allow estimation of the risk that a women with chlamydia infection will go on to develop tubal infertility or ectopic pregnancy. The long potential delay between initial infection and these endpoints and their other causes are the main limitations to prospective cohort studies. Wallace et al., in a systematic review of studies published up to 2008, found one relevant retrospective cohort study of adolescent women and their fertility outcomes in Indianapolis, USA [121]. There was no statistical evidence of a difference in the proportions achieving live births between women with (62%) and without (50%) a history of a chlamydia infection. There was a high risk of bias, however, because only 21% (104/496) of the cohort was contacted at follow up. Ness et al. have reported on the fertility outcomes of women who had been treated for PID as part of an RCT. Overall, 19% were diagnosed with infertility [160]. There were no differences in pregnancy rates or reported infertility in women with or without a subsequent STI diagnosis, but chronic pelvic pain was reported more frequently in those with subsequent STI [162].

The fertility outcomes after PID from all causes have been documented in prospective studies [160,163–167]. Weström followed >1000 women with laparoscopically diagnosed PID from the 1960s to the 1980s and compared them with women with normal laparoscopic findings. Overall 16% of women with PID were diagnosed with infertility (after 1 year of trying to become pregnant). Of these, 11% had tubal factor infertility. The severity of PID was associated with tubal factor infertility; 0.6% of women with mild salpingitis compared with 21% of women with an episode of severe salpingitis. The presence or absence of chlamydia at the time of PID diagnosis was not reported in these studies, but *N. gonorrhoeae* was the most common cause of PID when these studies were started. In a study in the same population from 1977-1980, Weström et al. estimated that 8.0% of women aged 15-34 years with chlamydia and 8.6% with gonorrhoea developed laparoscopically salpingitis [162] but the basis for this calculation was not described in detail.

Information about the component parts of the causal pathway from chlamydia infection to ectopic pregnancy and infertility (Figure 15) has, however, been combined using simple arithmetic calculations to estimate the probability of developing disease endpoints. The probabilities of ectopic pregnancy from any cause of 0.02% and of tubal infertility from any cause of 0.07% in women with past exposure to chlamydia were estimated by van Valkengoed et al. [118]. Land et al. used two different approaches and obtained estimates of 0.6-2.1% and 0.1-4.6% [119]. These estimates are based on selected observational studies that make assumptions about the causal nature of associations and do not take account of statistical uncertainty. They suggest overall, however, a low risk of developing the most severe endpoints of chlamydial disease.

Chronic pelvic pain

Chronic pelvic pain has been defined as menstrual or nonmenstrual pain of at least six months' duration [160,168]. In acute PID, a fibrinoid exudate can cover the serosal surfaces of the uterus, tubes, and ovaries. Pelvic pain is presumed to follow resolution of PID with scarring and fibrosis, which can lead to adhesion of the tubes, ovaries, bowel, and omentum to the pelvic structures and to each other [168]. There are few prospective studies that have investigated the incidence of chronic pelvic pain after PID of any cause [160,169,170]. In this review, no prospective studies with chronic pelvic pain as a long term complication of asymptomatic chlamydia infection were identified.

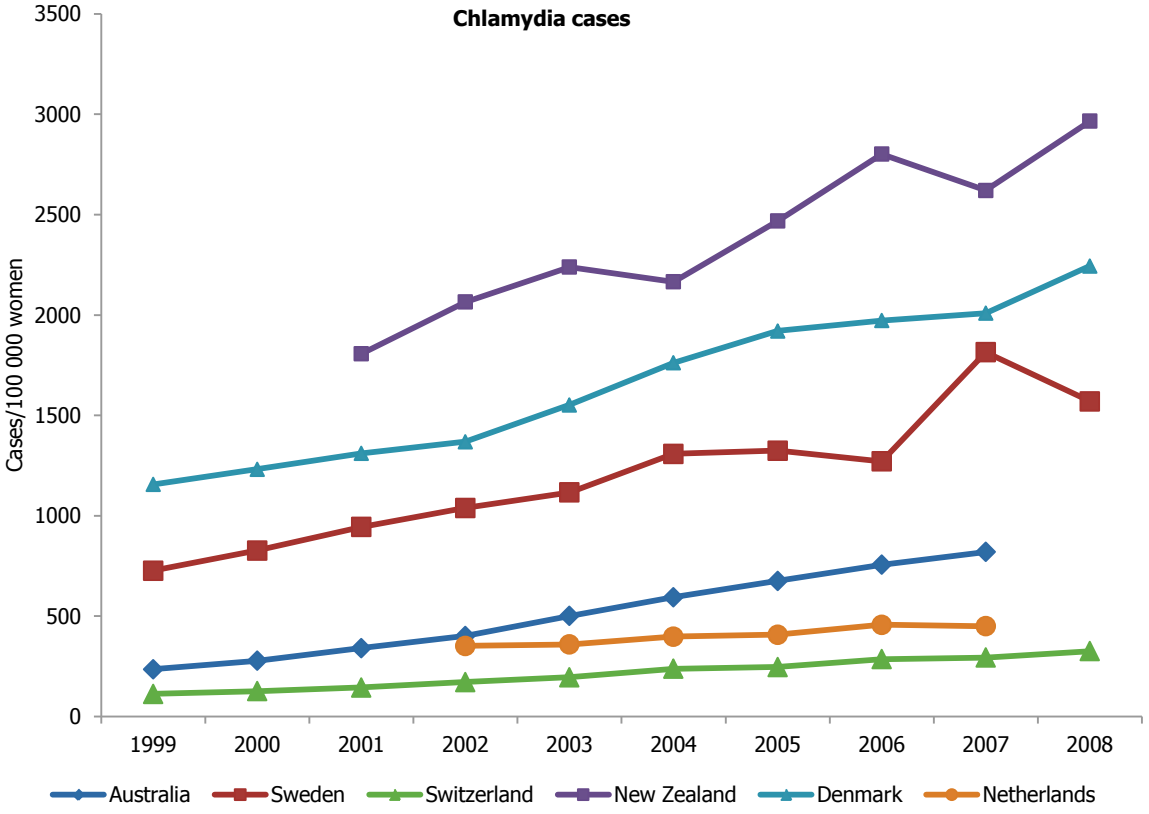
Chronic pelvic pain has been reported in reviews of studies in 18% to 75% of women with PID compared with only 5% to 25% of unaffected women [168]. The most comprehensive longitudinal study was conducted by Ness et al. in the PID Evaluation and Clinical Health (PEACH) trial of PID treatment with inpatient or outpatient antibiotic regimens. Overall about a third of women treated reported chronic pelvic pain after two years of follow up [160]. Half of the women reporting any pelvic pain and 16% (119/749) of all women treated for PID were categorised as having high pain and disability [168]. After up to seven years after treatment, 42% (328/789) women reported chronic pelvic pain, including 35% of women who had no further episode of PID during follow up and 69% of women with recurrent PID.

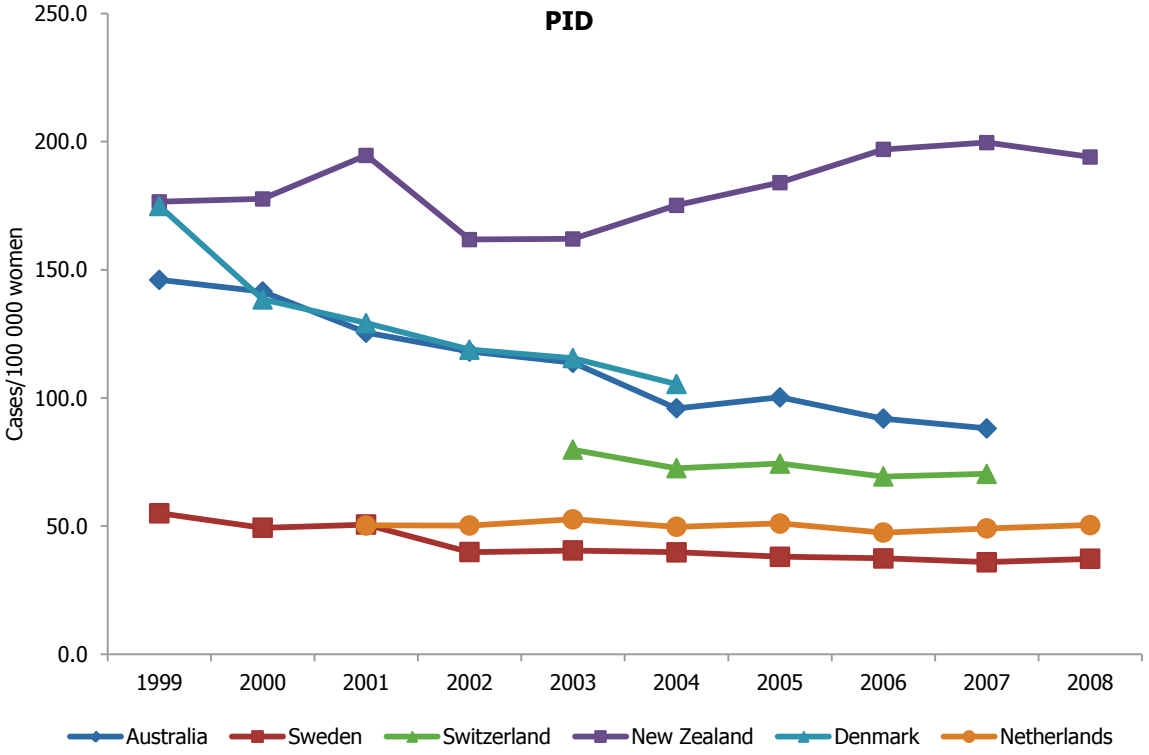
Trends in the incidence of reproductive complications of chlamydia infection

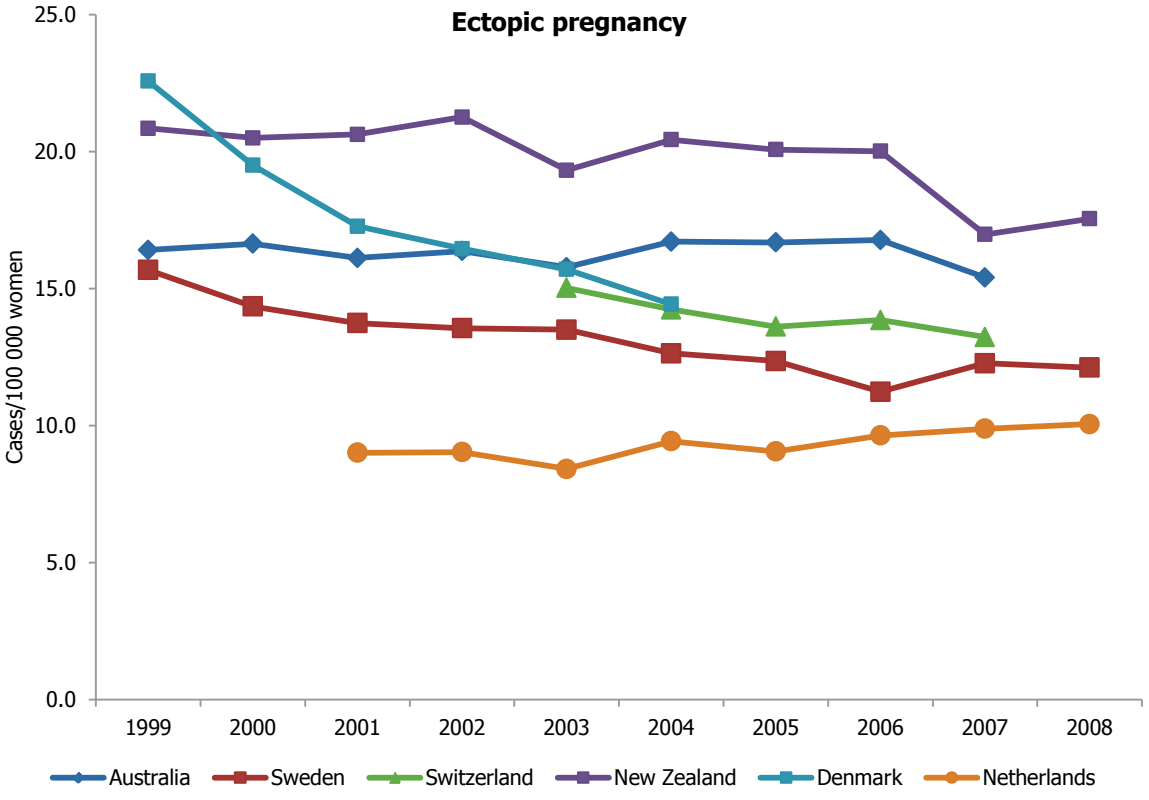
Data from national surveillance systems and hospital discharge registries can be obtained to examine trends in diagnoses of chlamydia and its complications in European countries. Data from Denmark, the Netherlands, Sweden and Switzerland (and Australia and New Zealand) from 1999–2008 were analysed to examine differences between countries in rates and trends of diagnosed chlamydia and chlamydia-associated complications (Figure 17) [114]. Differences between registries, diagnosis and recording, and clinical management need to be taken into consideration in the interpretation of these data. The least between country variation was seen with ectopic pregnancy rates (1.5 fold difference between European countries) and PID rates (3-fold). The greatest variation was seen with diagnosed infertility rates (200-fold difference between European countries). It is more likely that these differences reflect patterns of treatment seeking and health care provision and funding rather than real differences in underlying incidence. International data about infertility obtained using consistent methods suggest that 1–2% of women aged 20–44 years do not achieve a live birth after who have stable levels of both primary and secondary infertility in Europe [171].

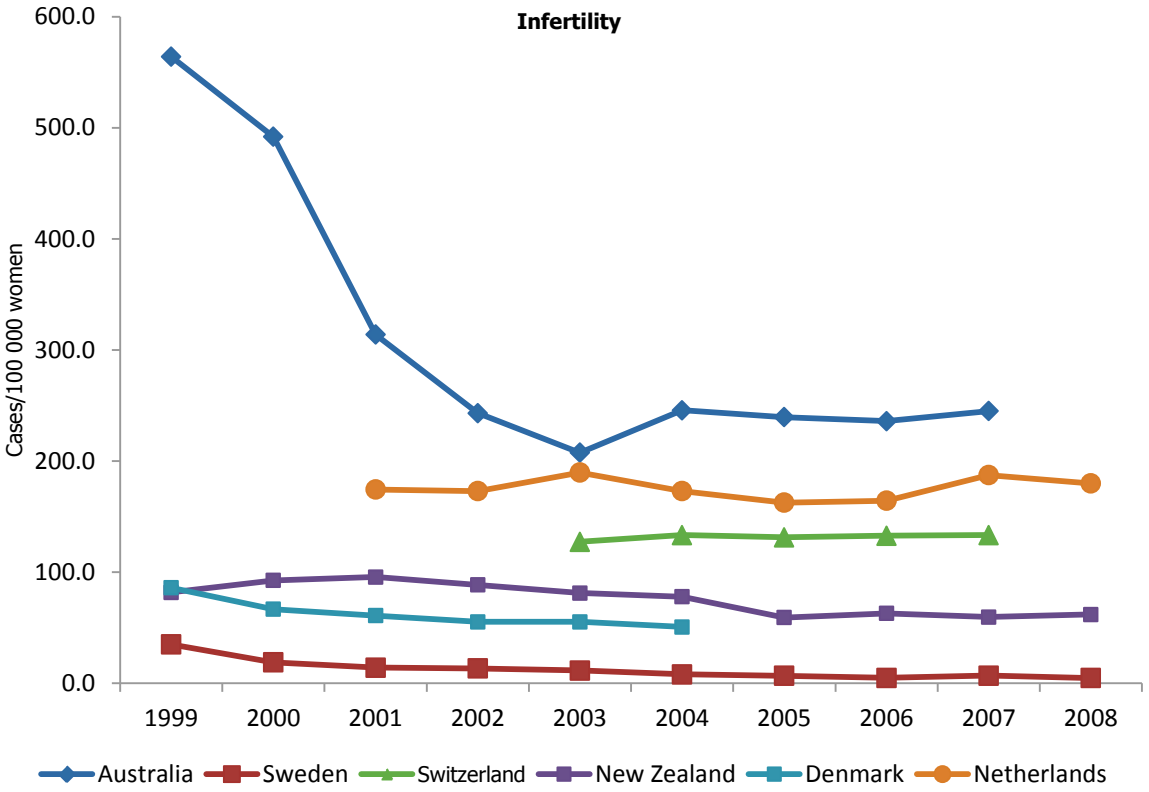
Overall, PID, ectopic pregnancy and infertility rates from all causes are stable or decreasing in the participating European countries (Figure 17).

Figure 17. Rates of *C. trachomatis* diagnosis, pelvic inflammatory disease (PID), ectopic pregnancy and female infertility in women aged 15–39 years 1999–2008, by country




PID
250.0
200.0
150.0
100.0
50.0
0.0
Cases/100 000 women
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
Australia
Sweden
Switzerland
New Zealand
Denmark
Netherlands


Ectopic pregnancy
25.0
20.0
15.0
10.0
5.0
0.0
Cases/100 000 women
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
Australia
Sweden
Switzerland
New Zealand
Denmark
Netherlands



All data except for ectopic pregnancy are directly age-standardised using the European standard population.

Data about complications from all countries except New Zealand are from national hospital registries; data from New Zealand are from hospital registries of six counties. Diagnoses were made using pre-specified International Classification of Diseases codes.

Data from Sweden and Denmark include only overnight hospitalisations; the other countries include both overnight and day cases.

Assuming an average lag of 10–20 years, diagnoses of ectopic pregnancy or infertility that result from chlamydia would reflect chlamydia infections occurring from around 1989 to 1998. PID cases are more likely to be diagnosed contemporaneously with chlamydia infection. Declining rates of PID diagnosis in hospital and primary care settings have also been reported from England [115], Canada [113] and the USA [2].

4. Efficacy, effectiveness and cost effectiveness of chlamydia control interventions

Randomised controlled trials (RCTs) are the least biased research study design for measuring the causal effect of a health service intervention. The findings from high quality RCTs of chlamydia screening and linked economic evaluations are therefore needed to determine whether the benefits of a screening programme outweigh the harms at reasonable cost [172]. In this section of the report, empirical studies designed to measure the effectiveness of screening and modelling studies to estimate cost-effectiveness are reviewed.

Efficacy and effectiveness of chlamydia screening interventions

The most recent systematic review of the effectiveness of chlamydia screening programmes included randomised and non-randomised controlled trials published up to October 2007 [173,174]. The review concluded that there was an absence of evidence from controlled trials about the effects of opportunistic chlamydia screening on either the transmission of chlamydia or prevention of PID [173]. This review updates the findings of the earlier review with studies published up to August 2012.

Description of included studies

The search strategy identified 261 new items, of which 180 were unique publications (Appendix 2, Figure 25). After applying the inclusion criteria and combining with the results of the original search, there were 12 publications [37,40,44,45,47,131–133,175–177] relating to seven completed or ongoing trials, identified by citation to the primary publication. Of these, three trials were included in the original review [131,132,175] and four were identified in the updated search. Characteristics of the included trials are summarised in Table 14, Appendix 2. An additional ongoing trial in Finland was identified from expert input, but no published trial record or publication has been found yet and it is not referred to further.

Primary outcomes

Four completed trials were done in EU Member States (Denmark, The Netherlands and the UK) [40,47,132,133]. Five trials examined the incidence of clinically diagnosed PID as an outcome [40,47,131–133]. In two trials, PID was the primary outcome [131,133]. In one trial, chlamydia screening uptake was examined first and PID was an outcome in women agreeing to be followed up [132]. One trial was designed to investigate strategies for offering home sampling for chlamydia in a random sample of the population. Examination of reproductive tract outcomes was done by record linkage up to 11 years later [47]. PID was a secondary outcome in the trial by van den Broek at al. but only 20% of women provided self-reported information about PID diagnosis [40] and the results are not included.

Two completed [40,175] and one ongoing [177] trial examine the effect on chlamydia transmission with chlamydia positivity or prevalence as an outcome. There were four individually randomised controlled trials, two cluster randomised controlled trials and two controlled trials with non-random methods of allocation to clusters.

Secondary outcomes

The searches did not find any trials of chlamydia screening in pregnant women at antenatal clinics or trials that reported on adverse effects of screening to the participant (psychological distress, partner violence, relationship breakdown), adverse pregnancy outcomes, or neonatal morbidity or mortality. Only one trial reported on the secondary outcomes ectopic pregnancy, female infertility and epididymitis in men (Andersen 2011), and did not find any difference between the screening and control groups. Therefore we report results in detail below, for primary outcomes only.

Risk of bias in included trials

There was a high risk of bias in the methods described by the authors in at least one domain for all included trials except Oakeshott et al. and Andersen et al. (Table 4). There was a risk of selection bias, based on criteria suggested by the Cochrane Collaboration, in the methods of both non-randomised trials. In the trial by van den Broek et al., allocation of clusters to intervention and control groups was not at random, but other measures were taken to reduce the risk of bias [40]. First, the identity of the clusters was masked before allocation. Second, the order of roll-out of the screening invitations was randomised and third, analysis of the primary outcome, adjusting for baseline differences, was the same as the crude analysis. In the trial by Cohen et al. the risk of selection bias was higher [175]. Chlamydia screening was introduced first in three schools (intervention group) and then, after two years, into a further five schools (control group). The demographic characteristics of the schools were reported to be similar in each group, but there might have been differences in unmeasured individual, school or area level characteristics that might have influenced the outcome. In the trial by Scholes et al., the process of random sequence generation was not described.

