Screening for genital chlamydia infection (Protocol)


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Screening for genital chlamydia infection

Nicola Low¹, Shelagh Redmond¹, Anneli Uusküla², Jan van Bergen³, Helen Ward⁴, Berit Andersen⁵, Hannelore Götz⁶

¹Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland. ²Department of Public Health, University of Tartu, Tartu, Estonia. ³Department of General Practice and Family Medicine, University of Amsterdam, Amsterdam, Netherlands. ⁴Department of Infectious Disease Epidemiology, Imperial College London, London, UK. ⁵Department of Public Health Programmes, Randers, Denmark. ⁶Department of Infectious Disease Control, Rotterdam-Rijnmond Public Health Service, Rotterdam, Netherlands

Contact address: Nicola Low, Institute of Social and Preventive Medicine (ISPM), University of Bern, Finkenhübelweg 11, Bern, CH-3012, Switzerland. low@ispm.unibe.ch.

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects and safety of chlamydia screening in pregnant and non-pregnant women and in men, compared with standard care, on chlamydia transmission and on complications of infection.

BACKGROUND

Description of the condition

Genital infections caused by Chlamydia trachomatis serovars D-K are the most prevalent bacterial sexually transmitted infection worldwide, with an estimated 106 million people being infected in 2008 (WHO 2012). In this protocol we use the term ‘chlamydia’ to describe these infections. Chlamydia is the most common notifiable infection in the USA, with 1,307,893 infections reported in 2011 compared with 309,341 cases of gonorrhoea, which is the second most common notifiable condition (CDC 2010). Chlamydia is also the most commonly reported infection in Europe (ECDC 2011), Australia (DoHA 2011) and Canada (PHAC 2006). Chlamydia is most common in young sexually active adults. The prevalence of chlamydia has been estimated to be about 3% to 5% in nationally representative samples of sexually experienced women and men aged 25 years and under in high-income countries (Fenton 2001; Klavs 2004; Miller 2004; Goulet 2010; Bozicevic 2011).

C. trachomatis is a gram negative obligate intracellular bacterium, which infects columnar epithelium in the lower genital tract in women and men and can also infect the rectum, pharynx, conjunctiva (Stamm 2008) and placenta (Rours 2011). Chlamydia infection causes complications, most commonly resulting from spread from the lower to the upper genital tract. Upper genital tract infection occurs in both sexes but is more common and has more severe consequences in women (Stamm 2008). In women, chlamydia ascends to the upper genital tract in approximately 10% of cases to cause symptomatic pelvic inflamma-
tory disease (PID) (Oakeshott 2010; Herzog 2012). The result-
ing tubal damage can then cause ectopic pregnancy, tubal infer-
tility and chronic pelvic pain (Paavonen 2008). Although about
45% of tubal infertility might be attributable to chlamydia infect-
(Price 2012), the probability of tubal infertility in women who have had chlamydia is estimated to be only 1% to 4% (Land
2010; Kavanagh 2013). Chlamydia infection in pregnancy is as-
associated with preterm labour (Rours 2011) and can infect the
neonate, causing ophthalmia neonatorum and atypical pneumo-
nia (Kohlhoff 2008). C. trachomatis can cause epididymo-orchitis
in men, but its role in prostatitis and male infertility is not well-
established (Stamm 2008). Chlamydia can also cause Reiter’s syn-
drome in men (Stamm 2008) and is a co-factor for HIV infection,
increasing both susceptibility and infectiousness (Fleming 1999).
Uncomplicated genital chlamydia infections are usually asym-
tomatic in both women and men (Stamm 2008) and untreated
infections last more than a year on average (Althaus 2010). C. trach-
omatis can be treated with tetracyclines (usually doxycycline) or
macrolide (usually azithromycin) antibiotics with short-term mi-
crobiological cure rates of 90% to 95% (Manhart 2013). Immuni-
ity after chlamydia infection is incomplete and repeated chlamy-
dia infection is common (Batteiger 2010a). In studies of women
enrolled from primary care and sexual health clinics and followed
up prospectively, about 25% of women treated for chlamydia had
the infection detected again in the year after treatment (Scott
LaMontagne 2007; Walker 2012). There are several reasons for re-
peated detection of chlamydia. In one prospective study amongst
young women in the USA, Batteiger et al. combined information
about sexual behaviour and genotype from 183 women with more
than one episode of chlamydia infection to estimate that about
66% of infections were probably acquired from a new partner,
17% were re-infections from untreated or inadequately-treated
sexual partners, 14% were probable antibiotic treatment failures
and 3% persisted without treatment (Batteiger 2010b). There is
some evidence to suggest that immunity after natural clearance
of chlamydia infection lasts longer than immunity after antibiotic
treatment (Geisler 2013).

