Published by Oxford University Press on behalf of the International Epidemiological Association
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International Journal of Epidemiology 2009;**38**:435–448
doi:10.1093/ije/dyn222

Effectiveness of chlamydia screening: systematic review

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Accepted 24 September 2008

Background Screening programmes are promoted to control transmission of and prevent female reproductive tract morbidity caused by genital chlamydia. The objective of this study was to examine the effectiveness of register-based and opportunistic chlamydia screening interventions.

Methods We searched seven electronic databases (Cinahl, Cochrane Controlled Trials Register, DARE, Embase, Medline, PsycINFO and SIGLE) without language restrictions from January 1990 to October 2007 and reference lists of retrieved articles to identify studies published before 1990. We included studies examining primary outcomes (pelvic inflammatory disease, ectopic pregnancy, infertility, adverse pregnancy outcomes, neonatal infection, chlamydia prevalence) and harms of chlamydia screening in men and non-pregnant and pregnant women. We extracted data in duplicate and synthesized the data narratively or used random effects meta-analysis, where appropriate.

Results We included six systematic reviews, five randomized trials, one non-randomized comparative study and one time trend study. Five reviews recommended screening of women at high risk of chlamydia. Two randomized trials found that register-based screening of women at high risk of chlamydia and of female and male high school students reduced the incidence of pelvic inflammatory disease in women at 1 year. Methodological inadequacies could have overestimated the observed benefits. One randomized trial showed that opportunistic screening in women undergoing surgical termination of pregnancy reduced post-abortal rates of pelvic inflammatory disease compared with no screening. We found no randomized trials showing a benefit of opportunistic screening in other populations, no trial examining the effects of more than one screening round and no trials examining the harms of chlamydia screening.

Conclusion There is an absence of evidence supporting opportunistic chlamydia screening in the general population younger than 25 years, the most commonly recommended approach. Equipoise remains, so high-quality randomized trials of multiple rounds of screening with biological outcome measures are still needed to determine the balance of benefits and harms of chlamydia screening.

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Keywords Chlamydia infections, pelvic inflammatory disease, mass screening, meta-analysis, randomized controlled trial, controlled clinical trial

Introduction

Chlamydia screening is widely promoted in high-income countries as an intervention to prevent reproductive tract morbidity, including infertility, in women by reducing chlamydia transmission.[1–3] A National Chlamydia Screening Programme in England[1] and regional Infertility Prevention Programs in the United States[4] offer chlamydia screening to eligible, sexually active individuals younger than 25 years when they attend consultations at specified health care, or other, settings. This approach is known as opportunistic screening (Box 1). The other main approach is register-based screening (Box 1, also known as call–recall, proactive or population based). Key features of register-based screening are an up-to-date register of those eligible for screening, which can be used to send proactive invitations for screening; identifying those who have not responded to an invitation and sending reminders; sending repeat invitations at regular defined intervals; compiling regular reports of the coverage; and follow-up of testing.[5] Register-based chlamydia screening is being piloted in three regions of the Netherlands from 2008.[6]

The way in which screening services are organized and delivered can affect their success. Regular screening and follow-up are needed to realize sustainable population benefits.[7] This might be particularly important for communicable diseases where asymptomatic and repeated infections are common.[8] These requirements are difficult to achieve and monitor with opportunistic approaches, which require the target group to use health services regularly, practitioners to offer repeat tests at appropriate intervals and administrative systems to track individuals attending multiple screening venues. Opportunistic cervical cancer screening, offered in the 1960s and 1970s by general practitioners and family planning clinics in the United Kingdom, was ineffective.[9] Older women at highest risk were screened infrequently or not at all, whilst those at low risk were screened repeatedly. The fall in the death rate from cervical cancer, which began before screening was introduced, did not accelerate until an organized call–recall system, which increased regular coverage to 80%, was introduced in 1988.[10]

The primary objective of a screening programme is to reduce mortality or morbidity.[5,9] The strength of evidence supporting chlamydia screening as a population-level intervention has, however, been challenged.[11,12,13,14] The objective of this study was to examine the research evidence about the effectiveness of screening to prevent chlamydia-associated morbidity and transmission systematically, with a focus on the organizational approach.

Methods

Data sources and searches

We searched Cinahl, Cochrane Controlled Trials Register, Database of Abstracts of Research Effectiveness, Embase, Medline, PsycINFO and SIGLE from January 1990 to October 2007. We searched the reference lists of included articles to identify additional relevant articles, including those published before 1990. We had no language restrictions. We used subject heading and free text terms that combined *Chlamydia trachomatis* infections or pelvic inflammatory disease with terms for screening (Supplementary Information 1).