There is a high risk of selection bias in the enrolment process in the trials by both Scholes et al. and Østergaard et al. as participants were randomised before enrolment [131,132]. Scholes et al. randomised women before ascertaining eligibility and enrolled women in the intervention group more actively than those in the control group. Østergaard et al. enrolled students after they knew which group they were in. In both trials the ratios of participants in intervention and control groups were distorted. There was a high risk of attrition bias in two trials in which <60% were analysed (Table 4). In the trial by Østergaard et al. there was also a risk of detection bias because outcome assessment was not blinded.

Table 4. Risk of bias in methodology of trials of the effectiveness of chlamydia screening

Outcome, first author, publication year	Selection bias, randomisation *	Selection bias, allocation *	Performance bias*	Detection bias*	Attrition bias*	Reporting bias*	Other biases* †
PID incidence							
Scholes, 1996 [131]	Unclear	High risk	High risk	Unclear	High risk	Unclear	Unclear
Ostergaard, 2000 [132]	Low risk	High risk	Low risk	Unclear	High risk	High risk	Unclear
Oakeshott, 2010 [133]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Unclear
Andersen, 2011 [47]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Unclear
Chlamydia transmission							
Cohen, 1999 [175]	High risk	High risk	Low risk	Low risk	High risk	Low risk	None
van den Broek, 2012 [40]	High risk	High risk	Low risk	Low risk	Low risk	Low risk	None
Hocking, 2011 [177]	Low risk	Low risk	Low risk	Low risk	NA	NA	None

** From Cochrane Collaboration risk of bias assessment tool [17]*

† Refers to diagnostic ascertainment bias

NA, not applicable, no results available yet

There is a risk of bias in all trials with PID as an outcome, even if assessment is blinded. Diagnostic ascertainment bias can occur if the physician assessing a woman with lower abdominal pain knows that she has been screened for chlamydia and/or knows the result of a test. The direction of the bias is unknown, however. Knowledge of a previous positive chlamydia test result might make a PID a more likely diagnosis, which would underestimate an effect of a screening intervention that detects more cases in the intervention than the control group. On the other hand, knowing that a woman has been screened and treated for chlamydia might make PID a less likely diagnosis if the physician thinks that early treatment will have reduced the risk of PID.

Effect of chlamydia screening on PID incidence

Study populations and intervention uptake

In four RCTs that reported the effect of chlamydia screening on the incidence of PID, [131] the chlamydia screening intervention was done on a single occasion. Two of these RCTs included women only [131,133] and two included both women and men [47,132]. Data from 21 373 women (206 PID events) were analysed for the primary outcome.

Table 5. Uptake of chlamydia screening in intervention and control groups in RCTs with PID incidence as an outcome

First author, publication year [ref]	Enrolment procedure	Uptake in intervention	Uptake in control
Scholes, 1996 [131]	Randomisation of individuals (1 intervention: 2 control); questionnaire sent to all randomised; respondents fulfilling criteria for high risk of chlamydia invited.	36 457 randomised 20 836 responded 3 111 at high risk, 2607 agreed	
		1 009 enrolled 645 (64%) screened	1 598 enrolled Number screened not known
Østergaard, 2000 [132]	Randomisation of schools (1:1); intervention students given home sampling kit, control students offered GP testing; questionnaire given to all; respondents fulfilling criteria for sexual experience included.	5 487 randomised	
		2 603 offered 1 254 responded 928 sexually active 867 (93%) screened 443 followed up	2 884 offered 1 097 responded 833 sexually active 63 (8%) tested 487 followed up
Oakeshott, 2010 [133,178]	Students enrolled and provided sample; randomisation of individuals (1:1); both groups offered opportunistic STI clinic testing if at risk or symptomatic.	Number approached not known 2 563 screened and randomised	
		1 259 (100%) immediate screening 269 (21%) opportunistic test 1 191 followed up	1 270 (0%) immediate screening 258 (20%) opportunistic test 1 186 followed up
Andersen, 2011 [47]	Intervention group sampled from health service register (~1:4); intervention group randomised to two home sampling strategies. Control group not contacted but had access to testing at GP and STI clinics.	15,459 women of eligible age	
		4 000 women invited 1 175 (29%) home-sample 255 (6%) opportunistic test only Followed up through registers	11 459 women 0 (0%) offered screening 1 076 (9%) opportunistic test Followed up through registers

GP, general practitioner; STI, sexually transmitted infection

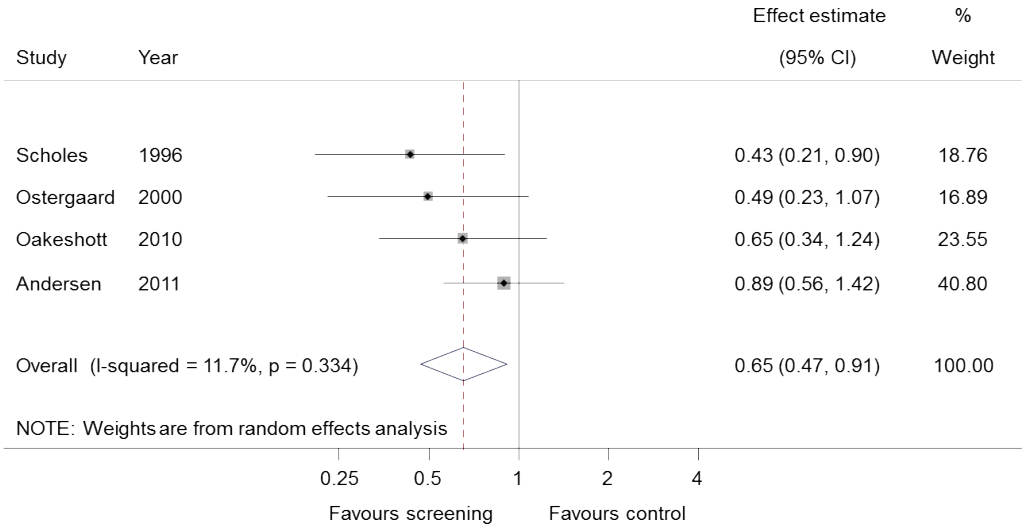
The design of the intervention and uptake affects the measure of association in different trials. Oakeshott et al. evaluated the efficacy of a once-off chlamydia screening test in their trial, which was the only one in which all participants were screened for chlamydia as a condition of enrolment [133]. Women were then randomised to having their specimens tested immediately (with treatment of positive cases) or having their specimens tested after one year (deferred testing and treatment).

Scholes et al. [131] and Østergaard et al. [132] evaluated the efficacy of the offer of a once-off chlamydia screening test. Individuals or schools were randomised first and then assessed for eligibility. The outcome was examined only in participants that responded to a questionnaire to identify those who were sexually active, or had additional markers of risk for chlamydia. The trial by Andersen et al. differed because the intervention was implemented under more realistic conditions [47]. Individuals were selected from the general population at random and either sent a home sampling kit or a card, which they had to send off to request a kit. No reminders were sent. Only participants in the intervention group were actively enrolled and 29% were tested.

Effect of screening on PID incidence

All four RCTs assessed the incidence of symptomatic PID one year after the intervention by self-report, chart review, or record linkage. All trials found fewer cases of PID in the intervention than the control group. The pooled average risk ratio of PID in the intervention compared with the control group was 0.64 (95% CI 0.45, 0.90) and there was very little statistical heterogeneity between trial results (Figure 18).

Figure 18. Results of four RCTs of chlamydia screening; cumulative one-year incidence of all cause PID in women offered screening compared with control groups



Results of each individual trial shown as solid black diamond, with 95% CI shown by lines either side. Overall estimate shown as diamond with point estimate at the vertical points and 95% CI as the horizontal extremes. The dotted line runs through the overall point estimate. Pooled estimate obtained from random effects meta-analysis.

Effect of chlamydia screening on chlamydia transmission

The two trials that evaluated the effect of chlamydia screening on chlamydia transmission measured effectiveness, rather than efficacy, because they evaluated multiple screening rounds in pragmatic settings under 'real-life' conditions.

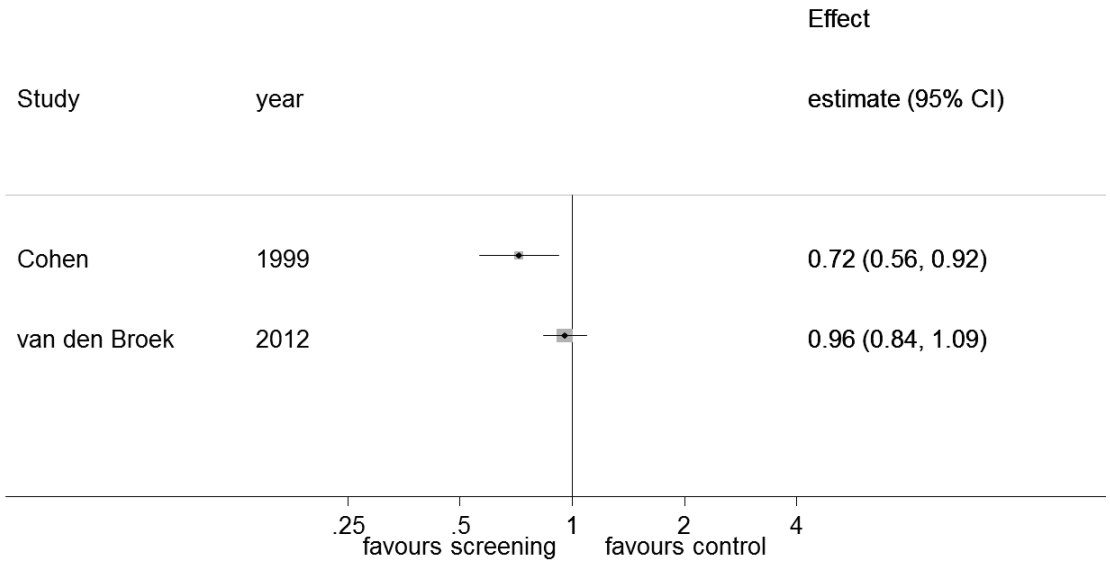
Study populations and intervention uptake

Both trials included both women and men. Both allocated clusters (schools or postcode areas) to intervention or control groups, which is appropriate for studying the effects of an intervention to control a communicable disease. In both trials screening was introduced earlier in intervention than control clusters. In both trials the percentage of positive chlamydia tests was compared between intervention clusters after two or three screening rounds and control groups at the first screening round.

The interventions and uptake of screening differed in the two trials. Cohen et al. introduced chlamydia screening in selected schools in New Orleans, USA beginning in the school year 1995-96 [175]. In the first three schools, all students in 9th to 12th grades (aged 15–18 years) were invited twice a year for two years. Participants, irrespective of sexual experience provided urine specimens at school during three-week testing periods. In the third year, students in both intervention and control schools were invited once. Amongst all students on the school register in intervention schools, 56% were tested in year 1 and 65% in year 2. In year 3, 52% in both intervention and control schools were tested. Van den Broek et al. studied chlamydia screening in the general population in three regions of the Netherlands [40]. Yearly invitations were sent by post to all 16–29 year olds listed on municipal registers, inviting them to log onto a website. In Amsterdam and Rotterdam, all sexually experienced respondents were asked to request a home sampling kit. In South Limburg, only those fulfilling specified risk criteria could take part. Amongst all those on the municipal register in intervention clusters, 16% were screened in year 1, 11% in year 2 and 10% in year 3. In the control clusters, 13% were screened in year 2.

The results of the two trials differed (I^2=75%) and were not pooled (Figure 19).

Figure 19. Results of two non-randomised controlled trials of annual chlamydia screening; chlamydia positivity in intervention groups offered yearly screening compared with control groups



Results of each individual trial shown as solid black diamond, with 95% CI shown by lines either side.

Cohen et al. found that overall chlamydia positivity decreased in intervention schools and was lower after five screening rounds (6.7%, 77/1150) than in control schools tested for the first time (9.3%, 247/2653, risk ratio 0.72 (95% CI 0.56, 0.92) Results presented separately by sex showed that the reduction in intervention schools was seen in boys (5.9%, 34/575 in the first round in year 1 and 3.2%, 19/588 in year 3, p=0.028) but not girls (12.1%, 62/513 in the first round in year 1 and 10.3%, 58/562 in year 3, p=0.359). The incidence also decreased in boys (4.5% from round 1-2 and 3.2% from round 4–5) but not girls (7.2% and 11.4%, respectively) [175]. Van den Broek et al. found no change in chlamydia positivity in intervention clusters after three screening rounds (4.1%) compared with control clusters at the first screening round (4.3%, risk ratio 0.96, 95% CI 0.84, 1.09).[40] There was no sex difference in positivity at baseline or change in positivity over time.

GRADE summary of findings and quality of evidence

The GRADE system was used to rate the quality of the evidence about the effects of chlamydia screening on preventing PID and reducing chlamydia transmission [21]. The question to be addressed was formulated, as required by the GRADEPro software [22], as a question about a healthcare decision. This differs from the systematic review questions. Two critical outcomes were assessed; PID and chlamydia positivity (Tables 6 and 7).

Table 6. GRADE assessment of quality of evidence for chlamydia screening effects

Author(s): ECDC Chlamydia Control in Europe project
Date: 2012-12-31
Question: should chlamydia screening vs. usual care be used in sexually active adults <30 years?
Settings:
Bibliography: ECDC Chlamydia Control in Europe project

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chlamydia screening	Usual care	Relative (95% CI)	Absolute	Quality	Importance
Pelvic inflammatory disease (follow-up 12 months: assessed with: Physician diagnosis or self-report)												
4	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	none	56/6 643 (0.84%)	150/14 730 (1%)	RR 0.64 (0.44–0.9)	4 fewer per 1 000 (from 1 fewer to 6 fewer)	moderate	critical
% positive chlamydia test results (follow-up 3 years; assessed with: Nucleic acid amplification test)												
2	Observational studies[2]	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Dose response gradient[4]	1 058/26 092 (4.1%)	514/8 876 (5.8%)	Not pooled	Not pooled	low	critical

[1] *Evidence includes randomised trials (Scholes et al. Ostergaard et al.) with a high risk of bias in methods*
[2] *Cohen et al. compared chlamydia positivity in non-randomly selected groups of schools with a high risk selection bias; van den Broek et al. was a non-randomised controlled trial with randomised wedge implementation.*
[3] *Cohen et al. had high screening uptake and found a reduction in prevalence in boys, not girls; van den Broek et al. had low screening uptake and found no evidence of a change between intervention and control areas.*
[4] *Cohen et al found a reduction in prevalence with high uptake; van den Broek found no reduction with low uptake.*

For the outcome PID the GRADE tool found moderate quality evidence of efficacy from four RCTs that chlamydia screening reduces the incidence of PID when compared to control groups receiving usual care. The estimated absolute risk reduction was four cases of PID from any cause per 1 000 women screened (Table 7). The level of evidence was downgraded from high to moderate because of the high risk of selection bias in the methods used in the earliest trials [131,132].

For the outcome of a change in chlamydia positivity, the GRADE tool found low quality of evidence from two effectiveness trials [40,175]. The quality of evidence from non-randomised study designs begins as low. The risk of selection bias, which was greatest for the trial by Cohen et al. [175], was a factor that downgraded the quality, but this was balanced by the finding of a dose response relationship in the effects of the two trials. The footnotes in Tables 6 and 7 give explanations about the features of each trial that contribute to the overall quality of the evidence.

Table 7. GRADE summary of findings table

Chlamydia screening compared to usual care for sexually active adults <30 years
Patient or population: sexually active adults <30 years
Settings:
Intervention: chlamydia screening
Comparison: usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% ci)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Usual care	Chlamydia screening				
Pelvic inflammatory disease Physician diagnosis or self-report Follow-up: 12 months	10 per 1 000	7 per 1 000 (5–9)	RR 0.64 (0.45–0.9)	21 373 (4 studies)	Moderate[1]	
% positive chlamydia test results Nucleic acid amplification test Follow-up 3 years	See comment	See comment	Not estimable	34 968 (2 studies)	Low[2,3,4]	

**the basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

CI: confidence interval; RR: risk ratio

GRADE: working group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: we are very uncertain about the estimate

[1]Evdience includes randomised trials (Scholes et al. Ostergaard et l.) with a high risk of bias in methods
[2]Cohen et al. compared chlamydia positivity in non-randomly selected groups of schools with a high risk selection bias; van den Broek et al. was a non-randomised controlled trial with randomised wedge implementation.
[3]Cohen et al. had high screening uptake and found a reduction in prevelence in boys, not girls; van den Broek et al. had low screening uptake and found no evidence of a change between intervention and control areas.
[4]Cohen et al found a reduction in prevelence with high uptake; van den Broek found no reduction with low uptake.

Cost-effectiveness of chlamydia screening programmes

The cost per quality-adjusted life year (QALY) is the measure for comparing the cost-effectiveness of interventions for different conditions that is recommended by most governments. The impact of a disease on quality of life is quantified as utility values [179]. Utility values indicate the desirability of different health states and are measured in a variety of ways such as the 'time trade-off', which measures preferences for a shorter but healthier life. Utilities are measured on a scale from 0 (dead) to 1 (perfect health) and QALYs are calculated by multiplying the years of life in a health state by the utility of the health state. Within a cost-effectiveness study incremental cost-effectiveness ratios are used to present the cost per QALY of one intervention compared to an alternative.

The cost-effectiveness of chlamydia screening cannot be measured using the cost per QALY gained by preventing cases of chlamydia because undiagnosed asymptomatic infections do not affect quality of life. The complications of chlamydia are also rarely fatal. The impact of chlamydia is therefore mainly through morbidity and decreases in quality of life resulting from PID and its sequelae [180].

The most recent systematic review of cost-effectiveness evaluations of chlamydia screening included 29 studies of opportunistic or register-based chlamydia screening up to August 2004 [23]. Only one of the included studies presented the results in terms of cost per QALY and only two studies used a transmission dynamic model, which is required for modelling the effects of interventions against infectious diseases that affect the prevalence of infection [181]. This review updates the earlier review.

Description of included studies

As of February 2012, 10 studies (11 publications) that reported the cost-effectiveness of chlamydia screening interventions with the outcome expressed as cost per QALY were included [117,130,182–190] (Appendix 3, Figure 26). The characteristics of all included studies are summarised in Table 8. Two studies in this review [117,182] were also included in the earlier systematic review [23]. Four studies were from EU Member States (Ireland [188], the Netherlands[184], Sweden [185] and the UK [117]). Nine studies examined opportunistic screening approaches and one examined a school-based register based program. Three studies (four publications) examined chlamydia screening amongst women only (USA [130,182,183] and Australia [190]) and all others examined the introduction of screening to both women and men or the addition of screening in men to existing screening in women [187]. In six studies, NAAT were used for diagnosis; in the other four studies, no diagnostic test was specified.

Table 8. Summary of characteristics of studies of the cost-effectiveness of chlamydia screening, by publication date

First author, country [ref]	Screening approach, gender, age	Viewpoint	Data sources	Costs, currency, year, discount %	Chlamydia diagnostic test	Primary outcome
Hu, 2004, 2006 USA [182,183]	Annual opportunistic Women only 15-29 years	Modified societal	Literature	US$, 2000 Discount rate not reported	NAAT, urine sample	Incremental cost per QALY gained
Adams, 2007 UK [117]	Annual opportunistic Men and women <25 years	Health service	Standard cost data and published studies	£, 2004 3.5%	NAAT, urine or self-collected vulvo-vaginal swab	Incremental cost per QALY gained
de Vries, 2008 Netherlands [184]	Repeated vs. one-off opportunistic. Men and women 15-29 years	Societal	Literature, except probability of PID (0.2)	€, 2002 4%	NAAT, urine samples pooled by five	Incremental cost per QALY gained
Deogan, 2010 Sweden [185]	One-off opportunistic (Chlamydia Monday) Men and women, age not reported	Societal	Literature	€, 2007 3%	Test not described, urine sample	Incremental cost per QALY gained
Fisman, 2008 USA [186]	Annual school-based Philadelphia (PHSSP) Men and women, age not reported	Modified societal	Literature	US$, 2005 3%	NAAT	Incremental cost per QALY gained
Gift, 2008 USA [187]	Single opportunistic, variety of venues. Men only, age not reported	Societal	Literature	US$, 2006 3%	NAAT, urine samples	QALY losses, Incremental cost per QALY gained
Gillespie, 2012 Ireland [188]	Annual opportunistic, three types of healthcare facilities Men and women, 18-29 years	Societal	Irish chlamydia screening initiative	€, 2008 3.5%	NAAT, urine samples or endocervical swab	Incremental cost per MOA and QALY gained
Smith, 2007 USA [130]	Opportunistic, different screening intervals High risk young women, age not reported	Not stated	Literature (GIFT Study)	US$, 2004 3%	Not described	Incremental cost per QALY gained
Tuite, 2012 Canada [189]	Annual opportunistic, Men and women, 10-39 years	Modified societal	Literature and model calibration	Can$, 2009 3%	NAAT, sample not described	Incremental cost per QALY gained
Walleser, 2006 Australia [190]	Annual opportunistic Women under 25 years	Health service	Literature and expert opinion	Aus$, year not stated 5%	NAAT, sample not described	Incremental cost per QALY gained

GIFT, Gynaecological Infections Follow-Through study; MOA, major outcome averted; NAAT, nucleic acid amplification test; PHSSP, Philadelphia Schools Screening Program; PID, pelvic inflammatory disease; QALY, quality-adjusted life year.

Assessment of health utilities

Health gains associated with chlamydia screening interventions were assessed in all studies using QALYs (Table 10). The impact on quality of life of symptomatic chlamydia infection and its complications was based on the same main source in all studies. An expert panel of the US Institute of Medicine assigned values for a variety of symptomatic conditions associated with chlamydia infection using the Health Utilities Index Mark II [191] (Appendix 3,Table 15). Smith et al. conducted a study of quality of life utilities after PID and compared the findings in women with and without a history of PID. Findings from Smith et al. informed the QALY weights in one study included in this review. Mean values of QALY weights obtained through the time trade-off approach were generally higher than those found in the Institute of Medicine study.