Description of the intervention

Screening of sexually active young adults is the only way to detect
most chlamydia infections because of the lack of symptoms or
clinical signs in most infected people. Screening is a process of
identifying apparently healthy people who may be at increased risk
of a disease or condition. They can then be offered information,
further tests and appropriate treatment to reduce their risk and/or
any complications arising from the disease or condition (UKNSC
2013).

There are two goals of screening for genital chlamydia infection:
first, to control the transmission of chlamydia and reduce the
prevalence of infection in the population; and second to reduce the
risk of complications, especially reproductive tract complica-
tions in women (Meyers 2007; NCSP 2010). Screening is a pro-
gramme, not a test (Raffle 2007). This means that screening in-
cludes the whole system of events needed to reach the endpoint of
reducing the risk of disease or complications. For chlamydia infec-
tion, screening includes offering a test to diagnose C. trachomatis,
treating people with a positive test, partner notification to identify
and treat sexual partners and repeated screening to detect and treat
newly acquired infection or re-infection.

The target group for chlamydia screening is usually defined by
age and sex. For example, chlamydia screening in the USA is rec-
ommended for women aged 25 years and under (CDC 2010), in
Australia for women under 25 years (RACGP 2007), and in the
UK for women and men aged 25 years and under (NCSP 2010).
Whilst behavioural and demographic factors can be used to iden-
tify groups at higher risk of chlamydia infection (Stergachis 1993;
Gotz 2005), risk factors differ between populations and selective
criteria can be difficult to apply in practice.

Chlamydia screening can be offered systematically, using a pop-
ulation register to invite people in the target age group (van den
Broek 2012). More commonly, screening is recommended as an
opportunist activity to be offered to eligible young adults attend-
ing healthcare services (RACGP 2007; CDC 2010; NCSP 2010).
Repeated screening is recommended in some countries, given the
frequency of repeated chlamydia and the fact that young adults
may change sexual partners over time. In England, the National
Chlamydia Screening Programme recommends a screening test
every year or after a change of sexual partner (NCSP 2010). Vis-
its for cervical cancer screening in young women can be used as
an opportunity to offer chlamydia screening in some countries,
where the target age groups and screening frequency overlap. In
the UK, however, cervical cancer screening is only recommended
for women over 25 years.

How the intervention might work

The way in which chlamydia screening might work depends on
the goal of screening. To reduce chlamydia prevalence and inci-
dence, the coverage of screening has to be high enough to iden-
tify and treat prevalent cases of chlamydia and to interrupt chains
of chlamydia transmission in the population. Screening also has
to be frequent enough to prevent repeated infections because of
the limited immunity after treatment. Mathematical models show
that chlamydia screening reduces prevalence over time; in several
models, screening of 30% or more of the target population each
year is needed to reduce chlamydia prevalence markedly (Regan
2008; Althaus 2012). There are two ways in which screening for chlamydia might
work to prevent reproductive tract complications (Peterman 2009;
Herzog 2013). First, direct prevention of PID occurs if screening
detects and treats an endocervical chlamydia infection in an in-
dividual woman before the infection ascends in the genital tract
to cause PID and subsequent tubal damage. The effectiveness of
screening depends on the timing of progression from lower to upper genital tract infection. If PID occurs immediately, or shortly after the initial lower genital tract infection, there is no opportunity for screening to work (Smith 2007; Herzog 2012). Randomised controlled trials (RCTs) have shown that the incidence of clinically diagnosed PID is lower in women actively invited for chlamydial screening compared to those receiving usual care (Scholes 1996; Ostergaard 2000; Oakeshott 2010; Andersen 2011). Women infected with chlamydia who are enrolled into trials have persisting prevalent infections with an unknown date of infection. The trial findings and supportive evidence from mathematical modelling studies suggest, therefore, that PID development can occur during the course of infection (Herzog 2012). Second, prevention of the transmission of chlamydia through screening and treatment has an indirect effect on the risk of PID because the risk of becoming infected with chlamydia in the first place falls. Prevention of PID should lead to a reduction in the incidence of ectopic pregnancy and tubal infertility if tubal scarring is prevented. It is, however, very difficult to measure the impact of chlamydia screening on these outcomes because women in the age groups at highest risk of chlamydia infection are usually contraception. In one RCT, the incidence of ectopic pregnancy and infertility after 11 years of follow-up were similar in women who had received a single invitation to be screened for chlamydia and women who received usual care (Andersen 2002). There are also potential harms of chlamydia screening. First, a woman who has been treated for chlamydia becomes susceptible and is at risk of repeated infection and PID. It has been suggested that the risk of PID is higher with subsequent chlamydia infections (Hillis 1997), possibly because repeated exposure to C. trachomatis antigens can cause immune mediated tubal damage (Brunham 2005). Second, being diagnosed with a sexually transmitted infection can have a negative emotional and psychological impact on the infected person (Mills 2006; Gottlieb 2011). In one study in the USA, sexual partnerships broke down for 33% of women with a positive chlamydia test result compared with 11% of those receiving a negative result (Gottlieb 2011). Third, the experience of screening can cause anxiety. In a study in the UK, however, chlamydia screening did not increase anxiety or depression and did not reduce self-esteem (Campbell 2006).