Box 1 Definitions used

Screening
Members of a defined population, who may not know they are at risk of a disease or its complications, are asked a question or offered a test to identify those who are more likely to be helped than harmed by further tests or treatment.[49]

Screening programme
A continuing public health service that ensures screening is delivered at sufficiently regular intervals to a high enough proportion of the target population to achieve defined levels of benefit at the population level, while minimizing harm.[12]

Register-based screening
Registers are used to identify and enumerate the target population (e.g. in a geographical area, practice list of a general practitioner or members of a health maintenance organization), to send invitations for screening, to send reminders to those who have not attended and to send regular repeat invitations at appropriate intervals. Invitations are sent to individuals irrespective of their record of health service use. Also known as population, proactive, call–recall, cyclical, active or systematic screening.[49]

Opportunistic screening
A health professional offers a screening test to patients attending health care or other defined settings for any reason. Individuals who do not use relevant health services will not have an opportunity to be offered screening. The health professional takes responsibility for repeating the test offer at appropriate intervals.[49]

Study selection

We included studies reporting primary biological outcomes of any approach to chlamydia screening in adult women and men, and harms resulting from screening. The following were considered as primary outcomes: chlamydia incidence or prevalence; pelvic inflammatory disease, ectopic pregnancy and infertility; adverse pregnancy outcomes; neonatal morbidity or mortality; and male infertility. Psychological distress, partner violence and relationship breakdown were considered as harms.

We included systematic reviews, randomized controlled trials, non-randomized comparative studies and observational time trend studies if they included data from at least two time points before the introduction of the intervention.[15] Two reviewers screened titles and abstracts to identify potentially relevant articles. Full-text articles were then read independently. Discrepancies were resolved by discussion to reach consensus about the list of articles to include.

Data extraction and quality assessment

We used published definitions of opportunistic and register-based screening to determine the approach used in included studies (Box 1). Two independent reviewers assigned the screening approach and extracted data. Discrepancies were resolved by discussion, or by consultation with a third reviewer. We used criteria published by the United Kingdom National Institute for Health and Clinical Excellence for each study design to assess the quality of reporting of the study methods.[15] Supplementary Tables 1a–d shows the details of the quality assessments and criteria.

Data synthesis and analysis

We used narrative methods to describe the evidence. If two or more trials examined the same intervention and outcome, we combined the results statistically in a meta-analysis using a random effects model. We examined statistical evidence of heterogeneity due to between-trial variation using the I^2 statistic.[16]

A detailed report of this study has been published.[13]

Results

Our literature searches identified 2323 unique references (Figure 1). We screened 418 full-text articles and