Table 9. Chlamydia-associated reproductive tract conditions and QALY weights used in cost-effectiveness analyses

Study, country	Source of QALY weights	Chlamydia-associated conditions	Comment*
Hu, 2004, 2006 USA [182,183]	IoM [191]	Cervicitis, PID, EP, TFI, CPP	Values adapted from IoM; PID, EP, outpatient only; CPP limited to 5 years.
Adams, 2007 UK [117]	Not stated	PID, EP, TFI	Values not published. Assumed to be based on IoM study.
de Vries, 2008 Netherlands [184]	IoM [191]	PID, EP, TFI, CPP	Values not published.
Deogan, 2010 Sweden [185]	IoM [191]	Cervicitis, PID, EP, TFI, CPP	Values as published by IoM.
Fisman, 2008 USA [186]	IoM [191]	PID, EP, TFI, CPP	Estimate that PID results in downstream loss of 1 QALY due to TFI and CPP.
Gift, 2008 USA [187]	IoM [191]	Cervicitis, PID, EP, TFI, CPP	Values differ slightly from IoM; duration CPP limited to 5 years, TFI 10 years.
Gillespie, 2012 Ireland [188]	IoM [191], Smith [180]	PID, EP, TFI	QALY losses estimated from two studies; PID 0.008, EP 0.010, TFI 0.871 (calculation not explicit).
Smith, 2007 USA [130]	IoM [191], Songer [192]	Symptomatic infection, PID, complication	Symptomatic infection same QALY weight as cervicitis in IoM study; durations of conditions not given.
Tuite, 2012 Canada [189]	Smith [180] IoM [191]	PID, EP, TFI, CPP	Base case QALY weights from Smith [180]; sensitivity analysis weights from IoM.
Walleser, 2006 Australia [190]	IoM [191]	PID, EP, TFI, CPP	'based on expert-based estimates using the Health Utility Index.' EP minimum lag 3 years; no lag for CPP or TFI.

CPP, chronic pelvic pain; EP, ectopic pregnancy; IoM, US Institute of Medicine study [190]; PID, pelvic inflammatory disease; QALY, quality-adjusted life year; TFI, tubal factor infertility.

** Comments give clarifications about source of QALY weights and durations of conditions compared with Institute of Medicine study, for which data for all chlamydia-associated conditions are given in Table 15.*

Table 9 shows the conditions, QALY weights and durations for which they were applied in each included study. All studies considered PID as a consequence of chlamydia infection and all also explicitly considered ectopic pregnancy and tubal factor infertility, except Smith et al. who mentioned 'complications' [180]. In addition, four studies assigned QALY weights to cases of symptomatic lower genital tract infection (0.90 for four weeks) [130,182,185,187] and six included chronic pelvic pain (0.60 for five years to remainder of life) [182,184,185,187,189,190].

Models used

Table 10 summarises characteristics of the modelling and cost-effectiveness analyses and results. Six studies used a transmission dynamic model in which screening and treatment of chlamydia infections can lead to a reduction in chlamydia infection prevalence over time and this also affects the number of sequelae of infection [117,184,186–189]. Of the dynamic models, one was an individual-based model used in two studies [117,188], which represents partnership formation, duration and separation explicitly. This takes into account individual level effects of successful partner notification (additional infections prevented) and re-infection (additional infections caused) [117,188]. The other studies used compartmental models [184,186,187,189], which assume that sexual contacts are instantaneous events within groups stratified by age and sexual activity. One model was used in two studies [186,189]. These models cannot fully take into account the impacts of partner notification and re-infection and tend to overestimate the effect of chlamydia screening on preventing transmission [193]. The other models used were Markov state-transition models in three studies [130,182,183,190] and a static decision analysis in one study [185]. These models assume that chlamydia prevalence does not change over time.

Table 10. Summary of model, selected base case parameter values and results, by publication year

Study, country	Model used, selected features; complications, sensitivity analysis	Selected base case parameters: screening uptake; chlamydia prevalence; probability of PID; cost of PID treatment	Results, authors conclusions
Hu, 2004, 2006 USA [182,183]	Markov state-transition model from chlamydia to complications. 6-month cycle. 1- and 2-way sensitivity analysis.	Screening uptake 100% for all strategies based on annual screening. Chlamydia prevalence 6%. Probability of PID 30%; CPP 18% after PID. Costs: outpatient PID US$490; inpatient PID US$4715; TFI US$5000.	'Annual *C. trachomatis* screening… is very cost-effective…' Annual screening 15-29 years followed by semi-annual screening for those with history of chlamydia most cost-effective; cost per QALY US$7490. ICER >US$50000 if PID probability <6%.
Adams, 2007 UK [117]	Stochastic individual based, sexual network model for chlamydia transmission. Decision tree for complications. Partner change very high in youngest (>8/year) Multivariable sensitivity analysis.	Screening uptake 50% based on annual screening. Chlamydia prevalence not reported. Probability of PID varied 0.01, 0.1, 0.3. Costs: PID £137; TFI £10798.	'All three screening strategies modelled are likely to cost the NHS money and improve health. If PID progression is less than 10% then screening at any level is unlikely to be cost-effective.' Screening men and women <20 years most cost-effective. ICER £14,371 per QALY gained if PID probability 10%.
de Vries, 2008 Netherlands [184]	Deterministic SIS model for chlamydia transmission. Decision tree for complications. Univariable sensitivity analysis.	Screening uptake 47% women, 33% men; interval varied from once-off or every 1, 2, 5, 10 years. Chlamydia prevalence 1.8%. Probability of PID 20%; CPP 18% after PID. Costs: outpatient PID €70; inpatient PID €4085; outpatient TFI €841; inpatient TFI €2420; IVF €3138.	'…with the exception of screening every year, incremental cost-effectiveness stays below the informal Dutch threshold of €20,000 per QALY.' Screening men and women 15-29 years every 2 years most cost-effective. ICER €6539 per QALY gained. Annual screening ICER €33469.
Deogan, 2010 Sweden [185]	Static decision tree. Sensitivity analysis shows model valid for changes in variables.	Screening uptake not known. Results based on 1480 people tested. Chlamydia prevalence 8%. Probability of PID 20%; CPP 16.5% after PID. Costs: outpatient PID €661; inpatient PID €2029; TFI €3105.	'Main result showed a discounted cost of €8346 per QALY, well below the Swedish point of reference of €50,000 per QALY.'
Fisman, 2008 USA [186]	Deterministic SIRS model for chlamydia transmission and progression to PID. Duration of infection 3.5 months; immunity 24 months after untreated chlamydia; partner change rates not explicitly presented. Sensitivity analysis not described.	Screening uptake 35%. Chlamydia prevalence 8% girls, 2% boys. Probability of PID 10%; CPP not reported. Costs: not reported.	'The current PHSSP is highly cost-effective relative to other commonly accepted interventions. Effectiveness and cost-effectiveness of this program are enhanced by including males.' Cost per QALY US$2000-3000.

Study, country	Model used, selected features; complications, sensitivity analysis	Selected base case parameters: screening uptake; chlamydia prevalence; probability of PID; cost of PID treatment	Results, authors conclusions
Gift, 2008 USA [187]	Deterministic model, Susceptible-Exposed-Infected-Sequelae. Partner change very high in core group (13/year men, 33/year women) 1- and 2-way sensitivity analysis.	Screening uptake 35% women, 1% men (high-risk; more partners, higher chlamydia prevalence). Chlamydia prevalence 2.9% women, 2.3% men. Probability of PID 15%; CPP 18% after chlamydia. Costs: PID US$175 (program), $2458 (societal); TFI not included in model.	'A program targeting high-risk men for screening… was cost saving compared with using equivalent program dollars to expand screening of lower-risk women.' ICER for expanding screening amongst women US$36948/QALY gained; screening men and women was cost saving compared to this.
Gillespie, 2012 Ireland [188]	Model adapted from Adams [117]). Partner change high in youngest (>8/year); infection duration 6 months. Multivariable sensitivity analysis.	Screening uptake 48% women, 22% men. Chlamydia prevalence: 8-9% 16-19 year olds. Probability of PID 10%. Costs: PID and TFI treatment not reported.	'The modelled screening scenario was projected to be more effective and more costly than the control strategy... For cost-effectiveness threshold values of €45 000 per QALY gained and lower, the probability of the screening being cost effective was estimated at <1%.' ICER cost per QALY gained €94717 compared with no screening.
Smith, 2007 USA [130]	Markov state-transition model for the natural history of PID. 1 month cycle. Variable time to PID development. High risk women. 1- and multi-way sensitivity analyses	Screening uptake 60%. Chlamydia incidence 6% per year. Probability of PID 30% in first month. Costs: PID US$2359.	'Relative to 12-month screening, 6-month screening decreases PID cases from 6.0% (1 month development time) to 19.4% (12 months).' ICER cost per QALY gained compared with the other strategies varies from $16,600 (12 months development time) to $31,800 (1 month) for high-risk women.
Tuite, 2012 Canada [189]	Deterministic SIRS model, adapted from Fisman [186]. Immunity 6 months after untreated chlamydia. Partner change rates not explicitly presented. 1- and multi-way sensitivity analyses.	Screening uptake increased from 0.2% to 10%. Chlamydia prevalence: 1.7% women, 0.8% men. Probability of PID: 10%; CPP 18% after chlamydia. Costs: symptomatic PID Can$1780.	'Compared with no change in screening, enhanced screening was estimated to be highly cost-effective, with an incremental cost-effectiveness ratio of $2910 per QALY.' Model projects increasing prevalence of chlamydia to 4.8% women, 2.6% men by 2009.
Walleser, 2006 Australia [190]	Markov state-transition model. 1 year cycle 1- and multi-way sensitivity analyses.	Screening uptake 40%. Chlamydia prevalence: 3.5% women. Probability of PID: 15% subclinical, 10% clinical; CPP 3% per year after PID. Costs: outpatient PID Aus$348; inpatient PID Aus$4741; TFI Aus$5093/year.	'Annual opportunistic screening for chlamydia in women under 25 is a potentially worthwhile undertaking.' ICER per QALY Aus$2968 for screening compared with no screening.

CPP, chronic pelvic pain; ICER, incremental cost-effectiveness ratio; IVF, in vitro fertilisation; PID, pelvic inflammatory disease; PHSSP, Philadelphia Schools Screening Program; PN, partner notification; QALY, quality-adjusted life year; SIS, susceptible-infected-susceptible; SIRS, susceptible-infected-recovered-susceptible; TFI, tubal factor infertility.

Smith et al. investigated the uncertainty about the timing of the development of PID after lower genital tract STI and the impact on the cost-effectiveness of combined chlamydia and gonorrhoea screening [130]. Screening resulted in more cases of PID prevented as the interval between infection and PID development increased from 1 to 12 months. In women at high risk of STI, screening was cost-effective irrespective of the PID development interval. The model predicted a higher cost per QALY gained in populations with a lower risk of STI (<5%), particularly with shorter PID development times. Most studies did not explicitly state assumptions about the time to PID development. In the model developed by Fisman et al. [186]and Tuite et al. [189], PID was assumed to occur at the mid-point of untreated infection. In Hu et al. the six month cycle of the Markov model suggests that PID occurs six months after initial chlamydia infection [182].

Cost-effectiveness findings

Authors of all studies, except the study from Ireland [188], concluded that at least one chlamydia screening strategy would be cost-effective at nationally accepted thresholds (Table 10).

Studies based on static models that reported the most favourable costs per QALY gained, tended to assume high chlamydia screening uptake, high baseline chlamydia prevalence and high estimates of the percentage of women experiencing complications of chlamydia. Hu et al. assumed that adherence to annual opportunistic screening by US women would be 100%, 30% of untreated women would develop PID and included health gains from cases of chronic pelvic pain prevented [182,183]. Smith et al. explicitly investigated a population of women at high risk of STI and implemented chlamydia screening in 60%, with 30% of untreated women developing PID [130]. Walleser et al. assumed chlamydia screening uptake of 40%, 25% of women would develop PID and infertile women desiring pregnancy would receive IVF annually for up to five years [190].

Studies based on dynamic models gave more variable findings. Dynamic models involve complex interactions that depend on assumptions about the sexual network and chlamydia transmission dynamics as well as progression to complications. The studies reporting the lowest and highest cost-effectiveness ratios for chlamydia screening, compared with no screening, were obtained from dynamic models. Fisman et al. reported a cost of $2 000–3 000 per QALY gained for annual high-school based screening in young men and women, based on a compartmental model [186]. Gillespie et al. found that annual opportunistic screening of men and women aged 18–29 years in health care settings would cost €94 000 per QALY gained using an individual based model [188]. In both models, chlamydia screening and treatment predict a strong impact on chlamydia prevalence because the turnover of infection in the population is high (short duration of untreated chlamydia in both and high rates of partner change in Gillespie et al).

Cost-effectiveness analyses were sensitive to assumptions about the probability of complications, which are known to be uncertain. Adams et al. reported their base case scenario for probabilities of PID 1%, 10%, 30% and found that annual opportunistic chlamydia screening strategies could not be cost-effective if the probability was less than 10% [117]. Hu et al. reported that incremental cost-effectiveness ratios would exceed $50 000 per QALY gained if the probability of PID was less than 6% (30% in base case). Tuite et al., however, reported an incremental cost-effectiveness ratio <$50 000 even when the probability of PID was 1% [189].

Dynamic modelling studies that reported lower cost effectiveness ratios were those that considered chronic pelvic pain as a complication of chlamydia infection (Table 10). These studies assumed a probability of chronic pelvic pain of 18% after chlamydia or after PID and applied a QALY weight of 0.6 for five years to the remaining lifetime of a woman. None of the included studies compared the cost per QALY gained with and without chronic pelvic pain.

5. Discussion

Summary of principal findings

- Ten EU/EEA Member States have conducted population-based cross-sectional surveys to measure the prevalence of chlamydia infection in a nationally representative sample of the population or in a sub-national sample of the population. Fourteen EU/EEA Member States have conducted cross-sectional surveys using non-population-based sampling methods. Three EU/EEA Member States have no study estimating chlamydia positivity or prevalence.
- Estimates of chlamydia prevalence in population-based studies varied by country, sex, age group, national or sub-national coverage and inclusion of all or only sexually experienced participants.
- Four EU/EEA Member States (France, Germany, Slovenia, UK) have reported findings from nationally representative surveys of sexually experienced adults ≤25 years, with response rates from 46 to 71%. Chlamydia point prevalence estimates in women aged 15–24 years ranged from 3.0% (18–24 year olds in UK) to 4.7% (18–24 year olds in Slovenia). Point prevalence estimates in men aged 15-24 years ranged from 0.4% (16–17 year olds in Germany) to 4.7% (18–24 year olds in Slovenia).
- Estimates of chlamydia prevalence in EU/EEA Member States were statistically consistent with those in other high income countries. In women the pooled average in six studies with available data in 15–26 year olds was 4.3% (95% CI 3.7, 5.0%) and in 5 studies with available data in men aged 18–26 years, 3.6% (95% CI 2.9, 4.3%). Chlamydia prevalence in one study in men under 18 years in Germany was lower than in men aged ≥18 years.
- Cross-sectional surveys with lower response rates are associated with higher estimates of chlamydia prevalence. Only two population-based surveys in this review had a response rate >70%.
- The probability of PID from any cause in asymptomatic women in the community with untreated chlamydia infection was estimated to be 9% (95% CI 4, 19%) after 12 months of follow up in one prospective study. This is lower than estimates from studies conducted in clinic settings.
- There is a strong association in prospective studies between chlamydia infection and pelvic inflammatory disease from any cause in women with both symptomatic and asymptomatic infection.
- The incidence of PID cases from all causes has fallen in many high income countries over time, from as early as 1975. The incidence of primary and secondary infertility in high income countries has remained stable since 1990.
- The proportion of tubal infertility cases that are caused by chlamydia has been estimated to be 45% (credible interval 28%, 62%) in a statistical modelling study that takes into account the sensitivity and specificity of serological tests for chlamydia antibodies.
- Chronic pelvic pain lasting of >six months has been reported in reviews of studies in 18% to 75% of women with PID compared with 5% to 25% of unaffected women. In one prospective study with up to seven years follow up after treatment for PID, 42% (328/789) women reported chronic pelvic pain.
- The pooled risk ratio of all cause PID after one year of follow up in women invited to have a chlamydia screening test was 0.64 (95% CI 0.45, 0.90, I^2=20%, 4 RCTs). In the three trials with >60% test uptake the pooled risk ratio was 0.52 (95% CI 0.34, 0.78, I^2=0%). In one trial with the lowest uptake the risk ratio was 0.89 (95% CI 0.56, 1.42). This is moderate quality evidence using the GRADE tool.
- Two non-randomised cluster controlled trials have examined the effect of chlamydia screening on chlamydia positivity over time. In three US high schools, overall chlamydia positivity (6.7%, 77/1150) after five screening rounds with uptake >50% was lower than in five control schools tested for the first time (9.3%, 247/2653, risk ratio 0.72 (95% CI 0.56, 0.92). In the Netherlands, three yearly screening invitations with uptake of 16% at the first round did not result in lower chlamydia positivity (4.1%) compared with control clusters at the first screening round (4.3%, risk ratio 0.96, 95% CI 0.84, 1.09).
- Ten studies in high income countries have reported on the cost-effectiveness of chlamydia screening interventions with the outcome expressed as cost per QALY gained. Most studies conclude that at least one strategy for chlamydia screening is cost-effective, based on nationally accepted thresholds. Assumptions about model structure and about the probability of complications of chlamydia in several studies tend to favour screening.

Chlamydia prevalence in the general population in Europe

The systematic review provides evidence about the estimated prevalence of chlamydia infection in EU/EEA Member States and other high income countries. Chlamydia prevalence estimates in nationally representative samples of sexually experienced 18–26 year olds were similar in women and men and statistically consistent between high income countries. Chlamydia prevalence estimates from population-based surveys conducted in sub-national populations in EU/EEA Member States were very heterogeneous. There might be true heterogeneity in chlamydia prevalence between different EU/EEA Member States. This could result from differences in sexual behaviours, practices and mixing, differences in access to health care and differences in chlamydia control activities. These differences cannot usually be disentangled from heterogeneity that results from differences in study design and conduct. There were differences between surveys in the objectives of the study, demographic groups included, in the survey response rate, in diagnostic methods, and in the representativeness of the study and source populations compared with the target population. There were too few studies available for most stratified analyses to be able to explain most of the heterogeneity.

Response rates in cross-sectional surveys of chlamydia prevalence tend to be low, in comparison with surveys estimating the prevalence of chronic diseases. The lowest response rates in national surveys were from specific surveys of chlamydia prevalence, e.g. CT-PILOT in the Netherlands, 41% [28]. The highest response rates were seen when specimens for chlamydia testing were taken as part of general health surveys, such as the NHANES[3] in the USA, 92% [92,93]. A response rate of 80% has been suggested as a criterion for an acceptable response rate in prevalence surveys, with a minimum of 70% if there is evidence that respondents and non-respondents have similar important socio-demographic characteristics [18]. Given the response rates of most surveys, selection bias in chlamydia prevalence surveys is likely. There is evidence from population-based surveys of chlamydia prevalence in EU/EEA Member States that participants have higher levels of sexual risk behaviour, symptoms and previous STI than non-participants [28,57,60]. Over-estimation of prevalence is therefore more likely than under-estimation [194]. As expected, the percentage participation in questionnaires about reasons for non-response to a survey is usually very low so non-response bias also becomes a problem in the interpretation of these surveys. It is not possible, however, to specify a level of response below which the value estimated should not be considered an estimate of prevalence.

Response rates and the likelihood of bias in chlamydia prevalence surveys were difficult to assess consistently. First, in national surveys with complex sampling methods, post-stratification weights are applied to make the sample population representative of the national population. Chlamydia testing is then often conducted in a sample of all participants and the response rate cited is for those providing a specimen as a proportion of those asked [57,74]. Selection bias is possible, despite a high reported response rate, if sexual behaviour and sexual risk in those responding to the general survey differ from non-respondents. These characteristics are not available for comparison, however. Second, response rates amongst sexually experienced adults cannot be calculated if sexual experience is an eligibility criterion and is not reported separately from other reasons for non-participation. Third, authors use different definitions for the eligible population, the population invited and the population responding. Standard definitions used by survey and market research companies were rarely adhered to. Reporting standards for prevalence surveys in epidemiological research might help to improve consistency in future.

[3] National Health and Nutrition Examination Surveys, USA

Reproductive tract complications of chlamydia infection in women

There is strong evidence that reproductive tract pathology is mediated by PID as the most common clinical manifestation of tubal damage, with ectopic pregnancy, tubal infertility and chronic pelvic pain as sequelae. Based on disease diagnosis registers, rates of diagnosis of PID have declined in the last 20–35 years in many countries, whilst rates of ectopic pregnancy and infertility from all causes have remained stable. The fall in PID rates has been observed in both inpatient and outpatient sources of data [113–115] and started when gonorrhoea was the most common cause of PID. The contribution of chlamydia control activities cannot be disentangled from other factors including antibiotic use, health promotion activities and other changes in sexual health status. The incidence of clinical PID following asymptomatic NAAT-detected chlamydia in women in the general population is probably lower (9%, 95% CI 4, 19% in 1 study [133]) than PID in symptomatic women with chlamydia infection detected by culture (12-30% in 3 studies [156–158]). The risk of PID from any cause in women with chlamydia infection compared to those without remains strong.

The proportion of women with tubal factor infertility caused by past chlamydia infection has been estimated to be 45% (95% credible interval 28, 62%) [138]. An important assumption in this study was that chlamydia antibody levels are higher if tubal factor infertility has been caused by chlamydia than in cases of tubal factor infertility in women with coincidental exposure to chlamydia. This affects assumptions about the sensitivity and specificity of serological tests for chlamydia antibody.