**Why it is important to do this review**

Screening for chlamydia infection is widely recommended (RACGP 2007; CDC 2010; NCSP 2010; Low 2012) and widely practised. Rates of chlamydia testing amongst young adults are high (4000 to 9000 per 100,000 population) in several high-income countries (Bender 2011). There is a strong rationale for early detection and treatment of chlamydia infection in asymptomatic young adults to reduce both transmission and complications (Low 2013). Widespread screening for asymptomatic chlamydia infection has the potential to cause harm, however, especially if the rate of repeated infection after treatment outweighs the benefits of detecting and treating asymptomatic infections, or if receiving a diagnosis of chlamydia results in the breakdown of a relationship (O’Farrell 2013). There are few data about long-term trends in chlamydia prevalence in countries that recommend chlamydia screening. In the USA, repeated cross-sectional studies show that chlamydia prevalence fell between 1999 and 2008 in 14 to 39 year olds as a whole, but not in 15 to 25 year old women, who are the target population for screening (Datta 2012). There is a systematic review of the effectiveness of chlamydia screening interventions in studies published up to 2007 (Low 2009). There are new RCTs showing that a one-off screening invitation could reduce the incidence of PID one year later (Scholes 1996; Ostergaard 2000). Also, we know that there are new completed trials with PID (Oakeshott 2010; Andersen 2011) and transmission (van den Broek 2012) as endpoints, and at least one ongoing trial (Hocking 2012). It is therefore important to develop a Cochrane review about this issue.

**Objectives**

To assess the effects and safety of chlamydia screening in pregnant and non-pregnant women and in men, compared with standard care, on chlamydia transmission and on complications of infection.

**Methods**

**Criteria for considering studies for this review**

**Types of studies**

Randomised controlled trials, non-randomised controlled trials. If there are no RCTs addressing a primary outcome of chlamydia screening, we will include non-randomised studies. Chlamydia screening is a complex population-based intervention, one aim of which is to reduce chlamydia prevalence in a population. This is an outcome that is unlikely to be studied in RCTs (Cochrane 2011). Cluster-randomisation is technically possible, but our previous systematic review did not find any RCTs that examined the effect of chlamydia screening on chlamydia transmission (Low 2009). With cluster allocation, trials will be eligible if the groups receive the intervention during different time periods, as long as baseline and outcome data were collected prospectively using the same criteria throughout the trial period. The risk of bias in methods of allocation will be assessed and results from randomised and non-randomised study designs will be analysed separately.
We will exclude cohort studies, case-control studies, and interrupted time-series studies.

**Types of participants**
Women and men (heterosexual or men who have sex with men) aged over 13 years in any setting. The minimum age group is arbitrary but aims to identify only studies of sexually transmitted chlamydia infections.

**Types of interventions**
Intervention: Screening for sexually transmitted genital chlamydia infection, defined as the offer of a test to apparently healthy people to identify those at increased risk of chlamydia infection. This definition is adapted from the UK National Screening Committee (UKNSC 2013). We will include any test used to diagnose genital chlamydia infection.
Comparison: Inactive control (no offer of screening or standard care).

**Types of outcome measures**
Eligible trials must include at least one of the pre-specified primary outcomes. The primary outcomes will be measures of morbidity that a chlamydia screening programme aims to prevent. One criterion for assessing the effectiveness of a screening programme is that ‘There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity’ (http://www.screening.nhs.uk/criteria).

**Primary outcomes**
We include one primary outcome for each goal of chlamydia screening:
- Outcome for *C. trachomatis* transmission: Prevalence of chlamydia infection in women and men at least 12 months after the start of the screening intervention. Prevalence is estimated as the number of positive chlamydia tests divided by the number of people tested.
- Outcomes for reproductive tract morbidity: Incidence of upper genital tract infection in women and men in the 12 months after the offer of screening. Pelvic inflammatory disease (women) or epididymitis (men) are clinical diagnoses, made using clinical criteria defined in advance by the authors. Examples include criteria published by the US Centers for Disease Control and Prevention (CDC 2010), or Hager and Eschenbach (Hager 1983).
- Outcome for chlamydia infection in pregnancy: Incidence of preterm delivery. Preterm delivery is defined as delivery at a gestational age of less than 37 weeks, with subgroups of gestational ages less than 32 weeks and less than 35 weeks (Rours 2011).