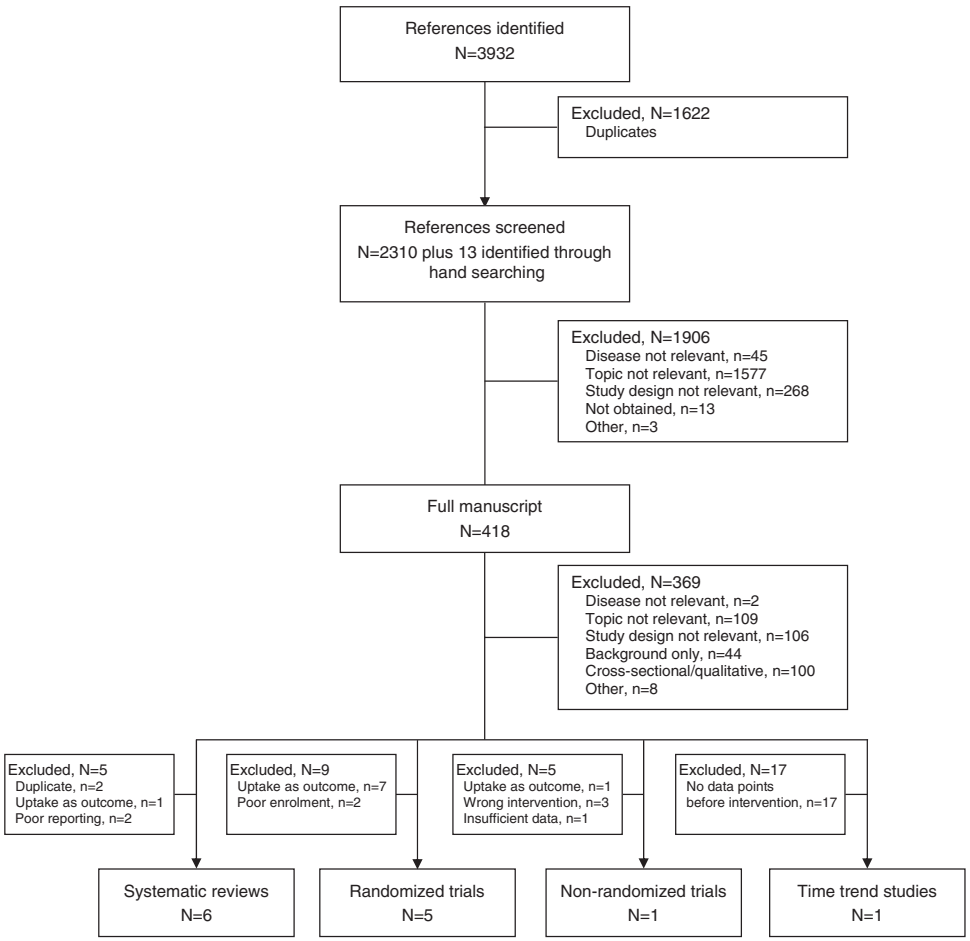

Figure 1 Flow diagram for results of electronic database and handsearching for articles on chlamydia screening

excluded 369. Of the remaining 49 studies, we excluded 36 (Supplementary Table 2, References s1–s36).[13] Seventeen of these were time trend studies that did not report data from the time period before the introduction of the screening intervention (s20–s36). Eight were controlled trials for which the outcome was screening uptake (s6, 7, 11, 13, 15–17, 19) and that have been summarized elsewhere.[13] We excluded two literature reviews that informed recommendations about screening in the United Kingdom (s1) and updated recommendations in Canada (s2) because there was no description, or reference to a description, that could determine whether or not they were systematic reviews. We included six systematic reviews,[17–22] five randomized trials,[23–27] one non-randomized comparative study[28] and one time trend study.[29]

We found no randomized controlled trials of the effects of opportunistic chlamydia screening in non-pregnant women, pregnant women in antenatal clinics or men. We found no randomized trial reporting the outcomes of infertility in women or men, ectopic pregnancy, adverse pregnancy outcomes, neonatal morbidity or mortality and no trials that examined the effects of more than one round of any screening intervention. We found no trials reporting harms of chlamydia screening.

Systematic reviews

Four systematic reviews[17–20] directly informed published national guidelines on chlamydia screening in Canada,[17] Scotland,[18] and the United States[2] (Table 1). The most recent review, by the United States Preventive Services Task Force,[20] updated an earlier full review.[19] Four reviews were based on searches of multiple electronic databases.[18,19,21,22] Our literature searches identified all studies cited by the reviews as evidence of effectiveness. No review separated studies according to the organizational approach to screening. Among five reviews that assessed the same trial of a register-based approach,[23] two graded this as good evidence[19,22] and one as fair evidence[17] to recommend screening of women at high risk of chlamydia. The Scottish guideline recommended opportunistic testing of women at high risk of chlamydia but noted that no randomized trial supported this.[18] This guideline is being updated.[30] One review graded the same study as a low-quality randomized trial with no recommendation.[21] Three reviews recommended chlamydia screening before termination of pregnancy.[18,21,22] Three reviews cited evidence from ecological time trend studies as supportive evidence in favour of chlamydia screening programmes.[19,21,22]

Register-based screening

We found three randomized controlled trials[23–25] and one non-randomized comparative study[28] reporting the effects of register-based chlamydia screening on the incidence of pelvic inflammatory disease or on chlamydia prevalence (Tables 2 and 3).

Effects on reproductive tract morbidity in women

Two randomized controlled trials (3537 women enrolled) found that the risk of pelvic inflammatory disease in women invited to be screened was about half that of control groups 1 year after a single round of register-based screening [summary risk ratio 0.46, 95% confidence interval (CI) 0.27–0.78, $I^2 = 0\%$].[23,24] There were biases in the design of both studies (Tables 2 and 3, Supplementary Table 1a). In the earliest published study,[23] the authors used the register of a health maintenance organization in the United States to identify, invite and follow-up their target population. Overall, 36 547 women were randomized first to screening and control groups, and consent for inclusion was sought if their responses to a postal questionnaire showed them to be single, non-pregnant and at high risk of chlamydia (score >3, based on age $\leqslant 24 = 1$, black race $= 2$, nulligravid $= 1$, douching in past 12 months $= 1$ and $\geqslant 2$ sexual partners in past 12 months $= 1$). Women randomized to the screening group only were also telephoned to increase the number with a risk assessment and allow screening appointments to be made. These practices changed the planned ratio in intervention and control groups from 1:2 to 1:1.6 (total 2607). Sixty-four per cent of women in the intervention group and an unknown proportion in the control group were screened for chlamydia. Østergaard *et al*.[24] conducted a cluster randomized trial in 17 high schools in Aarhus County, Denmark (8909 students). Sexually active female and male students responding to the invitation were asked to collect urine and/or vaginal specimens at home, or told that they could be tested at a local health clinic. Response rates were higher in those assigned to the intervention (32% of those randomized) than control group (24%). Participants in the intervention group were given additional information about the importance of partner notification if diagnosed with chlamydia.[31] Ascertainment of pelvic inflammatory disease was unblinded, and loss to follow-up 1 year later was nearly 50% (Supplementary Table 1a).