There are still no direct estimates of the probability that a woman with asymptomatic untreated chlamydia infection will have an ectopic pregnancy or develop tubal factor infertility. The risk of long term complications in women with clinical PID from all causes is related to the severity of laparoscopically detected abnormalities, with an estimated 0.6% of women with mild PID developing tubal factor infertility, compared with 21% of women with severe PID [166]. These probabilities have not been directly related to the presence of chlamydia infection at PID diagnosis. Most women with chlamydial PID have mild or moderate clinical disease, however. Thus, when estimating the probability of tubal factor infertility following chlamydial PID, an average estimate should be weighted towards the probability following mild PID. A low overall probability of tubal factor might explain in part the lack of association observed in the few studies that have examined long term reproductive tract outcomes in women with chlamydia or PID [121].

Impact of chlamydia screening on female reproductive tract complications of chlamydia

Trial methodology affects the interpretation and implications of studies of the effectiveness of chlamydia screening. In practice, the reduction in PID incidence that would be expected from chlamydia screening is likely to be lower than the summary estimate of 35% obtained from the meta-analysis. In three of four RCTs [131–133] the uptake of the screening intervention was higher than the levels that have been achieved in practice. Only the RCT by Andersen et al. [47] had a level of uptake of the chlamydia screening test that has been observed in practice and this is in Scandinavian countries with established opportunistic chlamydia screening. A limitation of the methods of the published RCTs is that all studied the effect of a single offer of a chlamydia test. It is not clear how the reduction in PID following a single screening test should be extrapolated into future years.

An observed reduction in the incidence of clinically diagnosed PID in an individually randomised trial is a direct effect of screening; the identification and treatment of asymptomatic infection must occur soon enough to prevent clinical symptoms of PID in women who receive screening compared with those who do not. Although knowledge about the timing of chlamydial disease progression is still limited [195], the published RCTs provide some evidence to support the hypothesis that *C. trachomatis* provokes persisting cellular immune responses [125] and that there is a window of opportunity in which chlamydia screening can interrupt tubal pathology. It is unclear whether the size of the effect on PID incidence that is observed in RCTs is all attributable to the specific effect of screening and treatment for chlamydia. A review of studies of women with clinically or laparoscopically diagnosed PID found that a median of about 30% had concurrent chlamydia infection. If it is assumed that 30% of PID episodes are caused by *C. trachomatis*, the meta-analysis in this review suggests that screening and treatment prevented all chlamydia-associated PID. This is unlikely because many chlamydia infections in the women enrolled in the RCTs would have been present for several months before detection and screening and treatment would have been too late to prevent ascension. It is possible that the antibiotics used to treat chlamydia also treated some other PID-causing bacteria, or had non-specific anti-inflammatory effects.

There is also an indirect effect of chlamydia screening on PID incidence, if the uptake of sustained screening is high enough to reduce chlamydia prevalence and therefore prevent exposure to infection. This is discussed in Section 4 in relation to cost-effectiveness studies.

Impact of chlamydia screening on transmission of chlamydia

Empirical evidence that chlamydia screening affects the transmission of chlamydia at the population level remains limited. The pragmatic nature of the two trials provides information about the effects of screening under real-life conditions where implementation has to be sustained over time. The cluster controlled trial by van den Broek showed that, at the screening uptake levels achieved, a systematic register-based approach to chlamydia screening for three years did not result in a change in chlamydia positivity when compared with existing levels of opportunistic testing in the Netherlands [40]. In the school-based programme evaluated by Cohen et al. the uptake of screening was sustained at much higher levels over time and chlamydia positivity was lower after three years in intervention than control schools [175]. The reduction only occurred in boys, however, and there were other selection biases in the non-randomised trial design that could have contributed to the overall observed effect. Furthermore, when screening was implemented in all participating schools, chlamydia positivity continued to increase over time [196]. Participation in register-based chlamydia screening decreased over time in both the Netherlands and the US. In the trial by van den Broek et al. the response to subsequent postal invitations fell year on year during the course of the trial [40]. In the New Orleans school-based programme, participation during the first three years remained high but fell subsequently owing to changes in the way that consent was obtained [196]. Sustaining levels of screening uptake over time is therefore an important issue for implementation.

Both trials help to show the importance of sexual transmission of *C. trachomatis* in a sexual network. In the Netherlands, low uptake over time probably diluted any impact of a population-wide chlamydia screening and treatment intervention through continued exposure to infection from people in the sexual network who are not screened [40]. In US high schools, high levels of chlamydia screening participation were achieved, but school students are not a closed population. One explanation for the early observed results of Cohen et al. [175] is that boys were more likely to be part of sexual networks in schools and screening, treatment and partner notification reduced transmission. If girls were more likely to have male partners who were not in their own or other participating schools, continued transmission from outside schools would sustain transmission [197]. An alternative is that funding for sexual health services became scarcer later in the course of the programme [197].

Repeated chlamydia infection in screen-detected and treated individuals limits the long-term impact of chlamydia screening on levels of circulating infection [193]. High levels of successful partner notification are needed to prevent repeated infection in a treated individual. The effectiveness of partner notification remains sub-optimal and untreated partners, or inadequately treated partners can re-introduce infection into an ongoing sexual partnership, or can leave other partners in a sexual network untreated. Repeated detection of chlamydia after screening and treatment is common. About 20–30% of treated women followed prospectively have a repeat positive chlamydia test by 12 months [198,199], despite routine partner notification efforts. In a prospective cohort study of young women who were screened for chlamydia every three months, the point prevalence of chlamydia remained at around 10% throughout follow up [200]. Repeated infection can result from antibiotic treatment failure, re-infection from an untreated partner or a new infection from a subsequent partner. The level of antibiotic treatment failure following single dose azithromycin might have been underestimated [200,201]. Higher levels of chlamydia screening uptake will result in higher levels of repeated infections from any cause.

Cost-effectiveness of chlamydia screening

Cost-effectiveness studies of chlamydia screening rely on accurate estimates of the incidence of chlamydia-associated PID and its sequelae and of assessments about their impact on quality of life as chlamydia and its complications are rarely fatal. The uncertainties about the natural history of chlamydia infection, described in the section on the cost-effectiveness of chlamydia screening programmes, are therefore propagated in cost-effectiveness studies. The impact of chlamydia is therefore mainly through morbidity and decreases in quality of life resulting from the disease. Most cost-effectiveness studies that use cost per QALY gained as an outcome have reported that chlamydia screening can be cost-effective at nationally accepted thresholds. This does not mean that chlamydia screening, as implemented, is cost-effective, however. Incremental cost-effectiveness ratios are sensitive to assumptions about the epidemiology and natural history of chlamydia, the uptake of screening, the type of model used and the assumptions about the impact and duration of chlamydia sequelae on quality of life.

High estimates of the probability of complications of chlamydia infection will result in an overestimate of the benefits of screening and treatment that are assumed to prevent complications. Early estimates of the probability of PID were obtained from studies of women in clinical settings who often had symptoms at presentation, or co-infection with gonorrhoea. An estimate of 20–30% for the probability of PID after untreated chlamydia infection has been extrapolated to asymptomatic women with NAAT-diagnosed infection in the community in cost-effectiveness studies published up to 2010 (Table 11). The most recent estimate from Oakeshott et al. [133], which is applicable to current practice, is much lower.

The probability of ectopic pregnancy, tubal infertility and chronic pelvic pain might also be overestimated by extrapolation of data from women admitted to hospital with PID [166] to those with mild to moderate PID diagnosed in outpatient settings. In some cost-effectiveness studies, a probability of complications in women with PID has been applied to all women with asymptomatic chlamydia infection [118]. In the systematic review in this report, two studies appear to have applied a probability of chronic pelvic pain of 18% to all women with chlamydia [187,189], rather than to the percentage that develops PID.

The number of cost-effectiveness studies using dynamic models to represent chlamydia transmission has increased markedly since the earlier systematic review [23]. The advantage of these models is that the impact of hypothetical chlamydia screening interventions on chlamydia prevalence can be taken into account in estimates of the numbers of cases of complications prevented. There are also disadvantages of dynamic models. First, most compartmental models cannot take into account the effects of unsuccessful partner notification and re-infection within sexual partnerships [193]. Second, they are more complicated to construct and understand than static models [202]. For example, there are dynamic models in the review presented in this report that show contradictory cost-effectiveness ratios for chlamydia screening interventions despite similar assumptions in important parameters such as the probability of progression to PID and screening uptake [188,189]. Descriptions in published articles do not give enough information to understand the reasons for these differences and direct model comparisons with re-analysis using harmonised parameter sets are required [202].

Implications for future research and practice

The literature reviews in this report provide information that allows the role of chlamydia control activities and screening as a public health intervention. The potential benefits of preventing chlamydia transmission and its complications need to be accurately determined and need to be balanced against the potential harmful effects on relationships, repeated infections and increasing antibiotic use. The findings of the report also suggest implications for future research and practice.

The ascertainment of chlamydia infection prevalence in a wide range of EU/EEA Member States would be valuable. Surveys among samples representative of national populations are limited to selected Northern and Central European countries and selection bias resulting from low response rates is a threat to the validity of estimates. The systematic review showed that higher response rates are achieved when chlamydia prevalence is measured as part of a more general survey.

There is still a need for well-designed and conducted RCTs of the effects of chlamydia screening. In particular, more information is needed about the impact of chlamydia screening and treatment on repeated infections and on PID at achievable screening uptake levels over time, and on objective markers of tubal damage. Ongoing trials will estimate the effect of repeated rounds of opportunistic screening on chlamydia prevalence estimated at the population level [177]. If chlamydia screening does reduce prevalence, this could reflect the shorter duration of infection and incidence might still be the same, particularly if re-infection from ongoing partners is common. Incidence might be a better outcome measure for RCTs, but this is challenging to measure in practice. Mathematical modelling studies could help to determine the relative contributions to the reduction in chlamydia transmission from shorter duration by picking up infection earlier and from reducing incidence.

PID remains an intermediate endpoint of reproductive tract damage. The estimation of the risk of long-term reproductive tract complications of chlamydia infection remains a challenge. There is a need for improved methods of diagnosis of PID and for markers of chlamydial infection that predict women at high risk of tubal damage and clinical and immunological research studies to help understand the pathogenesis of chlamydial disease [203]. Statistical modelling methods to synthesise evidence from different sources of existing studies of chlamydia infection, progression and complications would help to overcome some of the ethical problems of clinical epidemiological studies. Bayesian evidence synthesis methods are a promising approach to such studies [204].

Epidemiological and economic research studies could improve the assessment of the impact on quality of life of symptomatic chlamydia infection and its complications. Studies that involve valuation of utilities against external metrics, such as time or risk of death and allow valuation from the perspective of women and from the general population would improve the quality of this body of evidence [180]. Improved estimates of the natural history of chlamydia and its impact on quality of life would help to provide more accurate assessments of the cost-effectiveness of chlamydia screening.

References

1. European Centre for Disease Prevention and Control. Sexually transmitted infections in Europe 2011. Stockholm: ECDC; 2013.
2. Centers for Disease Control and Prevention (2011) Sexually Transmitted Disease Surveillance 2010.
3. Holmes KK, Sparling PF, Stamm WE, Piot P, Wasserheit JN, Corey L, et al. (2008) Sexually Transmitted Diseases. New York: McGraw-Hill.
4. Cohen MS, Hoffman IF, Royce RA, Kazembe P, Dyer JR, Daly CC, et al. (1997) Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. AIDSCAP Malawi Research Group. Lancet 349: 1868-1873.
5. Last, J. M. (2001) A Dictionary of Epidemiology. Oxford: Oxford University Press.
6. Yeh JM, Hook EW, III, Goldie SJ (2003) A refined estimate of the average lifetime cost of pelvic inflammatory disease. Sexually Transmitted Diseases 30: 369-378.
7. Haggerty CL, Schulz R, Ness RB (2003) Lower quality of life among women with chronic pelvic pain after pelvic inflammatory disease. Obstet Gynecol 102: 934-939.
8. Trent M, Lehmann HP, Qian Q, Thompson CB, Ellen JM, Frick KD (2011) Adolescent and parental utilities for the health states associated with pelvic inflammatory disease. Sex Transm Infect 87: 583-587. sextrans-2011-050187 [pii];10.1136/sextrans-2011-050187 [doi].
9. Ward H, Fredlund H, Gotz H, Goulet V, Robinson A, Uuskula A (2009) ECDC Guidance. Chlamydia control in Europe, June 2009. ISBN 978-92-9193-165-1.
10. Low N, Cassell JA, Spencer B, Bender N, Martin HA, van BJ, et al. (2011) Chlamydia control activities in Europe: cross-sectional survey. Eur J Public Health doi:10.1093/eurpub/ckr046. ckr046 [pii];10.1093/eurpub/ckr046 [doi].
11. Low N, Cassell JA, Spencer B, Bender N, Martin-Hilber A, van Bergen J, et al. (2008) Technical Report. Review of Chlamydia Control Activities in EU Countries.
12. Low N (2007) Screening programmes for chlamydial infection: when will we ever learn? BMJ 334: 725-728.
13. Centers for Disease Control and Prevention (2010) Sexually Transmitted Diseases Treatment Guidelines, 2010. MMWR - Morbidity & Mortality Weekly Report 59: 44-45.
14. Royal Australian College of General Practitioners (2007) Guidelines for Preventive Activities in General Practice. 1-104.
15. National Chlamydia Screening Programme (2010) National Chlamydia Screening Programme, England. Core requirements. 5th Edition, update 2 - August 2010.
16. Meyers DS, Halvorson H, Luckhaupt S (2007) Screening for Chlamydial Infection: An Evidence Update for the U.S. Preventive Services Task Force. Ann Intern Med 134-141.
17. Higgins JPT, Altman DG, Sterne JAC, Cochrane Statistical Methods Group, Cochrane Bias Methods Group (2011) Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration.
18. Boyle MH (1998) Guidelines for evaluating prevalence studies. Evidence-Based Mental Health 1: 37-40.
19. Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Statistics in Medicine 21: 1539-1558.
20. Riley RD, Higgins JP, Deeks JJ (2011) Interpretation of random effects meta-analyses. BMJ 342: d549.
21. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. (2004) Grading quality of evidence and strength of recommendations. BMJ 328: 1490. 10.1136/bmj.328.7454.1490 [doi];328/7454/1490 [pii].
22. Brozek JL, Oxman A, Schunemann HJ, Akl EA, Santesso N et al. (2004) GRADEprofiler. http://www.gradeworkinggroup.org, version GRADE Working Group.
23. Roberts TE, Robinson S, Barton P, Bryan S, Low N (2006) Screening for Chlamydia trachomatis: a systematic review of the economic evaluations and modelling. Sex Transm Infect 82: 193-200.
24. Low N, McCarthy A, Macleod J, Salisbury C, Campbell R, Roberts TE, et al. (2007) Epidemiological, social, diagnostic and economic evaluation of population screening for genital chlamydial infection. Health Technol Assess 11: 1-184.
25. van Valkengoed IG, Morre SA, van den Brule AJ, Meijer CJ, Deville W, Bouter LM et al. (2000) Low diagnostic accuracy of selective screening criteria for asymptomatic Chlamydia trachomatis infections in the general population. Sex Transm Infect 76: 375-380.
26. van Valkengoed IG, Boeke AJ, Morre SA, van den Brule AJ, Meijer CJ, Deville W et al. (2000) Disappointing performance of literature-derived selective screening criteria for asymptomatic Chlamydia trachomatis infection in an inner-city population. Sex Transm Dis 27: 504-507.

27. Van Valkengoed GM, Boeke AJP, Van den Brule AJC, Morre SA, Dekker JH, Meijer CJLM et al. (1999) Systematic screening for asymptomatic Chlamydia trachomatis infections by home obtained mailed urine samples in men and women in general practice. Nederlands Tijdschrift voor Geneeskunde 143: 672-676.

28. van Bergen J, Gotz HM, Richardus JH, Hoebe CJ, Broer J, Coenen AJ (2005) Prevalence of urogenital Chlamydia trachomatis increases significantly with level of urbanisation and suggests targeted screening approaches: results from the first national population based study in the Netherlands. Sex Transm Infect 81: 17-23.

29. van Bergen JEAM, Gotz HM, Richardus JH, Hoebe CJPA, Broer J, Coenen AJJ (2005) Chlamydia trachomatis infection in 4 regions in the Netherlands: Results of a population-based study conducted through municipal health services and implications for screening. Nederlands Tijdschrift voor Geneeskunde 149.

30. Veldhuijzen IK, van Bergen JEAM, Gotz HM, Hoebe CJPA, Morre SA, Richardus JH, Pilot Ct Study Group (2005) Reinfections, persistent infections, and new infections after general population screening for Chlamydia trachomatis infection in the Netherlands. Sex Transm Dis 32.

31. Gotz HM, Van Bergen JE, Veldhuijzen IK, Broer J, Hoebe CJ, Richardus JH (2005) A prediction rule for selective screening of Chlamydia trachomatis infection. Sex Transm Infect 81: 24-30.

32. Gotz HM, Hoebe CJ, Van Bergen JE, Veldhuijzen IK, Broer J, de GF, Verhooren MJ, et al. (2005) Management of Chlamydia cases and their partners: results from a home-based screening program organized by municipal public health services with referral to regular health care. Sex Transm Dis 32: 625-629. 00007435-200510000-00006 [pii].

33. Gotz HM, van Bergen JEAM, Veldhuijzen IK, Hoebe CJPA, Broer J, Coenen AJJ, et al. (2006) Lessons learned from a population-based chlamydia screening pilot. International Journal of STD & AIDS 17.

34. Gotz HM, Veldhuijzen IK, Habbema JD, Boeke AJ, Richardus JH, Steyerberg EW (2006) Prediction of Chlamydia trachomatis infection: application of a scoring rule to other populations. Sex Transm Dis 33: 374-380. 10.1097/01.olq.0000194585.82456.51 [doi].

35. van Bergen J, Gotz H, Richardus JH, Hoebe C, Broer J, Coenen T, Pilot Ct Study Group (2006) Prevalence of urogenital Chlamydia trachomatis infections in the Netherlands suggests selective screening approaches. Results from the PILOT CT Population Study. Drugs of Today 42 Suppl A.

36. Van Bergen JE, Fennema JS, van den Broek IV, Brouwers EE, de Feijter EM, Hoebe CJ, et al. (2010) Rationale, design, and results of the first screening round of a comprehensive, register-based, Chlamydia screening implementation programme in the Netherlands. BMC Infect Dis 10: 293. 1471-2334-10-293 [pii];10.1186/1471-2334-10-293 [doi].

37. van den Broek IVF, Hoebe CJPA, van Bergen JEAM, Brouwers EEHG, de Feijter EM, Fennema JSA et al. (2010) Evaluation design of a systematic, selective, internet-based, Chlamydia Screening Implementation in the Netherlands, 2008-2010: implications of first results for the analysis. BMC Infect Dis 10: 89.

38. Greenland KE, Op de Coul EL, Van Bergen JE, Brouwers EE, Fennema HJ, Gotz HM, et al. (2011) Acceptability of the Internet-Based Chlamydia Screening Implementation in the Netherlands and Insights Into Nonresponse. Sex Transm Dis . 10.1097/OLQ.0b013e318204546e [doi].

39. Op de Coul ELM, G+Âtz HM, van Bergen JEAM, Fennema JSA, Hoebe CJPA, Koekenbier RH, et al. (2012) Who Participates in the Dutch Chlamydia Screening? A Study on Demographic and Behavioral Correlates of Participation and Positivity. Sex Transm Dis 39.

40. van den Broek IV, Van Bergen JE, Brouwers EE, Fennema HJ, Gotz HM, Hoebe CJ, et al. (2012) Effectiveness of yearly, register based screening for chlamydia in the Netherlands: controlled trial with randomised stepped wedge implementation. BMJ 345: e4316.

41. Bennedsen M, Nygard B, Berthelsen L, Jensen JS, Lind I (2001) [Prevalence of Chlamydia among young men. A screening among men liable for military service and coming before the military board]. Ugeskr Laeger 163: 4583-6.

42. Munk C, Morre SA, Kjaer SK, Poll PA, Bock JE, Meijer, CJ, et al. (1999) PCR-detected Chlamydia trachomatis infections from the uterine cervix of young women from the general population: prevalence and risk determinants. Sex Transm Dis 26: 325-328.

43. Kjaer SK, van den Brule AJ, Bock JE, Poll PA, Engholm G, Sherman ME et al. (1996) Human papillomavirus--the most significant risk determinant of cervical intraepithelial neoplasia. Int J Cancer 65: 601-606. 10.1002/(SICI)1097-0215(19960301)65:5<601::AID-IJC8>3.0.CO;2-6 [pii];10.1002/(SICI)1097-0215(19960301)65:5<601::AID-IJC8>3.0.CO;2-6 [doi].

44. Ostergaard L, Andersen B, Olesen F, Moller JK (1998) Efficacy of home sampling for screening of Chlamydia trachomatis: randomised study. BMJ 317: 26-27.

45. Andersen B, Olesen F, Moller JK, Ostergaard L (2002) Population-Based Strategies for Outreach Screening of Urogenital Chlamydia trachomatis Infections: A Randomized, Controlled Trial. J Infect Dis 185: 252-258.

46. Moller JK, Andersen B, Olesen F, Lignell T, Ostergaard L (1999) Impact of menstrual cycle on the diagnostic performance of LCR, TMA, and PCE for detection of Chlamydia trachomatis in home obtained and mailed vaginal flush and urine samples. Sex Transm Infect 75.

47. Andersen B, van Valkengoed I, Sokolowski I, Moller JK, Ostergaard L, Olesen F (2011) Impact of intensified testing for urogenital Chlamydia trachomatis infections: a randomised study with 9-year follow-up. Sex Transm Infect 87: 156-161.