**Secondary outcomes**
Outcomes measured in all participants:
- Proportion of participants receiving the intervention, defined as the number tested for chlamydia divided by the number eligible and invited to take part.
- Harms of screening, including psychological distress, partner violence, relationship breakdown, using definitions described by the authors.

Outcomes measured in women who were not pregnant during the trial or in men:
- Prevalence of chronic female pelvic pain, defined as patient-reported pain in the lower abdomen or pelvis lasting at least six months (Paavonen 2008).
- Prevalence of female or male infertility, defined using a clinical definition of lack of pregnancy despite unprotected intercourse for 12 months or more (Paavonen 2008).

Outcomes measured in women who were pregnant during the trial, or in their infant:
- Incidence of *C. trachomatis* neonatal conjunctivitis, defined as *C. trachomatis* isolated from the conjunctiva by culture or detected by nucleic acid amplification test (Kohlhoff 2008).
- Incidence of *C. trachomatis* neonatal pneumonia, defined as signs of lower respiratory tract infection presenting between 4 and 12 weeks with *C. trachomatis* isolated from the nasopharynx by culture or detected by nucleic acid amplification test (Kohlhoff 2008).

The following outcome will not be included: uptake of chlamydia screening. Screening uptake is an intermediate outcome. The relationship between uptake of screening and the primary outcomes has not been quantified so, for a given level of screening uptake, it is not possible to predict the expected reduction in chlamydia prevalence or incidence of pelvic inflammatory disease.

**Search methods for identification of studies**
We will attempt to identify trials meeting the inclusion criteria irrespective of their language, publication date and publication status (published, unpublished, in press, and in progress). We will use both electronic searching in bibliographic databases and hand-searching, as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011a). The results of all searches will be downloaded and managed using Endnote bibliographic software. Duplicate records of the same study will be deleted.

**Electronic searches**
We will contact the Trials Search Coordinator (TSC) of the Sexually Transmitted Infections Cochrane Review Group in order to
implement a comprehensive search strategy which seeks to capture as many relevant trials as possible in electronic databases. For this purpose, we will use a combination of controlled vocabulary (MeSH, Emtree, DeCS, including exploded terms) and free-text terms (considering spelling variants, plurals, synonyms, acronyms and abbreviations) for "genital Chlamydia infection" and "screening", with field labels, truncation, proximity operators and boolean operators. The sensitivity of the search strategies will be improved by including keywords from relevant trials detected by earlier searches. We present the search strategies in Appendix 1 (Electronic search strategies).

Specifically, we will search in the following electronic databases:

- MEDLINE, Ovid platform: inception to present.
- MEDLINE In-Process & Other Non-Indexed Citations, Ovid platform: inception to present.
- MEDLINE Daily Update, Ovid platform: inception to present.
- EMBASE.com: inception to present.
- The Cochrane Central Register of Controlled Trials (CENTRAL), Ovid platform: inception to present.
- LILACS, iAHx interface: inception to present.
- CINAHL: inception to present.
- Database of Abstracts of Reviews of Effects (DARE): inception to present.
- PsyCINFO: inception to present.

We will searching MEDLINE using the Cochrane highly sensitive search strategy for identifying RCTs: sensitivity and precision maximizing version (2008 revision), Ovid format (Higgins 2011a). The LILACS search strategy will be combined with the RCT filter of the iAHx interface. These searches will be updated within 6 months before publication of the review.

Searching other resources

We will attempt to identify additional relevant trials using the following methods:

1. Searching in the Sexually Transmitted Infections (STI) Cochrane Review Group's Specialised Register, which includes RCTs and controlled clinical trials, from 1944 to 2012, located through:
   - Electronic searching in MEDLINE, EMBASE and CENTRAL.

2. Searching trials registers:
   - WHO International Clinical Trials Registry Platform (ICTRP) portal (http://apps.who.int/trialsearch/): inception to present.
   - ClinicalTrials.gov (http://clinicaltrials.gov/): inception to present.

3. Searching Web of Science®: inception to present.
5. Contacting authors of all RCTs identified by other methods. A comprehensive list of trials included in the review along with the criteria for considering studies will be sent to the first author of each included study, asking for any additional studies published or unpublished that might be relevant.
6. Handsearching conference proceeding abstracts from the following events:

7. Handsearching previous systematic reviews and other relevant publications on the same topic.
8. Handsearching reference lists of all relevant RCTs identified by other methods.

Data collection and analysis

Selection of studies

Two review authors (NL, SR) will review titles and abstracts of articles identified by the search strategy independently, using a pilot-tested form to document potential eligibility. Disagreements
will be discussed. We will obtain the full text manuscripts of all articles agreed as being potentially eligible by both review authors, articles about which the authors still disagree after discussion, and articles with no abstract if there is insufficient information available from the title or publication type to make a decision. If the disagreement cannot be resolved by discussion, the full text of the article will be obtained.

The abstracts of articles identified through searching other resources will be assessed using the same criteria as for studies identified through electronic database searches.

Two independent review authors will examine full text articles using a pilot-tested form to assess eligibility for inclusion. Studies identified by both authors as being eligible for inclusion will be included in the review. Where there are discrepancies, the authors will discuss the article and reach a consensus decision. If there is no agreement, a third independent author will adjudicate to make a final decision about eligibility.

We will use a flow chart to document the numbers of articles assessed and included or excluded at each stage, with a summary of reasons for exclusion. The flow chart will show the total number of studies included in the review and the total number of articles pertaining to these studies. We will record briefly the characteristics of studies excluded from the review if readers might expect them to have been included.

**Data extraction and management**

We will develop and pilot standardised forms to extract data about:

- Study location and setting
- Trial design and power calculation
- Ethical approval
- Inclusion and exclusion criteria
- Baseline characteristics of trial participants including sex, age, sexual orientation, pregnancy status for women, diagnostic test used to detect *C. trachomatis*
- Types of intervention: opportunistic or systematic invitation for screening; number of screening rounds, screening interval
- Types of comparison group: usual care, alternative screening method
- Types of outcome: primary, secondary
- Reporting of methodological characteristics (see next section, *Assessment of risk of bias in included studies* for details)

We will extract the following numerical data:

- Number of people assessed for eligibility
- Numbers randomised to intervention and comparison groups
- Numbers receiving screening in intervention and comparison groups (at each screening round if multiple rounds)
- Numbers included in analyses in intervention and comparison groups
- Numbers with outcomes in intervention and comparison groups

One author (SR) will extract data about study characteristics and a second will check these details. They will resolve discrepancies by discussion or a third independent author will adjudicate.

Two appropriately authors (from all co-authors) will extract and enter numerical data independently from each included study into Epidata using a structured form. If there are multiple publications relating to the same study, data items can be extracted from different publications. If there are discrepancies between publications about a data item, we will use the data presented in the main trial publication (the publication that includes the results for the primary outcome) or the first chronological publication reporting that data item.

Articles in languages other than English will either be translated first and then duplicate data extraction conducted as above or, if there are two review authors who understand the language of publication, they will extract the data directly.

The two files will be compared using the validation function available in Epidata. Discrepancies in data extraction or data entry will be resolved by consensus. If there is no agreement a third independent author will adjudicate to make a final decision. The agreed data will be entered into Review Manager 5 (RevMan) software.

If there are insufficient details given to allow the extraction of numerical data, the study will be included and the results described.

**Assessment of risk of bias in included studies**

We will assess the methods reported to have been used in the design and execution of all included trials. The assessment will determine whether there is a risk of bias that would over- or underestimate the effect of the intervention on one or more outcomes (Higgins 2011a). This assessment relies on reports of methods described by trial authors in publications and, where available, trial protocols. For any trial, the findings of the assessment can only say whether there is a risk of biased results, and cannot determine whether the results themselves are or are not biased.

For both randomised and non-randomised trials we will assess the risk of five specific sources of bias: selection bias, performance bias, detection bias, attrition bias and reporting bias; and will record any other biases related to a particular trial.

For RCTs we will use the Cochrane Collaboration’s ‘Risk of bias’ tool and criteria in the *Cochrane Handbook* (Table 8.5,b) to assess these in the relevant domains of the reported methods and results (Cochrane 2011).

Selection bias is only the domain for which there are important differences in assessing the risk of bias in randomised and non-randomised controlled trials. For non-randomised controlled trials we will use the UK National Institute of Health and Care Excellence (NICE) ‘methodology checklist’ for cohort studies to assess the risk of selection bias (NICE 2012). The NICE methodology checklist format follows that of the Cochrane Collaboration tool, with criteria to assess bias in each domain and a choice of low, high or unclear risk of bias. We will use the Cochrane risk of bias tool to...
assess non-randomised controlled trials for risks of performance, detection, attrition and reporting biases. Assessors will record whether there is a low, high or unclear risk of bias in each domain of each included trial and give a justification for their decision. For each included trial there will be two independent assessors, including at least one expert in trial methodology (NL) and at least one expert in chlamydia screening (HG). They will resolve discrepancies by discussion. If they cannot agree, a third author will adjudicate.

The domains and their source are summarised here:

1a) Random sequence generation (possible selection bias, Cochrane 'Risk of bias' tool)
Selection bias could occur if allocation to intervention or control groups can be predicted in advance and if participants or clusters of participants are enrolled selectively. The method used to generate the allocation sequence should be unpredictable and should balance prognostic factors, on average, across intervention and comparison groups. We will assess the method as being at:

- low risk of bias (adequate description of a truly random process, e.g., random number tables, computer generated random numbers);
- high risk of bias (explicit description of an allocation process that is not truly random, e.g., odd or even dates of birth of individuals, clusters of participants selected for implementation of the intervention with subsequent enrolment of comparison groups);
- unclear risk of bias (description that does not include enough information to decide whether sequence generation was truly random or not).