48. Brannstrom M, Josefsson GB, Cederberg A, Liljestrand J (1992) Prevalence of genital Chlamydia trachomatis infection among women in a Swedish primary health care area. Scandinavian Journal of Infectious Diseases 24.

49. Jonsson M, Karlsson R, Rylander E, Boden E, Edlund K, Evander M, Gustavsson A, Wadell G (1995) The silent suffering women--a population based study on the association between reported symptoms and past and present infections of the lower genital tract. Genitourin Med 71: 158-162.

50. Jonsson M, Karlsson R, Persson K, Juto P, Edlund K, Evander M, et al. (1995) The influence of sexual and social factors on the risk of Chlamydia trachomatis infections: A population-based serologic study. Sex Transm Dis 22: 355-363.

51. Karlsson R, Jonsson M, Edlund K, Evander M, Gustavsson A, Boden E, et al. (1995) Lifetime number of partners as the only independent risk factor for human papillomavirus infection: a population-based study. Sex Transm Dis 22.

52. Novak DP, Edman AC, Jonsson M, Karlsson RB (2003) The internet, a simple and convenient tool in Chlamydia trachomatis screening of young people. Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin 8: 171-176.

53. Novak DP, Lindholm L, Jonsson M, Karlsson RB (2004) A Swedish cost-effectiveness analysis of community-based Chlamydia trachomatis PCR testing of postal urine specimens obtained at home. Scandinavian Journal of Public Health 32.

54. Domeika M, Oscarsson L, Hallen A, Hjelm E, Sylvan S (2007) Mailed urine samples are not an effective screening approach for Chlamydia trachomatis case finding among young men. Journal of the European Academy of Dermatology & Venereology 21.

55. Stephenson J, Carder C, Copas A, Robinson A, Ridgway G, Haines A (2000) Home screening for chlamydial genital infection: is it acceptable to young men and women? Sex Transm Infect 76: 25-27.

56. Pierpoint T, Thomas B, Judd A, Brugha R, Taylor-Robinson D, Renton A (2000) Prevalence of Chlamydia trachomatis in young men in north west London. Sex Transm Infect 76: 273-276.

57. Fenton KA, Korovessis C, Johnson AM, McCadden A, McManus S, Wellings K et al. (2001) Sexual behaviour in Britain: reported sexually transmitted infections and prevalent genital *Chlamydia trachomatis* infection. Lancet 358: 1851-1854.

58. Johnson AM, Mercer CH, Erens B, Copas AJ, McManus S, Wellings K et al. (2001) Sexual behaviour in Britain: partnerships, practices and HIV risk behaviours. Lancet 358: 1835-1842.

59. McCadden A, Fenton KA, McManus S, Mercer CH, Erens B, Carder C, et al. (2005) Chlamydia trachomatis testing in the second British national survey of sexual attitudes and lifestyles: respondent uptake and treatment outcomes. Sex Transm Dis 32.

60. Macleod J, Salisbury C, Low N, McCarthy A, Sterne JA, Holloway A, et al. (2005) Coverage and uptake of systematic postal screening for genital Chlamydia trachomatis and prevalence of infection in the United Kingdom general population: cross sectional study. BMJ 330: 940-942.

61. Low N, McCarthy A, Macleod J, Salisbury C, Horner PJ, Roberts TE, et al. for the Chlamydia Screening Studies Group (2004) The chlamydia screening studies: rationale and design. Sex Transm Infect 80: 342-348.

62. Bracebridge S, Bachmann MO, Ramkhelawon K, Woolnough A (2012) Evaluation of a systematic postal screening and treatment service for genital Chlamydia trachomatis, with remote clinic access via the internet: a cross-sectional study, East of England. Sex Transm Infect .

63. Haar K (2012) Prävalenz von urogenitalen Chlamydia trachomatis-Infektionen bei Teilnehmern des bundesweiten Kinder- und Jugendgesunheitssurveys (KiGGS). Berlin School of Public Health . Masterarbeit for MPH.

64. Kamtsiuris P, Lange M, Schaffrath Rosario A (2007) [The German Health Interview and Examinations Survey for Children and Adolescents (KiGGS): Sample design, response and nonresponse analysis]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 50.

65. Kurth B-M, Kamtsiuris P, Holling H, Schlaud M, Dolle R, Ellert U, et al. (2008) The challenge of comprehensively mapping children's health in a nation-wide health survey: Design of the German KiGGS-Study. BMC Public Health 8.

66. Thierfelder W, Dortschy R, Hintzpeter B, Kahl H, Scheidt-Nave C (2007) [Biochemical measures in the German Health Interview and Examination Survey for Children and Adolescents (KiGGS)]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 50.

67. Desai S, Meyer T, Thamm M, Hamouda O, Bremer V (2011) Prevalence of Chlamydia trachomatis among young German adolescents, 2005-06. Sexual Health 8.

68. Haar K (2012) Chlamydia epidemiology in Germany.

69. Scheidt-Nave C, Kamtsiuris P, Goesswald A, Hoelling H, Lange M, Busch MA, et al. (2012) German health interview and examination survey for adults (DEGS) - design, objectives and implementation of the first data collection wave. BMC Public Health 12.

70. Steen TW, Hjortdahl P, Storvold G, Vilimas K, Elstrom P, Esholdt I et al. (2005) [Prevalence of genital Chlamydia trachomatis infection in the age group 18-29 years in Oslo]. Tidsskrift for Den Norske Laegeforening 125.

71. Klovstad H, Grjibovski A, Aavitsland P (2012) Population based study of genital Chlamydia trachomatis prevalence and associated factors in Norway: A cross sectional study. BMC Infect Dis 12.

72. Uuskula A, Kals M, Denks K, Nurm UK, Kasesalu L, Dehovitz J, McNutt LA (2008) The prevalence of chlamydial infection in Estonia: a population-based survey. International Journal of STD AIDS 19: 455-458.

73. Uuskula A, Kals M, McNutt L-A (2011) Assessing non-response to a mailed health survey including self-collection of biological material. European Journal of Public Health 21.

74. Goulet V, de BB, Raherison S, Prudhomme M, Semaille C, Warszawski J (2010) Prevalence of Chlamydia trachomatis: results from the first national population-based survey in France. Sex Transm Infect 86: 263-270. 86/4/263 [pii];10.1136/sti.2009.038752 [doi].

75. Bajos N, Bozon M, Beltzer N, Laborde C, Andro A, Ferrand M, et al. (2010) Changes in sexual behaviours: from secular trends to public health policies. AIDS 24. Research Support, Non-U.S. Gov't.

76. Goulet V, de Barbeyrac B, Raherison S, Prudhomme M, Velter A, Semaille C, et al. (2011) National survey on Chlamydia trachomatis in France (NatChla Study, CSF 2006 Survey) To whom should screening be proposed? [Enquet nationale de prévalence de l'infection à Chlamydia trachomatis (volet NatChla de l'enquete CSF 2006) À quelles personnes proposer un dépistage?]. Bulletin epidemiologique hebdomadaire 12: 160-164.

77. Klavs I, Rodrigues LC, Wellings K, Kese D, Hayes R (2004) Prevalence of genital Chlamydia trachomatis infection in the general population of Slovenia: serious gaps in control. Sex Transm Infect 80: 121-123.

78. Klavs I, Rodrigues LC, Wellings K, Kese D, Svab I (2002) Feasibility of testing for Chlamydia trachomatis in a general population sexual behaviour survey in Slovenia. International Journal of STD & AIDS 13 Suppl 2.

79. Franceschi S, Smith JS, van den Brule A, Herrero R, Arslan A, Anh P-T-H, Bosch FX, et al. (2007) Cervical infection with Chlamydia trachomatis and Neisseria gonorrhoeae in women from ten areas in four continents. A cross-sectional study. Sex Transm Dis 34.

80. de Sanjose S, Almirall R, Lloveras B, Font R, Diaz M, Muñoz N, et al. (2003) Cervical Human Papillomavirus Infection in the Female Population in Barcelona, Spain. Sex Transm Dis 30.

81. Bozicevic I, Grgic I, Zidovec-Lepej S, Cakalo JI, Belak-Kovacevic S, Stulhofer A, et al. (2011) Urine-based testing for Chlamydia trachomatis among young adults in a population-based survey in Croatia: feasibility and prevalence. BMC Public Health 11: 230. 1471-2458-11-230 [pii];10.1186/1471-2458-11-230 [doi].

82. Baud D, Jaton K, Bertelli C, Kulling JP, Greub G (2008) Low prevalence of Chlamydia trachomatis infection in asymptomatic young Swiss men. BMC Infect Dis 8: 45.

83. Ku L, St.Louis M, Farshy C, Aral S, Turner CF, Lindberg LD, et al. (2002) Risk Behaviors, Medical Care, and Chlamydial Infection Among Young Men in the United States. Am J Public Health 92.

84. Miller WC, Ford CA, Morris M, Handcock MS, Schmitz JL, Hobbs MM, et al. (2004) Prevalence of chlamydial and gonococcal infections among young adults in the United States. JAMA 291: 2229-2236.

85. Ford CA, Jaccard J, Millstein SG, Bardsley PE, Miller WC (2004) Perceived risk of chlamydial and gonococcal infection among sexually experienced young adults in the United States. Perspectives on Sexual & Reproductive Health 36.

86. Iritani BJ, Ford CA, Miller WC, Hallfors DD, Halpern CT (2006) Comparison of self-reported and test-identified chlamydial infections among young adults in the United States of America. Sexual Health 3.

87. Geisler WM, Chyu L, Kusunoki Y, Upchurch DM, Hook EW, III (2006) Health insurance coverage, health care-seeking behaviors, and genital chlamydial infection prevalence in sexually active young adults. Sex Transm Dis 33: 389-396. 10.1097/01.olq.0000194584.80513.4a [doi].

88. Manhart LE, Holmes KK, Hughes JP, Houston LS, Totten PA (2007) Mycoplasma genitalium among young adults in the United States: An emerging sexually transmitted infection. Am J Public Health 97.

89. Stein CR, Kaufman JS, Ford CA, Leone PA, Feldblum PJ, et al. (2008) Screening young adults for prevalent chlamydial infection in community settings. Ann Epidemiol 18: 560-571. S1047-2797(08)00057-4 [pii];10.1016/j.annepidem.2008.03.002 [doi].

90. Stein CR, Kaufman JS, Ford CA, Feldblum PJ, Leone PA, et al. 2008) Partner age difference and prevalence of chlamydial infection among young adult women. Sex Transm Dis 35.

91. Annang L, Walsemann KM, Maitra D, Kerr JC (2010) Does education matter? Examining racial differences in the association between education and STI diagnosis among black and white young adult females in the U.S. Public Health Reports 125 Suppl 4.

92. Datta SD, Torrone E, Kruszon-Moran D, Berman S, Johnson R, Satterwhite CL, et al. (2012) Chlamydia trachomatis Trends in the United States Among Persons 14 to 39 Years of Age, 1999-2008. Sex Transm Dis 39.

93. Datta SD, Sternberg M, Johnson RE, Berman S, Papp JR, McQuillan G, et al. (2007) Gonorrhea and Chlamydia in the United States among Persons 14 to 39 Years of Age, 1999 to 2002. Ann Intern Med 147: 89-96.

94. Forhan SE, Gottlieb SL, Sternberg MR, Xu F, Datta SD, McQuillan GM, et al. (2009) Prevalence of Sexually Transmitted Infections Among Female Adolescents Aged 14 to 19 in the United States. Pediatrics eds.

95. Allsworth JE, Ratner JA, Peipert JF (2009) Trichomoniasis and other sexually transmitted infections: Results from the 2001-2004 national health and nutrition examination surveys. Sex Transm Dis 36.

96. Beydoun HA, Dail J, Tamim H, Ugwu B, Beydoun MA (2010) Gender and age disparities in the prevalence of chlamydia infection among sexually active adults in the United States. Journal of Women's Health 19.

97. Centers for Disease C, Prevention (2011) CDC Grand Rounds: Chlamydia prevention: challenges and strategies for reducing disease burden and sequelae. MMWR - Morbidity & Mortality Weekly Report 60.

98. Hocking JS, Willis J, Tabrizi S, Fairley CK, Garland SM, Hellard M (2006) A chlamydia prevalence survey of young women living in Melbourne, Victoria. Sexual Health 3: 235-240.

99. Miller GC, McDermott R, McCulloch B, Fairley CK, Muller R (2003) Predictors of the prevalence of bacterial STI among young disadvantaged Indigenous people in north Queensland, Australia. Sex Transm Infect 79.

100. Miller G, McDermott R, McCulloch B, Leonard D, Arabena K, Muller R (2002) The Well Person's Health Check: a population screening program in indigenous communities in north Queensland. Australian Health Review 25.

101. Miller PJ, Torzillo PJ, Hateley W (1999) Impact of improved diagnosis and treatment on prevalence of gonorrhoea and chlamydial infection in remote aboriginal communities on Anangu Pitjantjatjara Lands. Medical Journal of Australia 170: 429-432.

102. Latif A, Smith K (2004) STI screening conducted in NT Department of Health and Community Services and Community Controlled Health Services in Central Australia in 2004. The Northern Territory Disease Control Bulletin 11.

103. Huang R-L, Torzillo PJ, Hammond VA, Coulter ST, Kirby AC (2008) Epidemiology of sexually transmitted infections on the Anangu Pitjantjatjara Yankunytjatjara Lands: results of a comprehensive control program. Medical Journal of Australia 189.

104. Hodgins S, Peeling RW, Dery S, Bernier F, LaBrecque A, Proulx JF, et al. (2002) The value of mass screening for chlamydia control in high prevalence communities. Sex Transm Infect 78: i64-i68.

105. Steenbeek A, Tyndall M, Sheps S, Rothenberg R (2009) An epidemiological survey of chlamydial and gonococcal infections in a Canadian arctic community. Sex Transm Dis 36.

106. Eggleston E, Rogers SM, Turner CF, Miller WC, Roman AM, Hobbs MM, et al. (2011) Chlamydia trachomatis infection among 15-to 35-year-olds in Baltimore, MD. Sex Transm Dis 38.

107. Eggleston E, Turner CF, Rogers SM, Roman A, Miller WC, Villarroel MA,et al. (2005) Monitoring STI prevalence using telephone surveys and mailed urine specimens: A pilot test. Sex Transm Infect 81.

108. Turner CF, Rogers SM, Miller HG, Miller WC, Gribble JN, Chromy JR, et al. (2002) Untreated gonococcal and chlamydial infection in a probability sample of adults. JAMA 287: 726-733.

109. Klausner JD, McFarland W, Bolan G, Hernandez MT, Molitor F, Lemp GF, Cahoon-Young B, et al. (2001) Knock-Knock: A Population-Based Survey of Risk Behavior, Health Care Access, and Chlamydia trachomatis Infection among Low-Income Women in the San Francisco Bay Area. J Infect Dis 183: 1087-1092.

110. Ruiz JD, Molitor F, McFarland W, Klausner J, Lemp G, Page-Shafer K, et al. (2000) Prevalence of HIV infection, sexually transmitted diseases, and hepatitis and related risk behavior in young women living in low-income neighborhoods of northern California. West J Med 172. Research Support, Non-U.S. Gov't.

111. Corwin P, Abel G, Wells JE, Coughlan E, Bagshaw S, Sutherland M, et al. (2002) Chlamydia trachomatis prevalence and sexual behaviour in Christchurch high school students. New Zealand Medical Journal 115(1158):U107.

112. Abel G, Brunton C (2005) Young people's use of condoms and their perceived vulnerability to sexually transmitted infections. Australian and New Zealand Journal of Public Health 29.

113. Rekart ML, Gilbert M, Meza R, Kim PH, Chang M, Money DM, et al. (2012) Chlamydia Public Health Programs and the Epidemiology of Pelvic Inflammatory Disease and Ectopic Pregnancy. J Infect Dis . jis644 [pii];10.1093/infdis/jis644 [doi].

114. Bender N, Herrmann B, Andersen B, Hocking JS, van Bergen J, Morgan J, et al. (2011) Chlamydia infection, pelvic inflammatory disease, ectopic pregnancy and infertility: cross-national study. Sex Transm Infect 87: 601-608.

115. French CE, Hughes G, Nicholson A, Yung M, Ross JD, Williams T, et al. (2011) Estimation of the Rate of Pelvic Inflammatory Disease Diagnoses: Trends in England, 2000-2008. Sex Transm Dis 38: 158-162.

116. Bjartling C, Osser S, Persson K (2000) The frequency of salpingitis and ectopic pregnancy as epidemiologic markers of Chlamydia trachomatis. Acta Obstetricia et Gynecologica Scandinavica 79: 123-128.

117. Adams EJ, Turner KM, Edmunds WJ (2007) The cost effectiveness of opportunistic chlamydia screening in England. Sex Transm Infect 83: 267-274.

118. van Valkengoed IG, Morre SA, van den Brule AJ, Meijer CJ, Bouter LM, Boeke AJ (2004) Overestimation of complication rates in evaluations of Chlamydia trachomatis screening programmes--implications for cost-effectiveness analyses. International Journal of Epidemiology 33: 416-425.

119. Land JA, Van Bergen JE, Morre SA, Postma MJ (2010) Epidemiology of Chlamydia trachomatis infection in women and the cost-effectiveness of screening. Hum Reprod Update 16: 189-204.

120. Haggerty CL, Gottlieb SL, Taylor BD, Low N, Xu F, Ness RB (2010) Risk of sequelae after Chlamydia trachomatis genital infection in women. J Infect Dis 201: S134-S155.

121. Wallace LA, Scoular A, Hart G, Reid M, Wilson P, Goldberg DJ (2008) What is the excess risk of infertility in women after genital chlamydia infection? A systematic review of the evidence. Sex Transm Infect 84: 171-175.

122. Boeke AJ, Van Bergen JE, Morre SA, van Everdingen JJ (2005) The risk of pelvic inflammatory disease associated with urogenital infection with Chlamydia trachomatis; literature review. Nederlands Tijdschrift voor Geneeskunde 149: 878-884.

123. Risser WL, Risser JM (2007) The incidence of pelvic inflammatory disease in untreated women infected with Chlamydia trachomatis: a structured review. Int J STD AIDS 18: 727-731.

124. Cates W, Jr., Rolfs RT, Jr., Aral SO (1990) Sexually transmitted diseases, pelvic inflammatory disease, and infertility: an epidemiologic update. Epidemiol Rev 12: 199-220.

125. Darville T, Hiltke TJ (2010) Pathogenesis of Genital Tract Disease Due to Chlamydia trachomatis. J Infect Dis 201: 114-125.

126. Hager WD, Eschenbach DA, Spence MR, Sweet RL (1983) Criteria for diagnosis and grading of salpingitis. Obstet Gynecol 61: 113-114.

127. Rice PA, Schachter J (1991) Pathogenesis of pelvic inflammatory disease. What are the questions? [see comments]. [Review] [152 refs]. JAMA 266: 2587-2593.

128. Stephens RS (2003) The cellular paradigm of chlamydial pathogenesis. Trends Microbiol 11: 44-51.

129. Brunham RC, Rey-Ladino J (2005) Immunology of Chlamydia infection: implications for a Chlamydia trachomatis vaccine. Nat Rev Immunol 5: 149-161.

130. Smith KJ, Cook RL, Roberts MS (2007) Time from sexually transmitted infection acquisition to pelvic inflammatory disease development: influence on the cost-effectiveness of different screening intervals. Value Health 10: 358-366.

131. Scholes D, Stergachis A, Heidrich FE, Andrilla H, Holmes KK, Stamm WE (1996) Prevention of pelvic inflammatory disease by screening for cervical chlamydial infection. N Engl J Med 334: 1362-1366.

132. Ostergaard L, Andersen B, Moller JK, Olesen F (2000) Home sampling versus conventional swab sampling for screening of chlamydia trachomatis in women: A cluster-randomized 1-year follow-up study. Clin Infect Dis 31: 951-957.

133. Oakeshott P, Kerry S, Aghaizu A, Atherton H, Hay S, Taylor-Robinson D, Simms I, Hay P (2010) Randomised controlled trial of screening for Chlamydia trachomatis to prevent pelvic inflammatory disease: the POPI (prevention of pelvic infection) trial. BMJ 340: c1642.

134. Chow JM, Yonekura L, Richwald GA, Greenland S, Sweet RL, Schachter J (1990) The association between *Chlamydia trachomatis* and ectopic pregnancy: a matched-pair, case-control study. JAMA 263: 3164-3167.

135. Miettinen A, Heinonen PK, Teisala K, Hakkarainen K, Punnonen R (1990) Serologic evidence for the role of Chlamydia trachomatis, Neisseria gonorrhoeae, and Mycoplasma hominis in the etiology of tubal factor infertility and ectopic pregnancy. Sex Transm Dis 17: 10-14.

136. Brunham RC, Maclean IW, Binns B, Peeling RW (1985) Chlamydia trachomatis: its role in tubal infertility. Journal of Infectious Diseases 152: 1275-1282.

137. Hennekens, C. H. and Buring, J. E. (1987) Epidemiology in medicine. Boston: Little, Brown and Company.

138. Price MJ, Ades AE, Welton NJ, Macleod J, Turner K, Simms I, Horner PJ (2012) How much tubal factor infertility is caused by Chlamydia? Estimates based on serological evidence corrected for sensitivity and specificity. Sex Transm Dis 39: 608-613. 10.1097/OLQ.0b013e3182572475 [doi];00007435-201208000-00007 [pii].

139. Mol BW, Dijkman B, Wertheim P, Lijmer J, Van d, V, Bossuyt PM (1997) The accuracy of serum chlamydial antibodies in the diagnosis of tubal pathology: a meta-analysis. Fertil Steril 67: 1031-1037.