1b) Allocation concealment (possible selection bias, Cochrane 'Risk of bias' tool)
Selection bias can occur if participants or clusters of participants are selectively enrolled and allocated to a particular group and if their characteristics are associated with the outcome. If the sequence has been randomly generated, selective enrolment can occur if the next assignment is known before allocation. Concealment of the allocation sequence up to the point of assignment prevents selective assignment to a particular intervention group. We will assess the methods of allocation concealment as:

- low risk of bias (adequate description of a process that prevented foreknowledge of allocation up to the point at which assignment was recorded, e.g., telephone or central randomisation);
- high risk of bias (description of a process that meant that those assigning participants or clusters of participants knew or could predict the allocation in advance);
- unclear risk of bias (insufficient details to be able to decide whether the allocation was concealed or not).

1c) Systematic differences between comparison groups (possible selection bias, NICE 'methodology checklist')
In a non-randomised trial, selection bias can occur because of the lack of a random allocation sequence and concealed allocation. If the person assigning individuals or clusters to a particular group knows about the distribution of factors associated with the outcome, they might introduce selection bias. We will assess the risk of selection bias as:

- low risk of bias (a) the reason for participant allocation to treatment groups is not expected to affect the outcomes of the study, (b) there were attempts made within the design or analysis to balance the comparison groups for potential confounders and (c) the groups were comparable at baseline for all known major confounders and prognostic factors);
- high risk of bias (any of (a) to (c) above not fulfilled);
- unclear risk of bias (insufficient details to be able to decide whether there was a risk of systematic differences between comparison groups).

2) Blinding of participants and personnel (possible performance bias)
Screening is an intervention that involves systematic differences in the delivery of a health service. Personnel who offer chlamydia screening tests might offer other sexual health information, advice or interventions, such as condoms, that could affect participants’ risk of chlamydia infection or another outcome. Such information and interventions could also be considered a part of the screening programme, however. Trial participants or clusters of participants in an inactive 'usual care' control group might also be considered blinded if they do not know that they are part of a trial. For each included trial, we will describe the intervention. We will consider studies as being at low risk of bias if participants were blinded or if the lack of blinding would be unlikely to affect results for a particular outcome.

3) Blinding of outcome assessment (possible detection bias)
For chlamydia screening interventions, adequate descriptions of blinding of those assessing the outcomes are important. We will group outcomes that are objectively assessed, e.g., chlamydia test results obtained from automated diagnostic systems, and those that are subjective, e.g., clinical diagnosis of pelvic inflammatory disease.

The incidence of clinically diagnosed pelvic inflammatory disease is a primary outcome of chlamydia screening interventions. The main symptom is lower abdominal pain, which is common and non-specific. Knowledge of group assignment could influence the interpretation of symptoms by both trial participants and personnel delivering the intervention in unpredictable ways. For example, healthcare providers who know whether a woman has been screened for chlamydia might be more likely to assign a diagnosis of pelvic inflammatory disease to a woman who presents with abdominal pain because of increased awareness of the complications of chlamydia infection. On the other hand, they might be reassured if the test was negative or if treatment had been given and then interpret abdominal pain with or without accompanying signs as resulting from another cause. Women who have accepted or declined screening might also modify their assessment of symp-
toms or their health-seeking behaviour. For subjective outcomes, we will assess methods as follows:

- low risk of bias (adequate description of assessment that reduced the risk of bias, e.g. uniform assessment of all trials participants by an independent assessor blinded to allocation, or assessment of diagnoses by an independent assessment panel blinded to allocation);
- high risk of bias (assessment of outcomes by personnel who knew the group assignment);
- unclear risk of bias (insufficient information to determine whether outcome assessment was blinded or not).

(4) Incomplete outcome data (possible attrition bias due to the amount, nature and handling of incomplete outcome data)
For each outcome or class of outcomes we will describe the completeness of data and exclusions from analysis in each included trial. We will state whether analyses were conducted and reported according to intention-to-treat or not. Where reported we will state numbers included in the analysis as a proportion of the totals randomised to intervention and comparison groups, reasons for attrition or exclusion, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in our analyses. We will use a cut-off of 20% to assign trials with missing outcome data as being at low or high risk of bias. In addition, we will assess methods as being at:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; ‘as treated’ analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias (insufficient information about missing data or exclusions from analysis).

(5) Selective outcome reporting (possible reporting bias)
Where available, we will assess the trial protocol and trial registration documents as well as articles or publications resulting from a trial. We will describe the documents available for each included study and assess the methods as follows:

- low risk of bias (adequate description that all pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (explicit evidence that not all pre-specified outcomes have been reported, that one or more reported primary outcomes were not pre-specified, that outcomes of interest are reported incompletely and cannot be used in the review, or that there are no results for a key outcome that would have been expected to have been reported);
- unclear risk of bias (insufficient information to decide whether selective reporting bias is likely or not).

(6) Other biases
For each included trial we will describe other potential sources of bias. For example, the effects of chlamydia screening can be assessed in cluster-randomised trials. We will describe design-specific risks of bias in domains such as recruitment, baseline imbalances and appropriate statistical analysis. We will report whether these are likely to result in a low, high or unclear risk of bias.

(7) Overall risk of bias
For each primary outcome we will assess the overall level of evidence provided by the included trials using the GRADE approach, as incorporated in Review Manager 5. We will produce a ‘Summary of findings’ table (Higgins 2011b). The level of evidence is summarised as high, moderate, low or very low. We will give justifications for changing the level of evidence depending on findings about: study limitations; consistency of results; directness of evidence; imprecision; publication bias.

Measures of treatment effect
All pre-specified primary and secondary outcomes are dichotomous.

The treatment effect or harmful effect for each, comparing the outcome in those receiving the screening intervention with the control group, can be expressed as a relative risk (RR) with 95% confidence intervals (CI). An advantage of the RR is that it can be interpreted easily for both high and low event rates. We will also calculate the risk difference (RD, 95% CI), the actual difference in the event rate between intervention and control groups. We will use the risk difference to calculate the number needed to treat to benefit (NNTB) or number needed to treat to harm (NNTH). For the primary outcome of chlamydia prevalence, we will report the overall effect estimate at the level of the cluster, and state whether the analysis has taken into account the correlation between individuals within a cluster. We will not combine estimates from individually and cluster-randomised trials.

Unit of analysis issues
If a trial involves more than one intervention group, we will describe all of the groups in the ‘Characteristics of included studies’ table. We will analyse only those relevant to the pre-specified primary and secondary outcomes; however. If necessary, we will combine results of multiple intervention or comparison groups so that only single pair wise comparisons are made.

Cluster-randomised trials of chlamydia screening interventions might measure the effect of the intervention in a geographic area or a school community. In trials of chlamydia screening, the intervention affects not only individuals who are screened and treated (direct effect), but their sexual partners and members of the same sexual network (indirect effect). The indirect effect of screening can reduce the level of repeated exposure to infection of individuals within a cluster.
Dealing with missing data

We will report the percentage of observations with missing data in each included trial. We will use sensitivity analysis to explore the effect of including or excluding trials with high levels of missing data. For each outcome we will attempt to analyse data according to the intention-to-treat principle, with all participants included in the group to which they were randomised and exclusion only of participants with missing outcome data.

Assessment of heterogeneity

We will report statistical heterogeneity in results between studies using $I^2$, $\tau^2$ and Chi$^2$ statistics obtained from analyses in Review Manager 5. We will use the $I^2$ statistic to quantify the percentage of variability between the results that is due to heterogeneity rather than sampling error (Higgins 2002). We will take into account the fact that $I^2$ values are affected by the number of studies, the magnitude and direction of effects in individual trials, and the strength of evidence of heterogeneity. In general, we will consider $I^2$ values less than 40% as showing little evidence of statistical heterogeneity.

Assessment of reporting biases

We will look for evidence of publication and other reporting biases using funnel plots that plot the effect size against precision. If there are more than 10 studies in a meta-analysis we will use statistical tests of funnel plot asymmetry for continuous (Egger 1997) or binary (Harbord 2005) endpoints.

Data synthesis

We will use narrative syntheses to describe the results of trials where there are too few studies for meta-analysis or where we consider that meta-analysis is not clinically meaningful. We will use forest plots to display results of trials examining the same outcome. Where appropriate, we will combine data using meta-analysis conducted in Review Manager 5. If there are trials that examine the same intervention and are assumed to measure the same underlying effect in similar populations, we will use a fixed-effect model. If there is clinical heterogeneity or statistical evidence of substantial statistical heterogeneity we will use a random-effects model to estimate the average treatment effect across trials. The results will be presented as the summary RR (95% CI) with $I^2$ and $\tau^2$ estimates. For meta-analyses with at least three studies combined using a random-effects model we will also calculate a prediction interval to examine the range of effect estimates that might be expected in different settings or populations (Riley 2011). We will not combine results from randomised and non-randomised trials in the same meta-analysis, but will compare these in a sensitivity analysis.