140. Johnson RE, Newhall WJ, Papp JR, Knapp JS, Black CM, Gift TL, et al. (2002) Screening tests to detect Chlamydia trachomatis and Neisseria gonorrhoeae infections--2002. MMWR 51: 1-38.

141. GORDON FB, Quan AL, . (1965) Isolation of the trachoma agent in cell culture. Proc Soc Exp Biol Med 118: 354-359.

142. Mardh PA, Ripa T, Svensson L, Westrom L (1977) Chlamydia trachomatis infection in patients with acute salpingitis. N Engl J Med 296: 1377-1379.

143. Moller JK, Herrmann B, Jensen JS, Westh H (2011) Molecular detection of Chlamydia trachomatis and Neisseria gonorrhoeae. In: Persing DH, editors. Molecular Microbiology: Diagnostic Principles and Practice. Washington D.C.: ASM Press. pp. 383-396.

144. Quinn TC, Gaydos C, Shepherd M, Bobo L, Hook EW, Viscidi R, Rompalo A (1996) Epidemiologic and microbiologic correlates of Chlamydia trachomatis infection in sexual partnerships. JAMA 276: 1737-1742.

145. Puolakkainen M, Hiltunen-Back E, Reunala T, Suhonen S, Lahteenmaki P, Lehtinen M, et al. (1998) Comparison of performances of two commercially available tests, a PCR assay and a ligase chain reaction test, in detection of urogenital Chlamydia trachomatis infection. J Clin Microbiol 36: 1489-1493.

146. Morre SA, van den Brule AJ, Rozendaal L, Boeke AJ, Voorhorst FJ, de Blok S,et al. (2002) The natural course of asymptomatic Chlamydia trachomatis infections: 45% clearance and no development of clinical PID after one-year follow-up. Int J STD AIDS 13 Suppl 2: 12-18.

147. Jacobson L, Westrom L (1969) Objectivized diagnosis of acute pelvic inflammatory disease. Diagnostic and prognostic value of routine laparoscopy. American Journal of Obstetrics & Gynecology 105: 1088-1098.

148. Simms I, Warburton F, Westrom L (2003) Diagnosis of pelvic inflammatory disease: time for a rethink. Sexually Transmitted Infections 79: 491-494.

149. Eschenbach DA, Buchanan TM, Pollock HM, Forsyth PS, Alexander ER, Lin, JS, et al. (1975) Polymicrobial etiology of acute pelvic inflammatory disease. New England Journal of Medicine 293: 166-171.

150. Low N, Egger M, Sterne JA, Harbord RM, Ibrahim F, Lindblom B, et al. (2006) Incidence of severe reproductive tract complications associated with diagnosed genital chlamydial infection: the Uppsala Women's Cohort Study. Sex Transm Infect 82: 212-218.

151. Bakken IJ, Skjeldestad FE, Lydersen S, Nordbo SA (2007) Births and ectopic pregnancies in a large cohort of women tested for Chlamydia trachomatis. Sex Transm Dis 34: 739-743.

152. Bakken IJ, Ghaderi S (2009) Incidence of pelvic inflammatory disease in a large cohort of women tested for Chlamydia trachomatis: a historical follow-up study. BMC Infect Dis 9: 130. 1471-2334-9-130 [pii];10.1186/1471-2334-9-130 [doi].

153. Andersen B, Ostergaard L, Puho E, Skriver MV, Schonheyder HC (2005) Ectopic pregnancies and reproductive capacity after Chlamydia trachomatis positive and negative test results: a historical follow-up study. Sex Transm Dis 32: 377-381.

154. Egger M, Low N, Davey Smith G, Lindblom B, Herrmann B (1998) Screening for chlamydial infections and the risk of ectopic pregnancy in a county in Sweden: ecological analysis. Br Med J 316: 1776-1780.

155. Paavonen J, Westrom L, Eschenbach D (2008) Chapter 56. Pelvic Inflammatory Disease. In: Holmes KK, Sparling PF, Stamm WE, Piot P, Wasserheit JN et al., editors. Sexually Transmitted Diseases. New York: McGraw Hill Medical. pp. 1017-1050.

156. Rees E (1980) The treatment of pelvic inflammatory disease. Am J Obstet Gynecol 138: 1042-1047.

157. Stamm WE, Guinan ME, Johnson C, Starcher T, Holmes KK, McCormack WM (1984) Effect of treatment regimens for Neisseria gonorrhoeae on simultaneous infection with Chlamydia trachomatis. New England Journal of Medicine 310: 545-549.

158. Paavonen J, Kousa M, Saikku P, Vartiainen E, Kanerva L, Lassus A (1980) Treatment of nongonococcal urethritis with trimethoprim-sulphadiazine and with placebo. A double-blind partner-controlled study. Br J Vener Dis 56: 101-104.

159. Ness RB, Smith KJ, Chang CC, Schisterman EF, Bass DC (2006) Prediction of pelvic inflammatory disease among young, single, sexually active women. Sex Transm Dis 33: 137-142.

160. Ness RB, Soper DE, Holley RL, Peipert J, Randall H, Sweet RL, et al. 2002) Effectiveness of inpatient and outpatient treatment strategies for women with pelvic inflammatory disease: results from the Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) Randomized Trial. Am J Obstet Gynecol 186: 929-937.

161. Akande VA, Hunt LP, Cahill DJ, Caul EO, Ford WC, Jenkins JM (2003) Tubal damage in infertile women: prediction using chlamydia serology. Hum Reprod 18: 1841-7.

162. Westrom L, Svensson L, Wolner-Hansen P, Mardh PA (1982) Chlamydial and gonococcal infections in a defined population of women. Scandinavian Journal of Infectious Diseases - Supplementum 32: 157-162.

163. Lepine LA, Hillis SD, Marchbanks PA, Joesoef MR, Peterson HB, Westrom L (1998) Severity of pelvic inflammatory disease as a predictor of the probability of live birth. Am J Obstet Gynecol 178: 977-981.

164. Westrom L (1980) Incidence, prevalence, and trends of acute pelvic inflammatory disease and its consequences in industrialized countries. Am J Obstet Gynecol 138: 880-892.

165. Westrom L (1975) Effect of acute pelvic inflammatory disease on fertility. Am J Obstet Gynecol 121: 707-713.

166. Westrom L, Joesoef R, Reynolds G, Hagdu A, Thompson SE (1992) 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 19: 185-192.

167. Trent M, Bass D, Ness RB, Haggerty C (2011) Recurrent PID, subsequent STI, and reproductive health outcomes: findings from the PID evaluation and clinical health (PEACH) study. Sex Transm Dis 38: 879-881. 10.1097/OLQ.0b013e31821f918c [doi];00007435-201109000-00018 [pii].

168. Soper DE (2010) Pelvic inflammatory disease. Obstet Gynecol 116: 419-428. 10.1097/AOG.0b013e3181e92c54 [doi];00006250-201008000-00025 [pii].

169. Trent M, Haggerty CL, Jennings JM, Lee S, Bass DC, Ness R (2011) Adverse adolescent reproductive health outcomes after pelvic inflammatory disease. Arch Pediatr Adolesc Med 165: 49-54. 165/1/49 [pii];10.1001/archpediatrics.2010.256 [doi].

170. Buchan H, Vessey M, Goldacre M, Fairweather J (1993) Morbidity following pelvic inflammatory disease. Br J Obstet Gynaecol 100: 558-562.

171. Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA (2012) National, Regional, and Global Trends in Infertility Prevalence Since 1990: A Systematic Analysis of 277 Health Surveys. PLoS Med 9: e1001356. doi:10.1371/journal.pmed.1001356.

172. Department of Health (2010) UK Screening Portal. UK National Screening Committee. Programme appraisal criteria. London: The Stationery Office. Available.

173. Low N, Bender N, Nartey L, Shang A, Stephenson JM (2009) Effectiveness of chlamydia screening: systematic review. International Journal of Epidemiology 38: 435-448.

174. Low N, Bender N, Nartey L, Redmond S, Shang A et al. (2006) Review 2 - Review of evidence for the effectiveness of screening for genital chlamydial infection in sexually active young women and men. NICE. Available.

175. Cohen DA, Nsuami M, Martin DH, Farley TA (1999) Repeated school-based screening for sexually transmitted diseases: a feasible strategy for reaching adolescents. Pediatrics 104: 1281-1285.

176. van den Broek IVF, van Bergen JEAM, Fennema HSA, Götz HM, Hoebe CJPA, Over E, et al. (2011) Main results and impact analysis of annual chlamydia screening in a large register-based programme in the Netherlands. Oral presentation O1-S09.03. 19th Biennial Meeting of the International Society STD Research. July 11-13, 2011. Quebec City, Canada. Sex Transm Infect 87: A45-doi:10.1136/sextrans-2011-050109.51.

177. Hocking JS, Spark S, Guy R, Temple-Smith M, Fairley CK, Kaldor J, et al. (2012) The Australian chlamydia control effectiveness polot (ACCEPt): first results from a randomised controlled trial of annual chlamydia screening in general practice. Oral presentation O8. Abstracts of the 4th joint BASHH-ASTDA meeting in Brighton, UK, 27-29 June 2012. Sex Transm Infect 88: A3-A4.

178. Oakeshott P, Kerry S, Atherton H, Aghaizu A, Hay S, Taylor-Robinson D, et al. (2008) Community-based trial of screening for Chlamydia trachomatis to prevent pelvic inflammatory disease: the POPI (prevention of pelvic infection) trial. Trials 9: 73.

179. Torrance GW (1986) Measurement of health state utilities for economic appraisal. J Health Econ 5: 1-30.

180. Smith KJ, Tsevat J, Ness RB, Wiesenfeld HC, Roberts MS (2008) Quality of life utilities for pelvic inflammatory disease health states. Sex Transm Dis 35: 307-311. 10.1097/OLQ.0b013e31815b07dd [doi].

181. Barton P, Bryan S, Robinson S (2004) Modelling in the economic evaluation of health care: selecting the appropriate approach. J Health Serv Res Policy 9: 110-118.

182. Hu D, Hook EW, III, Goldie SJ (2004) Screening for Chlamydia trachomatis in women 15 to 29 years of age: a cost-effectiveness analysis. Ann Intern Med 141: 501-513.

183. Hu D, Hook EW, III, Goldie SJ (2006) The impact of natural history parameters on the cost-effectiveness of Chlamydia trachomatis screening strategies. Sex Transm Dis 33: 428-436.

184. de Vries R, Van Bergen JE, de Jong-van den Berg LT, Postma MJ, PILOT-CT Study Group (2008) Cost-utility of repeated screening for Chlamydia trachomatis. Value in Health 11.

185. Deogan CL, Bocangel MK, Wamala SP, Mansdotter AM (2010) A cost-effectiveness analysis of the Chlamydia Monday--a community-based intervention to decrease the prevalence of chlamydia in Sweden. Scand J Public Health 38: 141-150. 1403494809357260 [pii];10.1177/1403494809357260 [doi].

186. Fisman DN, Spain CV, Salmon ME, Goldberg M (2008) The Philadelphia High-School STD Screening Program: key insights from dynamic transmission modeling. Sex Transm Dis 35: S61-S65.

187. Gift TL, Gaydos CA, Kent CK, Marrazzo JM, Rietmeijer CA, Schillinger JA, et al. (2008) The program cost and cost-effectiveness of screening men for Chlamydia to prevent pelvic inflammatory disease in women. Sex Transm Dis 35: S66-S75.

188. Gillespie P, O'Neill C, Adams E, Turner K, O'Donovan D, Brugha R, et al. (2012) The cost and cost-effectiveness of opportunistic screening for Chlamydia trachomatis in Ireland. Sex Transm Infect 88: 222-228.

189. Tuite AR, Jayaraman GC, Allen VG, Fisman DN (2012) Estimation of the burden of disease and costs of genital Chlamydia trachomatis infection in Canada. Sex Transm Dis 39: 260-267. 10.1097/OLQ.0b013e31824717ae [doi];00007435-201204000-00004 [pii].

190. Walleser S, Salkeld G, Donovan B (2006) The cost effectiveness of screening for genital Chlamydia trachomatis infection in Australia. Sex Health 3: 225-234.

191. Institute of Medicine (1999) Vaccines for the 21st Century. A Tool for Decisionmaking. Washington, D.C.: National Academy Press.

192. Songer TJ, Lave JR, Kamlet MS, Frederick S, Ness RB (2004) Preferences for fertility in women with pelvic inflammatory disease. Fertil Steril 81: 1344-1350. 10.1016/j.fertnstert.2003.09.064 [doi];S0015028204000810 [pii].

193. Heijne JCM, Althaus CL, Herzog SA, Kretzschmar M, Low N (2011) The Role of Reinfection and Partner Notification in the Efficacy of Chlamydia Screening Programs. Journal of Infectious Diseases 203: 372-377.

194. Low N, Macleod J, Salisbury C, Egger M (2003) Bias in chlamydia prevalence surveys. Lancet 362: 1157-1158.

195. Herzog SA, Heijne JC, Althaus CL, Low N (2012) Describing the progression from Chlamydia trachomatis and Neisseria gonorrhoeae to pelvic inflammatory disease: systematic review of mathematical modeling studies. Sex Transm Dis 39: 628-637. 10.1097/OLQ.0b013e31825159ff [doi];00007435-201208000-00010 [pii].

196. Low N, Forster M, Taylor SN, Nsuami MJ (2012) Repeat chlamydia screening among adolescents: cohort study in a school-based programme in New Orleans. Sex Transm Infect 88.

197. Cohen DA (2009) School-based STD screening: what next? Sex Transm Infect 85: 160-162. 85/3/160 [pii];10.1136/sti.2008.034520 [doi].

198. Scott LaMontagne D, Baster K, Emmett L, Nichols T, Randall S, McLean L, Meredith P, Harindra V, et al. (2007) Incidence and reinfection rates of genital chlamydial infection among women aged 16 24 years attending general practice, family planning and genitourinary medicine clinics in England: a prospective cohort study by the Chlamydia Recall Study Advisory Group. Sex Transm Infect 83: 292-303.

199. Walker J, Tabrizi SN, Fairley CK, Chen MY, Bradshaw CS, Twin J, et al. (2012) Chlamydia trachomatis incidence and re-infection among young women--behavioural and microbiological characteristics. PloS One 7: e37778. 10.1371/journal.pone.0037778 [doi];PONE-D-11-23013 [pii].

200. Batteiger BE, Tu W, Ofner S, Van Der PB, Stothard DR, Orr DP, et al. (2010) Repeated Chlamydia trachomatis genital infections in adolescent women. J Infect Dis 201: 42-51.

201. Horner PJ (2012) Azithromycin antimicrobial resistance and genital Chlamydia trachomatis infection: duration of therapy may be the key to improving efficacy. Sex Transm Infect 88: 154-156. sextrans-2011-050385 [pii];10.1136/sextrans-2011-050385 [doi].

202. Regan DG, Wilson DP (2008) Modelling sexually transmitted infections: less is usually more for informing public health policy. Trans R Soc Trop Med Hyg 102: 207-208.

203. Gottlieb SL, Martin D, Xu, Byrne, I., Brunham (2010) Summary: The Natural History and Immunobiology of Chlamydia trachomatis Genital Infection and Implications for Chlamydia Control. J Infect Dis 201: 190-204.

204. Ades AE, Welton NJ, Caldwell D, Price M, Goubar A, Lu G (2008) Multiparameter evidence synthesis in epidemiology and medical decision-making. J Health Serv Res Policy 13 Suppl 3: 12-22. 13/suppl_3/12 [pii];10.1258/jhsrp.2008.008020 [doi].

205. Kjær SK, van den Brule AJC, Bock JE, Poll PA, Engholm G, Sherman ME, et al. (1996) Human papillomavirus—the most significant risk determinant of cervical intraepithelial neoplasia. International Journal of Cancer 65.

Appendix 1. Additional material for systematic review of prevalence of chlamydia infections

Search strategy

The following databases were searched from 1990 to October 2011 without language restrictions: Ovid Medline; Embase; Popline; The Cochrane Library. The search terms are listed in full below. In addition we searched reference lists of potentially eligible studies and asked experts in the project team if they were aware of any other studies.

Search terms

Medline search dated 17 October 2011 given as an example

	Searches	Results
1	(CHLAMYDIA INFECTIONS not ("CHLAMYDOPHILA PNEUMONIA" or TRACHOMA or "LYMPHOGRANULOMA VENERUM")).mp.	11 805
2	PREVALENCE.mp	343 391
3	europe/ or exp austria/ or exp belgium/ or europe, eastern/ or exp baltic states/ or exp bulgaria/ or exp czech republic/ or exp hungary/ or exp poland/ or exp romania/ or exp slovakia/ or exp slovenia/ or exp yugoslavia/ or exp finland/ or exp france/ or exp germany/ or exp great britain/ or exp greece/ or exp iceland/ or exp ireland/ or exp italy/ or exp liechtenstein/ or exp luxembourg/ or exp mediterranean region/ or exp netherlands/ or exp portugal/ or exp scandinavia/ or exp spain/ or exp switzerland/ or czechoslovakia/ or european union/	961 550
4	1 and 2 and 3	483
5	Limit 4 to (humans and yr="1990 –Current")	433
6	Australia or Canada or New Zealand or United States	802 773
7	1 and 2 and 6	145
8	Limit 7 to (humans and yr="1990 –Current")	136
9	5 or 8	567

Figure 20. Flow chart of studies included in systematic review of chlamydia epidemiology in Europe

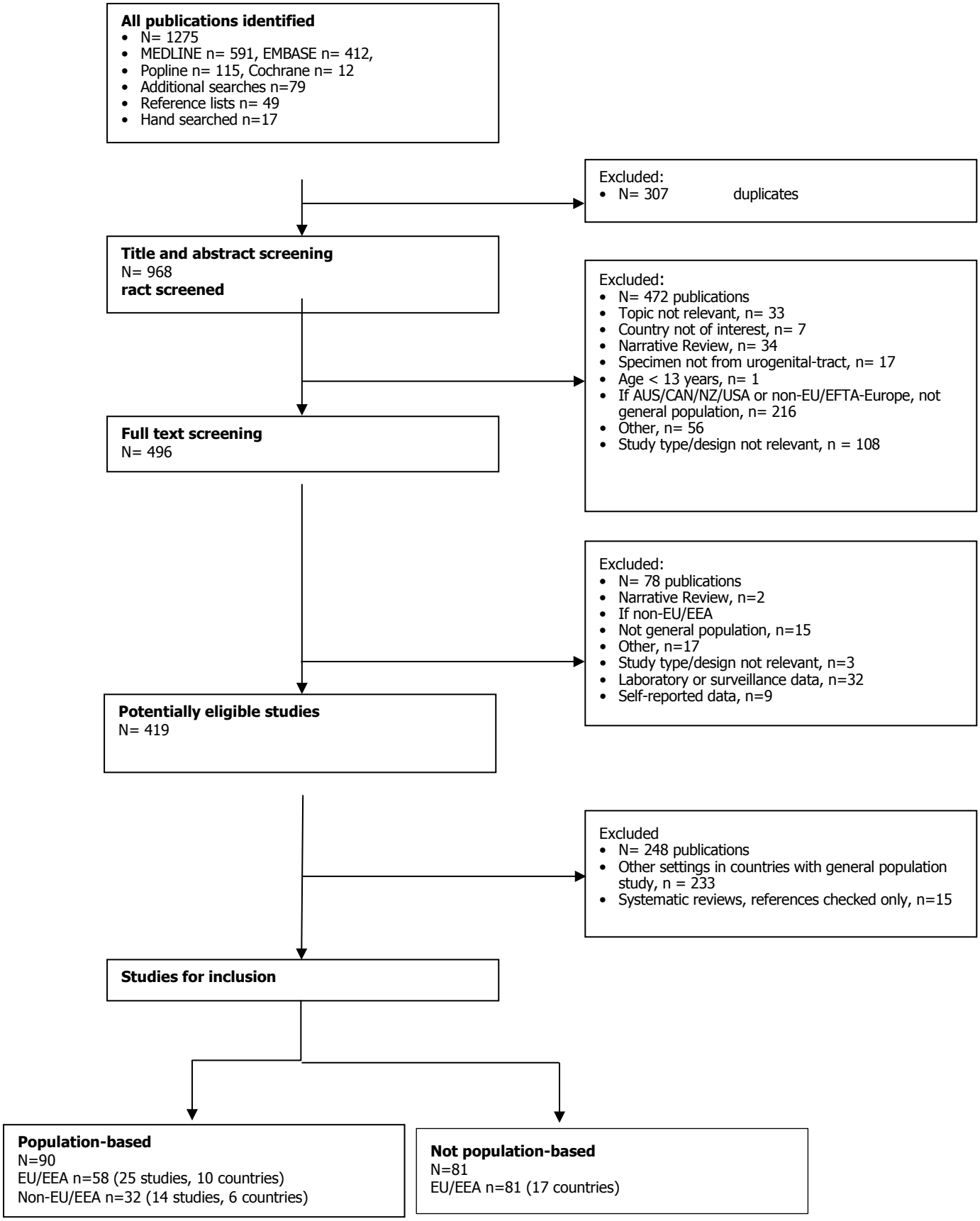


Figure 21. Assessment of the risk of bias in chlamydia prevalence studies in EU/EEA Member States

	Target population representative of country	Target population clearly defined	Source population representative of target	Sample size calculation	Adequate sample size achieved	Probability sampling	Respondents match target population	Response rate 70% limit	Response rate 60% limit	Standardised questionnaire	NAAT used	Appropriate analysis	Confidence intervals
Denmark													
Ostergaard, 1998	−	?	?	?	?	+	−	−	−	+	+	+	+
Munk, 1999	−	+	−	−	?	+	−	−	−	+	+	+	+
Bennedsen, 2001	?	+	+	?	?	+	−	−	−	+	+	+	+
Andersen, 2002	?	?	?	?	?	+	?	−	−	+	+	+	+
Estonia													
Uuskula, 2008	?	+	+	+	?	+	−	−	−	+	+	+	+
France													
Goulet, 2010	+	+	+	+	?	+	?	−	−	+	+	+	+
Germany													
Desai, 2011 Haar/KIGGS	+	+	+	+	?	+	+	−	+	+	+	+	+
Haar/DEGS, 2012	+	+	+	+	−	+	+	−	−	+	+	+	+
The Netherlands													
van Valkengoed, 2000	−	+	?	−	?	+	−	−	−	+	+	+	+
van Bergen, 2005	?	+	?	+	+	+	−	−	−	+	+	+	+
van Bergen, 2010	?	+	+	+	?	+	−	−	−	+	+	+	+
Norway													
Steen, 2005	−	+	?	?	?	+	−	−	−	+	+	+	+
Klovstad, 2012	?	+	+	−	?	+	−	−	−	+	+	+	+
Slovenia													
Klavs, 2004	+	+	+	−	?	+	−	−	+	+	+	+	+
Spain													
Franceschi, 2007	−	+	?	+	−	+	−	−	−	+	+	+	+
Sweden													

	Target population representative of country	Target population clearly defined	Source population representative of target	Sample size calculation	Adequate sample size achieved	Probability sampling	Respondents match target population	Response rate 70% limit	Response rate 60% limit	Standardised questionnaire	NAAT used	Appropriate analysis	Confidence intervals
Brannstrom, 1992	−	+	+	−	?	−	?	−	+	+	−	+	+
Jonsson, 1995	−	+	?	+	?	+	+	+	+	+	−	+	+
Novak, 2003	−	?	?	−	?	−	?	−	−	+	+	+	+
Novak, 2004	−	?	?	−	?	+	?	−	+	+	+	+	−
Domeika, 2007	−	?	?	−	?	?	−	−	−	+	+	?	+
UK													
Pierpoint, 2000	−	+	?	−	?	+	−	−	−	+	+	+	+
Stephenson, 2000	−	?	?	−	?	+	−	−	−	+	+	+	+
Fenton, 2001	+	+	−	−	?	+	−	+	+	+	+	+	+
Low, 2007	?	+	?	+	−	+	−	−	−	+	+	+	+
Bracebridge, 2012	?	?	?	−	?	+	−	−	−	+	+	+	+

Response rate (defined as number tested/number asked to participate)

+ more than 80% + = 70-80% − less than 70% ? unclear/cannot be calculated (70% limit) OR

+ more than 80% + = 60-80% − less than 60% ? unclear/cannot be calculated (60% limit)

NAAT used and confidence intervals for positivity/prevalence estimates were included or could be calculated.