Subgroup analysis and investigation of heterogeneity

If there is evidence of substantial heterogeneity ($I^2$ greater than 40%) for the primary outcome measures and if there are enough trials, we will use subgroup analyses to explore it. We will explore the following subgroups:

- Sex of the patient
- Level of sexual behaviour risk of the study population (high risk, low risk)
- Uptake of the intervention (greater or less than 50%)
- Intensity of the intervention (single offer, multiple screening rounds)

For fixed-effect models based on inverse variance meta-analysis, we will use tests of interaction to examine differences between groups. For random-effects models and fixed-effect models using methods other than inverse variance we will inspect confidence intervals for the subgroup estimates.

Sensitivity analysis

We will conduct sensitivity analyses to investigate the influence of methodological aspects of the review that might influence the results. We pre-specify the following sensitivity analyses:

1. The treatment effect for pelvic inflammatory disease incidence in RCTs assessed as being at low versus high risk of detection bias, i.e. blinded versus non-blinded assessment.
2. The treatment effect for each primary outcome in RCTs assessed at being at low versus high risk of selection bias.
3. The treatment effect for chlamydia prevalence in RCTs versus non-randomised studies.
4. The treatment effect for each primary outcome in intention-to-treat versus per protocol study populations.

We will explore additional factors in sensitivity analysis if they arise during analysis.

Acknowledgements

None
Additional references

Althaus 2010

Althaus 2012

Andersen 2002

Andersen 2011

Batteiger 2010a

Batteiger 2010b

Bender 2011

Bozicevic 2011

Brunham 2005

Campbell 2006

CDC 2010

Cochrane 2011

Datta 2012

DoHA 2011

ECDC 2011

Egger 1997

Fenton 2001

Fleming 1999

Geiser 2013
Geiser WM, Lensing SY, Press CG, Hook EW III. Spontaneous resolution of genital Chlamydia trachomatis infection in women and protection from reinfection. *Journal of Infectious Diseases* 2013;10.1093/infdis/jit094[0. [PUBMED: 23470847]

Gottlieb 2011

Gotz 2005

Goulet 2010

Hager 1983

Harbord 2005

Herzog 2012

Herzog 2013

Higgins 2002

Higgins 2011a

Higgins 2011b

Hillis 1997

Hocking 2012

Kavanagh 2013

Klavs 2004

Kohlihoff 2008

Land 2010

Low 2009

Low 2012

Low 2013

Manhart 2013

Meyers 2007

Miller 2004

NCSP 2010

NICE 2012

O’Farrell 2013

Oakeshott 2010

Ostergaard 2000

Paavonen 2008

Peterman 2009

PHAC 2006

Price 2012

RACGP 2007

Raffle 2007

Regan 2008

Riley 2011

Rours 2011

Schles 1996

Scott LaMontagne 2007

Smith 2007

Stamm 2008

Stergachis 1993
UKNSC 2013

van den Broek 2012

Walker 2012

WHO 2012

* Indicates the major publication for the study

**APPENDICES**

**Appendix 1. Electronic search strategies**

**MEDLINE and CENTRAL (Ovid platform)**

1 exp Mass Screening/
2 screening$.tw.
3 tested.tw.
4 testing.tw.
5 or/1-4
6 exp Chlamydia/
7 chlam?.tw.
8 exp Chlamydia trachomatis/
9 exp Chlamydia Infections/
10 or/6-9
11 randomized controlled trial.pt.
12 controlled clinical trial.pt.
13 randomized.ab.
14 placebo.ab.
15 clinical trials as topic.sh.
16 randomly.ab.
17 trial.ti.
18 or/11-17
19 exp animals/ not humans.sh.
20 18 not 19
21 5 and 10 and 20

Note: the CENTRAL search strategy does not include the terms #11 to #20.

**EMBASE.com**

#1 mass screening'/exp
#2 screening*:ti,ab
#3 screening'/exp

Screening for genital chlamydia infection (Protocol)
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Screening for genital chlamydia infection (Protocol)

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Contributions of Authors

Nicola Low drafted the protocol.

Shelagh Redmond conducted preliminary electronic databases searches.

Helen Ward, Anneli Uusküla, Jan van Bergen, Hannelore Götz commented on and suggested revisions to the protocol.

Declarations of Interest

Berit Andersen is co-author of a completed trial that will be considered for inclusion in the review.

Jan van Bergen, Hannelore Götz and Nicola Low were co-authors on a completed trial that will be considered for inclusion in the review (Chlamydia Screening Implementation project, The Netherlands).

Nicola Low is a co-investigator on an ongoing trial that will be considered for inclusion in the review (Australian Chlamydia Control Effectiveness Pilot. ACCEPt).

Authors of included studies will not be involved in assessing and extracting data of their own studies.

Sources of Support

Internal sources

· No sources of support supplied

External sources

· European Centre for Disease Prevention and Control, Sweden.

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