+ yes − no

All other items + adequate − inadequate ? unclear/not enough information provided

Figure 22. Assessment of risk of bias in chlamydia prevalence studies in non-EU/EEA European countries

	Target population representative of country	Target population clearly defined	Source population representative of target	Sample size calculation	Adequate sample size achieved	Probability sampling	Respondents match target population	Response rate 70% limit	Response rate 60% limit	Standardised questionnaire	NAAT used	Appropriate analysis	Confidence intervals
Europe, non-EU/EEA countries													
Croatia													
Bozicevic, 2011	+	+	?	+	?	+	−	−	−	+	+	+	+
Switzerland													
Baud, 2008	?	+	?	−	?	+	?	?	?	+	+	+	+
USA													
Klausner, 2001	−	+	+	+	+	+	−	−	+	+	+	+	+
Ku, 2002	?	+	?	−	?	+	+	−	−	+	+	+	−
Turner, 2002	−	+	+	−	?	+	+	+	+	+	+	+	+
Miller, 2004	+	+	+	−	?	+	+	+	+	+	+	+	+
Eggleston, 2011	?	+	+	−	?	+	−	−	−	+	+	+	+
Datta, 2012	+	+	+	−	?	+	−	+	+	+	+	+	+
Canada													
Hodgins, 2002	−	?	?	−	?	−	?	−	−	+	+	+	−
Steenbeek, 2009	−	+	?	−	?	−	−	+	+	+	+	+	−
Australia													
Miller, 2003	−	?	?	−	?	−	+	−	−	+	+	+	+
Latif, 2004	−	?	?	?	?	?	?	−	−	?	+	+	−
Hocking, 2006	?	+	+	+	−	+	−	−	−	+	+	+	+
Huang, 2008	−	+	?	−	?	?	+	?	?	?	+	+	−
New Zealand													
Corwin, 2002	−	+	?	+	−	+	−	+	+	+	+	+	+

Response rate (defined as number tested/number asked to participate)

+ more than 80% + = 70-80% − less than 70% ? unclear/cannot be calculated (70% limit) OR

+ more than 80% + = 60-80% − less than 60% ? unclear/cannot be calculated (60% limit)

NAAT used and confidence intervals for positivity/prevalence estimates were included or could be calculated.

+ yes' − 'no' All other items + adequate − inadequate ? unclear/not enough information provided

Table 11. Between study heterogeneity in estimates of chlamydia prevalence in studies done in the EU/EEA

Group		Women		Men	
		Number of studies	I^2, %	Number of studies	I^2, %
All ages	Sexually experienced	13	97.6	12	91.3
	Whole study population	10	85.8	11	92.9
Young adults	Sexually experienced	12	72.8	10	83.7
	Whole study population	12	80.6	10	92.4

Table 12. Summary of characteristics of included population-based studies of chlamydia prevalence from EU/EEA Member States

Country	First author and year of main publication *(+ related publications)*[†]	Sex	Age, years	Number invited for testing	Overall response rate, reported by authors	Calculated response rate, n tested/ n invited, %	Setting and sampling method
Denmark	Østergaard, 1998[44] *(Ostergaard, 2000[132])*	F&M	mean 18.0 women 18.2 men	2 603 women (928 eligible) 1 733 men (442 eligible)	48% women 34% men	33.3% sexually experienced women 24.8% sexually experienced men	Random sample (half) of all high schools in Aarhus County. All students invited. Eligible if sexually experienced. (Only data from home sampling group included)
Denmark	Munk, 1999[42] *(Kjaer, 1996[205])*	F	20-29	16 345 eligible 11 088 in cohort 525 samples tested	not reported only tested 5% of cohort samples	67.8% enrolled in cohort and had cervical samples taken	Random sample of women born in Denmark, in catchment area of Righospitalet, Copenhagen taking part in a cohort study, who had given a cervical swab sample.
Denmark	Bennedsen, 2001[41]	M	17-32	2 500	57%	53.8%	All men in Northern Jutland, Aarhus or Copenhagen counties liable for military service and seen by a medical board
Denmark	Andersen, 2002[45] *(Møller, 1999[46] Andersen, 2011[47])*	F&M	21-23	4 000 women 5 000 men	1: 39% women 27% men 2: 33% women 17% men	1: 32.5% women 25.9% men 2: 26.3% women 15.4% men	Simple random sample from all residents of Aarhus County aged 21-23 years. Group 1 received sampling kit, group 2 requested kit by post
Estonia	Uusküla, 2008[72] *(Uusküla, 2011[73])*	F&M	18-35	1 398 reachable	34% overall 48% women 32% men	34.8 % overall	Stratified random sample of residents of Tartu county.
France	Goulet, 2010[74] *(Bajos, 2010[75] Goulet 2011) [76]*	F&M	18-44	4 957 eligible by age and sexual experience	52% of those eligible 54% women 49% men	52% overall 54.4% women 49.3% men	NatChla: random subsample of sexually experienced people from national population-based survey on sexual behaviour with two-phase stratified sampling (CSF study).
Germany	Haar, 2012[63] *(Desai, 2011[67], Kurth, 2008[65] Thierfelder, 2007 [66] Kamtsiuris, 2007[64])*	F&M	12-17	5 755 in this age group	66.6% of 0-17 year olds 63% for 14-17 year olds	not enough information to calculate	Tested urine samples from participants aged 12-17 in nationally representative sample of 0-17 year olds (KIGGS study)
Germany	Haar, unpublished[68] *Scheidt-Nave, 2012[69]*	F&M	18-79	7 988 DEGS participants of whom 7116 had examination and interview data	42% in those newly asked 62% in those who took part in 1998 survey	43.6% for 18-79 year olds	Tested urine samples from participants in nationally representative sample of 18-79 year olds (DEGS study unpublished preliminary results)
Netherlands	van Valkengoed, 2000[25] *(van Valkengoed, 2000[26] van Valkengoed, 1999[27])*	F&M	15-40	5 714 women 5 791 men	51% women 33% men	50.8% women 33.0% men	Random sample of patients on the lists of 16 general practices in Amsterdam

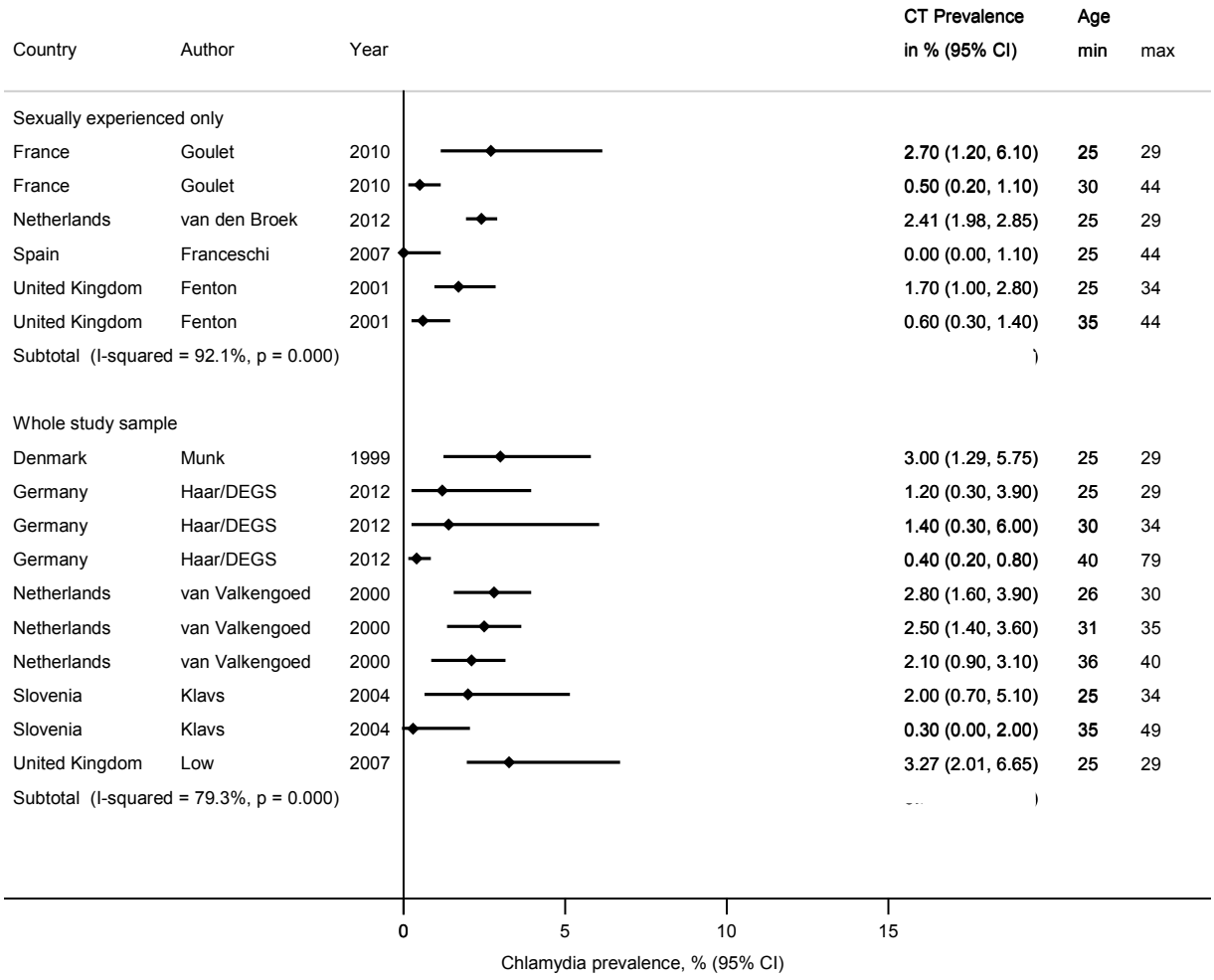
Country	First author and year of main publication *(+ related publications)*[†]	Sex	Age, years	Number invited for testing	Overall response rate, reported by authors	Calculated response rate, n tested/ n invited, %	Setting and sampling method
Netherlands	van Bergen, 2005[28] *(Götz, 2006[34] van Bergen, 2006[35] Götz, 2006[33] Veldhuijzen, 2005[30] Götz, 2005[31] van Bergen, 2005[29] Götz, 2005[32])*	F&M	15-29	20 791	41% overall 47% women 33% men	40.3% overall	Stratified probability sample of randomly selected men and women in 4 regions according to population density. Regions not sampled at random.
Netherlands	van Bergen, 2010[36] *(Op de Coul, 2012[39] Greenland, 2011[38] van den Broek, 2010[37] van den Broek, 2012[40] Götz 2012)*	F&M	16-29	139 919 Amsterdam 103 335 Rotterdam (numbers from van den Broek 2012 1st invitation)	17.2% Amsterdam 15.8% Rotterdam	17.2% Amsterdam 15.8% Rotterdam	All 16-29 year old residents of Amsterdam, Rotterdam, parts of South Limburg. Sexually active people invited to request test kit. South Limburg excluded because eligibility depended on response to questionnaire assessing risk of chlamydia.
Norway	Steen, 2005[70]	F&M	18-29	646	36% overall 43% women 25% men	36.3% overall 43.8% women 25.0% men	All patients on the list of a group practice in Oslo (Saeter physician group)
Norway	Klovstad, 2012[71]	F&M	18-25	10 000 invited, 1 670 returned sample	16.7% overall 18.9% women 11.9% men	16.7% overall 18.9% women 11.9% men	Simple random sample of 10,000 people aged 18-25 and living in Rogaland county using unique personal identification number.
Slovenia	Klavs, 2004[77] *(Klavs, 2002[78])*	F&M	18-49	2 616	55.3% overall 60.0% women 50.9% men	60.0% women 50.9% men	Stratified two stage probability sample of the general population of Slovenia. All participants invited to provide specimen for chlamydia testing.
Spain	Franceschi, 2007[79] *(de Sanjose 2003[80])*	F	15-44	1 821 invited 916 reached or accepted	63-69% depending on age group	66.1% for 15-49 years	Random age stratified sample of the adult female general population from census list of 4 urban communities in metropolitan Barcelona, part of a larger HPV study
Sweden	Brännstrom, 1992[48]	F	15-34	543 reached and sexually experienced	68.9%	68.9%	All sexually experienced women aged 15-34 in a primary health care area in Nättraby
Sweden	Jonsson, 1995[49] *(Jonsson, 1995[50] Karlsson, 1995[51])*	F	19,21,23,25	816 reached	70% eligible participated	68.3%	All women aged 19, 21, 23 or 25 living in primary health care area of Ålidhem community centre in Umeå.
Sweden	Novak, 2003[52]	M	22	1 074	38.5% including questionnaire only or refusal	35.6%	All males aged 22 living in Umeå.
Sweden	Novak, 2004[53]	F&M	20-24	200	55% overall 65% women 45% men	not enough information to calculate	Simple random sample of 100 men and 100 women aged 20-24 living in Umeå

Country	First author and year of main publication *(+ related publications)*[†]	Sex	Age, years	Number invited for testing	Overall response rate, reported by authors	Calculated response rate, n tested/ n invited, %	Setting and sampling method
Sweden	Domeika, 2007[54]	M	19-24	1 936 reached	24% responded	14.5%	1000 men living in Uppsala county (from population register), and 1000 Uppsala university students (from student register database). Sampling method unclear
United Kingdom	Stephenson, 2000[55]	F&M	18-35	166 women 175 men reachable	39% women 46% men in available sample	42.5% overall 39.0% women 46% men	Random sample of patients on the lists of 3 general practices in North West London and Avon
United Kingdom	Pierpoint, 2000[56]	M	18-35	919 invited by post and reachable	45.3% in postal survey	45.3% in postal survey	Postal recruitment of all men aged 18-24 and a random sample of men aged 25-35 in 4 general practices, NW London
United Kingdom	Fenton, 2001[57] *(Johnson, 2001[58]* *McCadden, 2005[59])*	F&M	18-44	5 026 invited to give urine sample (total 11 161)	65.4% response rate overall to Natsal, 71% of those invited provided sample	71.1% women 68.7% men (from technical report)	Random sample of sexually experienced people taking part in a stratified probability sample of people aged 16-44 years resident in the United Kingdom (Natsal-2 study)
United Kingdom	Low, 2007 *(Macleod, 2005[60]* *Low, 2004[61])*	F&M	16-39	14 382 reached	34.5% overall 39.5% women 29.5% men	32.9% overall (unadjusted)	General population in Birmingham and Bristol areas, random sample selected from 27 general practice lists.
United Kingdom	Bracebridge, 2012[62]	F&M	18-24	29 917	11.5% overall	11.5% overall 13.2% women 9.8% men	All people aged 18-24 registered with any GP in North East Essex Primary Care Trust

GP, general practitioner; HPV, human papillomavirus; M, men; W, women

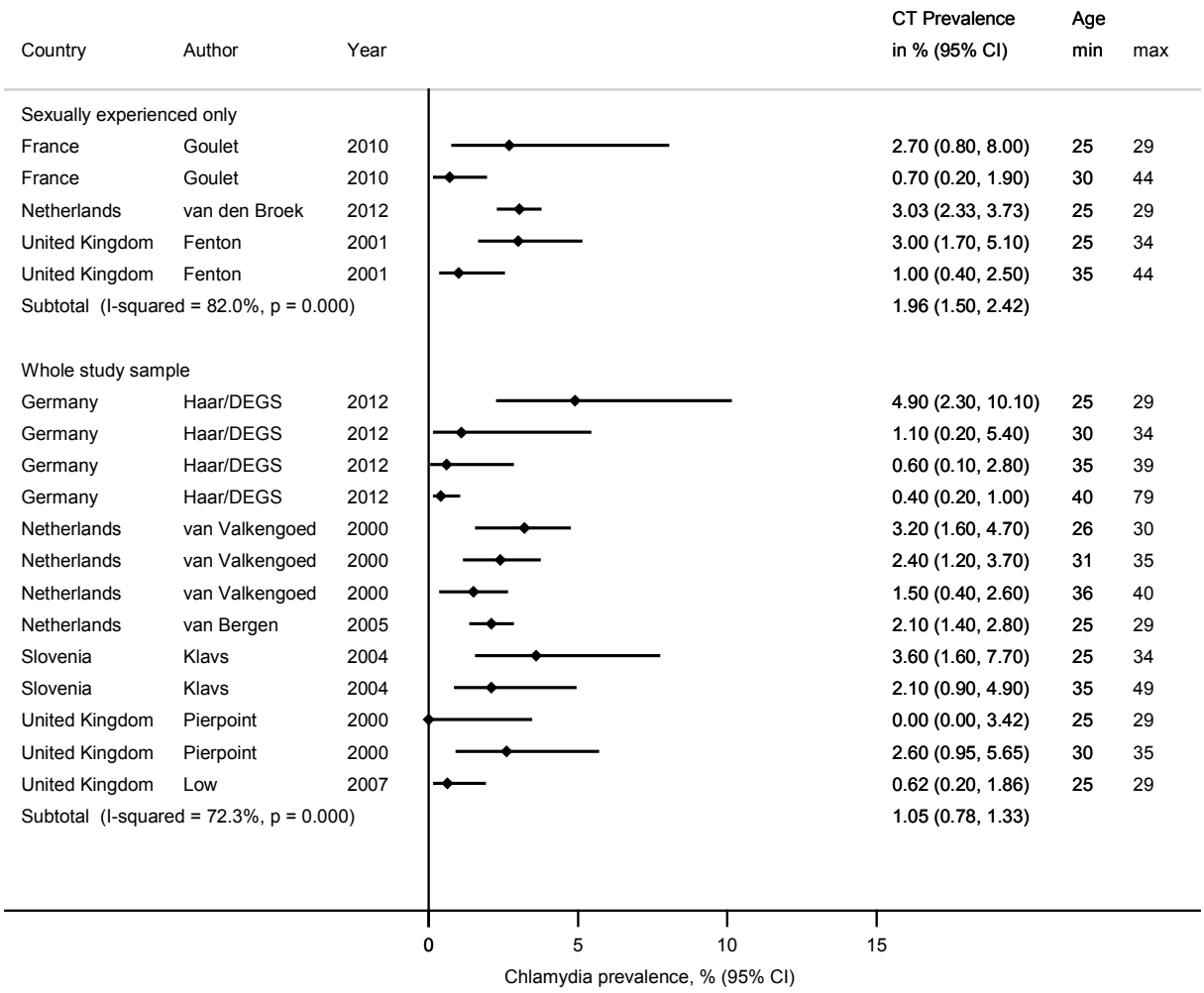
[†] *Additional publications are those that use data from the same study but report subsidiary findings, or report methodological aspects of the study*

Figure 23. Estimates of chlamydia prevalence, EU/EEA Member States, women aged ≥25 years



CT, Chlamydia trachomatis; CI, confidence interval; min, minimum age in years; max, maximum age in years. Forest plot shows each row as a study or separate age group in the same study. The diamond shows the point estimate of prevalence, the lines either side are the 95% CI. Estimates are shown separately for sexually experienced participants only or for the whole sample; the studies in each group are not necessarily the same because comparable data are not available for all studies.

Figure 24. Estimates of chlamydia prevalence, EU/EEA Member States, results for men aged ≥25 years



CT, Chlamydia trachomatis; CI, confidence interval; min, minimum age in years; max, maximum age in years. Forest plot shows each row as a study or separate age group in the same study. The diamond shows the point estimate of prevalence, the lines either side are the 95% CI. Estimates are shown separately for sexually experienced participants only or for the whole sample; the studies in each group are not necessarily the same because comparable data are not available for all studies

Table 13. Summary of characteristics of included population-based studies from non-EU/EEA European countries, EU applicant countries and non-EU/EEA high income countries

Country, Region	Main publication *(+ related publications)*	Sex	Overall age, years	Number of participants invited for testing	Overall response rate, reported by authors	Calculated response rate, n tested/ n invited, %	Setting and sampling method
Croatia	Bozicevic, 2011	W&M	18-25	1 005	32.5 % of sexually active provided urine 37.5% women 27.9% men	32.5 % overall 37.5% women 27.9% men	Nationally representative sample from all 21 counties in Croatia, with multi-stage probability sampling.
Switzerland	Baud, 2008	M	18-26	521 eligible and gave written consent	99.2% of those eligible	not enough information to calculate	Young Swiss men attending obligatory medical board before army recruitment (French speaking region only).
Australia	Miller, 2003 *(Miller, 2002* *Miller, 1999)*	W&M	15-40+	6 431 indigenous and aged >15 yrs 2 862 participated in WPHC	44.5% indigenous population aged >15 participated in WPHC	43.8% overall	All people living in 26 rural indigenous Australian and Torres Strait Islander communities in northern Queensland taking part in Well Person's Health Check (WPHC).
Australia	Latif, 2004	W&M	15-35	2 703 eligible listed 1 219 screened	45.1% eligible screened 50.1% women 39.3% men	45.1% overall 50.1% women 39.3% men	Indigenous Australian people aged 15-35 living in Alice Springs area
Australia	Hocking, 2006	W	18-35	1 532 eligible households 979 women interviewed 657 gave urine sample	43% provided urine sample	42.9%	Simple random sample from Melbourne residential telephone directory.
Australia	Huang, 2008	W&M	14-40	ca. 1 300 in 1996	61-75% (1996-2006)	not enough information to calculate	All resident indigenous Australians living in the Anangu Pitjantjatjara Yankunytjatjara Lands.
Canada	Hodgins, 2002	W&M	15-39	1 075 women 1 130 men	29% women 16% men	22.6% overall 29.3% women 16.2% men	All adults from remote Inuit communities in Nunavik region. All sexually experienced or those aged 15-39 especially encouraged to take part.
Canada	Steenbeek, 2009	W&M	15-65	224	not reported	estimated 80.8% overall	All men and women aged 15-65 living in a rural Inuit community from Baffin Region, Nunavut
New Zealand	Corwin, 2002 *(Abel, 2005)*	W&M	16+	1 582 invited 1 136 consented 582 sexually active	71.6% took part 84% of sexually active provided urine sample	29.9% overall	Random sample of 50% of classes in all private and public high schools, Christchurch. Only tested sexually active.
USA	Klausner, 2001 *(Ruiz, 2000)*	W	18-29	2 148 eligible 1 439 enrolled 1 370 tested 1 314 sexually active	67% enrolled	61.2%	All English- or Spanish-speaking women aged 18-29 in a random sample of low income housing blocks from 1990 census (<10th percentile) Study done in 3 counties in CA (main HIV study in 5 counties)

Country, Region	Main publication *(+ related publications)*	Sex	Overall age, years	Number of participants invited for testing	Overall response rate, reported by authors	Calculated response rate, n tested/ n invited, %	Setting and sampling method
USA	Ku, 2002	M	18-19 22-26	1 995 survey: 1 729 interviewed (response rate 75%) 1 988 survey: 1 880 interviewed aged 15-19 (response rate 74%), of whom 75% re-interviewed aged 22-26 yrs	1995 survey: 470 samples/578 interviewed who were aged 18-19 1988 survey: 995 samples/ 1377 re-interviewed aged 22-26 yrs	81.3% of those asked aged 18-19 72.3% of those asked aged 22-26	National Surveys of Adolescent Males (NSAM) nationally representative sample of never-married non-institutionalized men aged 15-19 (1995 survey), and aged 22-26 (aged 15-19 in 1988 survey but re-interviewed in 1995) NB oversampling of Black and Hispanic youths
USA	Turner, 2002	W&M	18-35	2 727 households screened 1 224 adults aged 18-45 728 were age eligible for screening (18-35)	79.5% age eligible respondents provided urine sample	79.5% overall	Stratified probability sampling of households in Baltimore, urine samples only requested from those aged 18-35.
USA	Miller, 2004 *(Annang, 2010* *Stein, 2008* *Stein, 2008* *Manhart, 2007* *Iritani, 2006* *Geisler, 2006* *Ford, 2004)* [1] [1]	W&M	18-26	Wave I: 18924 Wave III: 14322	Wave I: 66.3% Wave III: 87.6% of those who agreed and were reachable gave urine samples	84.0% overall	US National Longitudinal Study of Adolescent Health (Add Health), nationally representative sample.
USA	Eggleston, 2011 *(Eggleston, 2005)*	W&M	15-35	4 998 eligible	58.7% eligible responders gave interviews, 73% of interview respondents gave urine sample	42.7% overall	Monitoring STI Survey Program probability sample of Baltimore residents.
USA	Datta, 2012 *(CDC, 2011* *Beydoun, 2010* *Allsworth, 2009* *Forhan, 2009* *Datta, 2007)*	W&M	14-39	20 836 selected 17 190 interviewed	83% of selected were interviewed, 96% of those interviewed were examined, 96% of those examined were tested	77.3% overall 80.4% women 74.5% men (from online results for 2007-2008)	US National Health and Nutrition Examination Surveys (NHANES): stratified multistage probability cluster sampling. Data from five 2-year survey cycles.

† *Additional publications are those that use data from the same study but report subsidiary findings, or report methodological aspects of the study*

Appendix 2. Additional material for systematic review of effectiveness of chlamydia screening programmes

Search strategy

The following databases were searched from the date of the previous review (October 2007) to February 2012 without language restrictions: Ovid Medline; Embase; The Cochrane Library. The search terms are listed in full in the protocol. We searched the World Health Organization International Clinical Trials Registry Platform from the earliest date until October 2012 using the search string 'chlamydia AND screening'. In addition we searched reference lists of reviews and potentially eligible studies and asked experts in the project team if they were aware of any other studies.

Search terms

Medline search dated 24 May 2012 given as an example

	Searches	Results
1	exp chlamydia infections/ or exp chlamydia trachomatis/ or exp chlamydia/	19 723
2	pelvic inflammatory disease.mp. or exp pelvic inflammatory disease/ or PID.mp.	11 920
3	female infertility.mp or exp Infertility, Female/	22 252
4	ectopic pregnancy.mp or Pregnancy, Ectopic/	11 408
5	2 or 3 or 4	43 192
6	exp chlamydia pneumoniae/	3 353
7	(chlamydia adj infection$).mp.	12 341
8	1 not 6	18 136
9	5 or 7 or 8	61 297
10	exp mass screening/	90 779
11	screening.mp.	30 9251
12	national chlamydia screening programme.mp.	45
13	(tested or testing).ab. or (tested or testing).ti.	787 110
14	10 or 11 or 12 or 13	1 057 138
15	exp randomized controlled trial/	327 252
16	random*.ab. or random*.ti.	557 368
17	15 or 16	647 080
18	9 and 14 and 17	367
19	limit 18 to (humans and yr="2007 - Current")	115

Figure 25. Flow chart of studies included in systematic review of the effectiveness of chlamydia screening

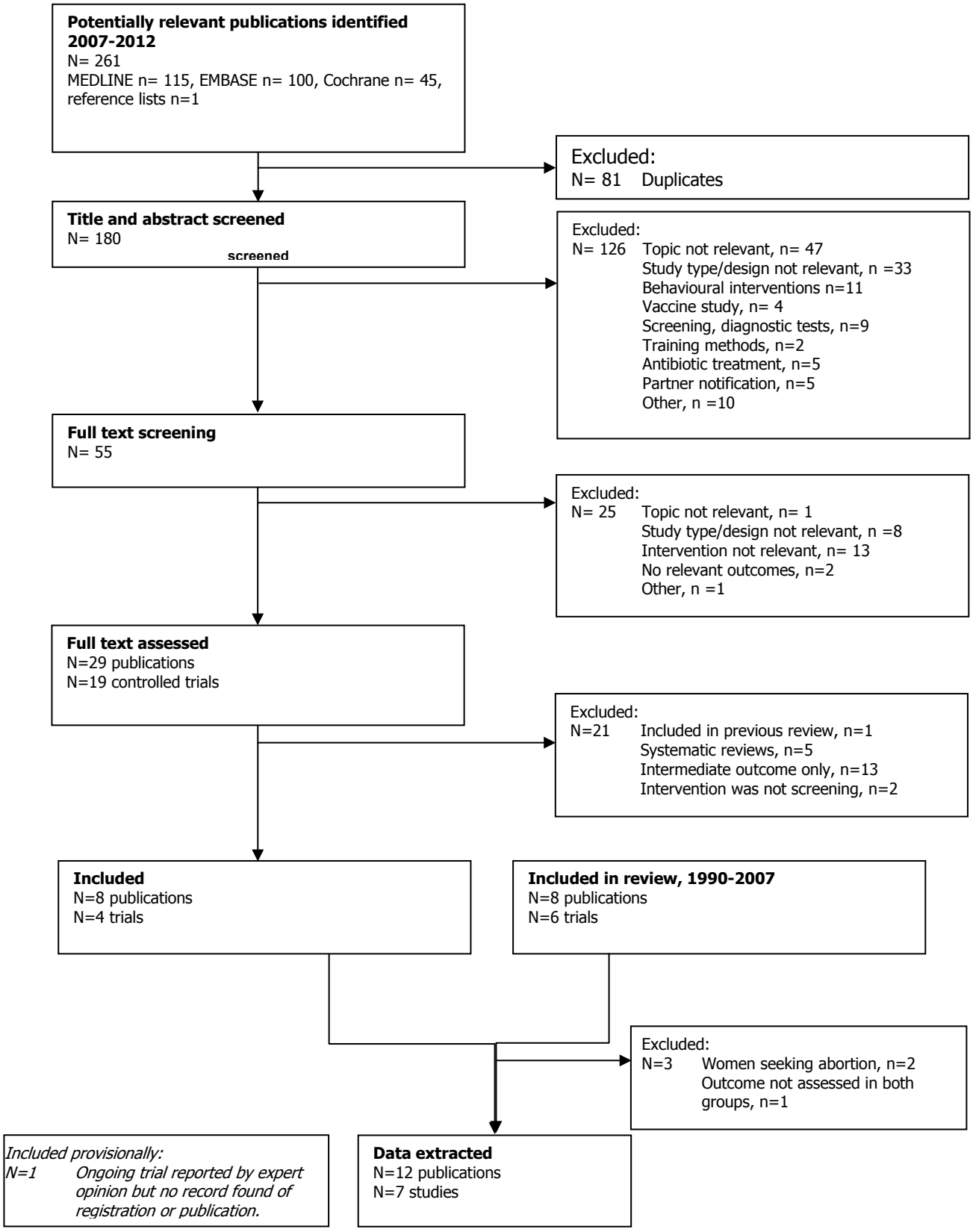


Table 14. Summary of studies included in systematic review of the effectiveness of chlamydia screening, by primary outcome and publication year

First author, publication year [ref]	Population; setting, country; dates	Study design; cluster, if appropriate	Intervention	Control condition
PID incidence				
Scholes, 1996 [131]	Sexually active women, 18-34 years, selected as being at high risk of chlamydia; health maintenance organisation, Seattle, USA; study dates Oct 1990-May 1992	Individual RCT	Invitation to be screened for chlamydia at a study health clinic. Cervical swabs tested by EIA and culture. Treatment for positive cases by primary care provider.	Usual care. Women could see primary care physician as required.
Østergaard, 2000 [132]	Sexually active women and men, mean age 18 years; schools, Aarhus County, Denmark; enrolment dates Jan 1997-Apr 1997	Cluster RCT; 17 schools	Home sampling kits sent. Urine or vaginal specimen, NAAT test. Information about chlamydia. Treatment and partner notification for positive cases by general practitioner.	Usual care. Offer of free chlamydia testing at STI clinic or other physician. Information about chlamydia. No partner notification advice.
Oakeshott, 2010 [133,178]	Sexually active women aged ≤27 years; universities and further education colleges, London, UK; enrolment dates Sep 2004-Oct 2006	Individual RCT	Vaginal swabs, self-taken in nearest lavatory at recruitment site. Tested by NAAT immediately after randomisation. Treatment and partner notification for positive cases by general practitioner or STI clinic.	Vaginal swabs, self-taken in nearest lavatory at recruitment site. Stored after randomisation for 12months and tested by NAAT. Treatment and partner notification for positive cases by general practitioner or STI clinic.
Andersen, 2011 [45,47]	Women and men aged 21-24 years at start of study, listed on health service register; Aarhus County, Denmark; enrolment dates Oct 1997-Dec 1997.	Individual RCT	Invitation to take urine or vaginal specimen at home, sent to laboratory for NAAT. Information about chlamydia. Treatment and partner notification for positive cases by general practitioner or STI clinic.	Usual care. Individuals could visit general practitioner or STI clinic as required.
Chlamydia transmission				
Cohen, 1999 [175]	Women and men aged 15-18 years (9th to 12th grade); schools, Louisiana, USA; enrolment dates Sep 1995-Sep 1998	Cluster CCT; 8 schools	Twice yearly invitation to be screened. Urine specimens taken at school, tested by NAAT. Information about STIs, consequences, prevention. Treatment and partner notification for positive cases by school nurse.	Usual care 1995-7 Invitation to be screened in 1997-8. Urine specimens taken at school, tested by NAAT. Treatment and partner notification for positive cases by school nurse.
van den Broek, 2012 [40]	Women and men aged 16-29 years, listed on municipal registers; 3 regions, The Netherlands. In one region, only those selected as being at high risk of chlamydia; enrolment dates Mar 2008-Feb 2011.	Cluster CCT; 191 postcode areas, step-wedge roll-out	Yearly invitation to be screened. Home sampling kits for urine or vaginal specimen requested by internet. Sent to laboratory for NAAT. Treatment and partner notification for positive cases by general practitioner or STI clinic.	Usual care. Individuals could visit general practitioner or STI clinic as required.
Hocking, 2011† [177]	Women and men aged 16-29 years, visiting general practices; rural towns in 4 states in Australia. Enrolment dates June 2010-Dec 2011.	Cluster RCT; rural town	Yearly opportunistic offer of screening. Multi-faceted intervention to support general practice staff. Urine specimens taken at general practice. Treatment and partner notification for positive cases by general practitioner.	Usual care. Individuals can visit general practitioner or STI clinic as required.
Lehtinen‡	Women taking part in vaccination trial	Cluster RCT	Yearly invitation to be screened.	Usual care.

† Publication describes study design, no results for primary outcome;
‡ No trial registration or publication found yet;
CCT, controlled clinical trial; EIA, enzyme-linked immunoassay; NAAT, nucleic acid amplification test; PID, pelvic inflammatory disease; RCT, randomised controlled trial; STI, sexually transmitted infection.

Appendix 3. Additional material for systematic review of cost-effectiveness of chlamydia screening programmes

Search strategy

The following databases were searched from the date of the previous review (XXX_2004) to February 2012 without language restrictions: Ovid Medline; Embase; The Cochrane Library. The search terms are listed in full in the protocol. In addition we searched reference lists of reviews and potentially eligible studies and asked experts in the project team if they were aware of any other studies.

Search terms

Medline search dated 14 February 2012 given as an example

	Searches	Results
1	exp chlamydia infections/ or exp chlamydia trachomatis/ or exp chlamydia/	19 355
2	pelvic inflammatory disease.mp. or exp pelvic inflammatory disease/ or PID.mp.	11 797
3	1 or 2	29 919
4	economic evaluation.mp. or economic evaluation/	3 771
5	cost-utility analysis.mp. or "cost utility analysis"/	869
6	cost-effectiveness analysis.mp. or "cost effectiveness analysis"/	4 196
7	quality of life.mp. or "quality of life"/ or QALY/	145 548
8	"cost minimisation"/ or "cost minimization"/ or "cost benefit analysis"/ or economics/	78 201
9	4 or 5 or 6 or 7 or 8	216 955
10	3 and 9	305
11	limit 10 to (humans and yr="2004 - 2011")	96

Figure 20. Flow chart of studies included in systematic review of the cost-effectiveness of chlamydia screening

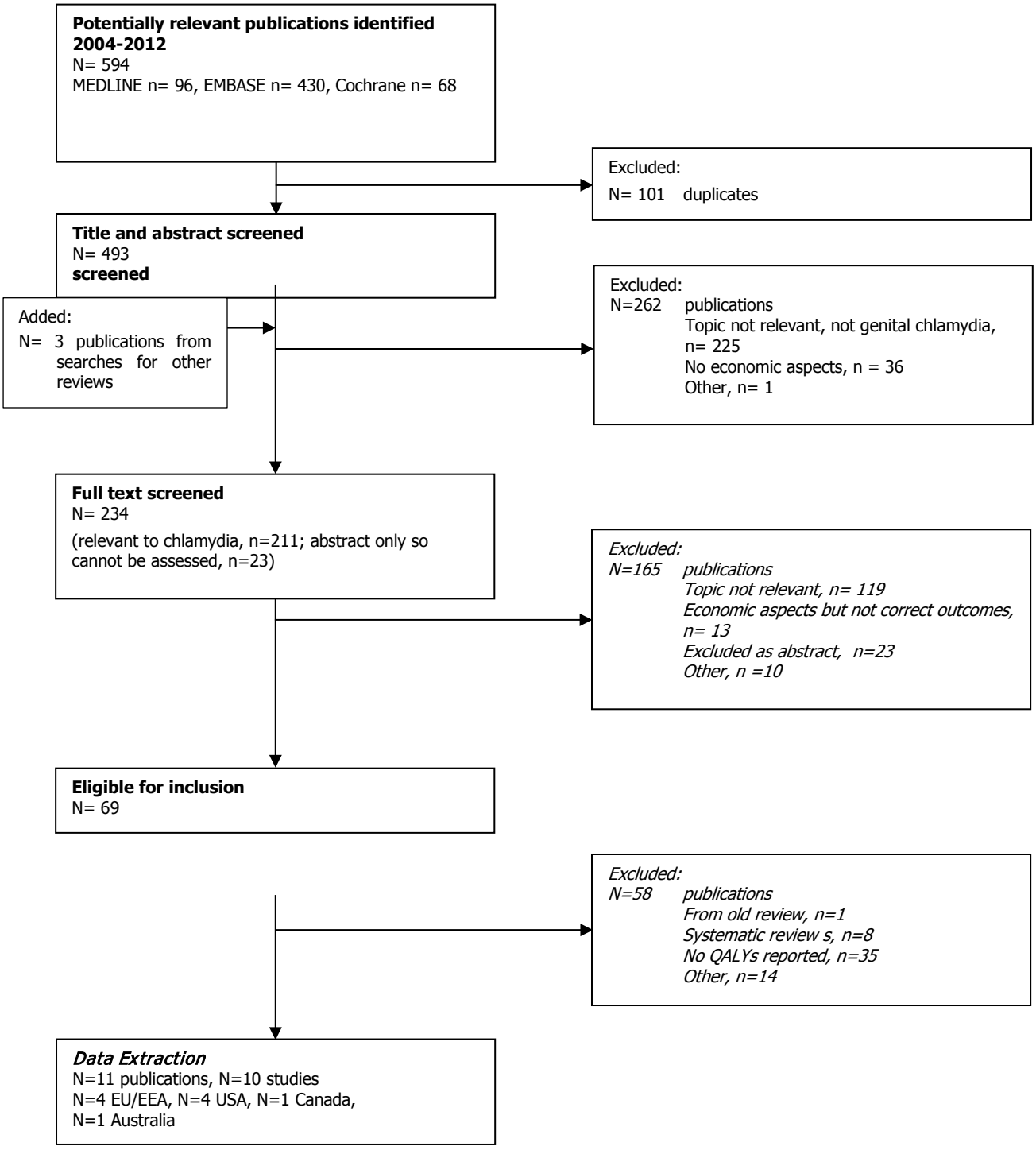


Table 15. QALY weights and duration

Condition	Health Utility Index value	Duration, years	Duration, days/weeks	Comment
Asymptomatic	1.00			
Cervicitis/Bartholinitis	0.90	0.0767	4 weeks	
PID				
Outpatient	0.63	0.0274	10 days	
Inpatient, no surgery	0.57	0.0055	2 days	
Inpatient, surgery	0.46	0.0055	2 days	
Outpatient treatment after inpatient	0.83	0.0274	10 days	
Ectopic pregnancy				
Outpatient	0.58	0.0767	4 weeks	5-year lag
Inpatient	0.23	0.0082	3 days	5-year lag
Outpatient treatment after inpatient	0.66	0.0767	4 weeks	
Chronic pelvic pain	0.60	22.7313	Remaining lifetime	5-year lag
Infertility	0.82	22.7313	Remaining lifetime	5-year lag

Table uses data from Institute of Medicine Table A2-2, p56 [204]. Health Utility Index Mark II values and the duration of each condition were assigned by consensus of an expert committee. Health Utility Index Mark II uses 7 domains: sensory, mobility, emotional, cognitive, self-care, pain, fertility, with 3-5 levels within each domain. A value of 1.00 represents the highest level of functioning within each domain. Scores in all 7 domains are multiplied to give the overall Health Utility Index value, which is equivalent to a QALY weight.