Effects on chlamydia transmission

Two randomized trials and one non-randomized comparative study reported effects of register-based screening on chlamydia prevalence, as a measure of chlamydia transmission (Tables 2 and 3).[24,25,28] There were biases in all studies (Supplementary Table 1a), and results could not be combined statistically because of differences in the ways the data were collected and reported. Østergaard *et al*.[24] found fewer diagnosed infections at follow-up in female students who had been proactively invited to provide home-collected vaginal specimens compared with controls who were told that they could visit their general practitioner (Tables 2 and 3). Cohen *et al*.[28] compared infection rates between three schools that had provided chlamydia screening over a 3-year-period with a

Table 1 Characteristics of systematic reviews of effectiveness of chlamydia screening on primary outcomes

Study	Search strategy and dates	Target population	Review questions[a]	Total hits	Included studies[a]	Evidence reviewed	Conclusions or recommendations	Comment
Davies *et al.*[17]	Medline January 1983 to December 1995 Update of 1984 Canadian Task Force on the Periodic Health Examination	Adolescents; women; women with infertility; women with ectopic pregnancy	Does screening reduce infection rates of C trachomatis?	Not stated	Not stated	201 references cited. One RCT of effectiveness of screening. Five studies in pregnant women. Prevalence studies in Canada	Fair evidence to recommend screening of high risk groups. Fair evidence to exclude routine screening of the general population Well-designed randomized community trial of screening for chlamydia in asymptomatic populations and follow-up evaluation of complications is warranted	Important methodological limitations not recognized or taken into account. Recommended screening approach not described. Identified lack of evidence for screening populations other than those at high risk during period covered by search
Stokes[21]	Medline, January 1980 to July 1996 Embase, 1991– 96	Sexually active non-pregnant women in general practice in the UK	Evidence for routine (unselective) screening Evidence for selective screening Evidence for screening pre-TOP/IUD insertion	1045	24	Unselective screening: no RCT; six economic evaluations supporting screening at prevalence above 6%; one time trend analysis in Sweden. Selective screening: one RCT in high risk women; two economic evaluations; one time trend analysis in Wisconsin. Screening pre-TOP: one RCT; seven cross-sectional studies; three non-randomized comparisons. Screening pre-IUD insertion: 1 non-randomized and 1 uncontrolled study	Unselective screening in general practice not recommended. Good evidence from one RCT that selective screening can reduce the incidence of PID. Screening recommended. Screening not recommended	Only one reviewer. Not all important limitations recognized or taken into account. Evidence from RCT of register-based approach generalized to opportunistic screening in general practice
SIGN[17]	Medline, Embase, Cochrane Library, Cinahl, Social Citation Index Dates not reported	Sexually active women and men in Scotland	In what circumstances should potential chlamydial infection be sought routinely in adults? What is the optimal management of patients identified as being chlamydia positive?	Not stated	Not stated	176 references cited. Two RCTs relevant to chlamydia screening cited	All women undergoing termination of pregnancy should be screened. Sexually active women under 25 and women over 25 with new or more than two sexual partners should be tested opportunistically at health care settings. All patients attending GUM clinics, all patients with STI and sexual partners of those with chlamydia should be tested. Sexual partners of people with suspected chlamydia should be tested	Did not identify all relevant trials. Recommendations based on observational studies showing increased risk of chlamydial infection, rather than evidence that early detection and treatment in particular groups of patients reduces the risk of complications. Evidence from RCT of register-based approach generalized to opportunistic screening in health care settings

(continued)

Table 1 Continued

Study	Search strategy and dates	Target population	Review questions[a]	Total hits	Included studies[a]	Evidence reviewed	Conclusions or recommendations	Comment
Honey[21]	Medline, PubMed, Embase, 1980 to June 2000	Young sexually active women	Does screening by any method reduce: the prevalence of chlamydia? Does screening reduce the incidence of upper tract infection?	>300	5	Reduction in chlamydia prevalence: two time trend analyses in Sweden; one non-randomized comparison in schools in USA. Reduction in PID: one RCT in women requesting TOP; one RCT in high risk women	Circumstantial evidence that screening programmes are associated with reductions in prevalence of PID and incidence of ectopic pregnancy. Screening for chlamydia using culture is effective in preventing PID in the short term	Papers independently reviewed. Most methodological limitations recognized. Study quality taken into account in grade of recommendation
Nelson *et al*.[19]	Medline, HealthStar, Cochrane Library, January 1994 to November 1999 Review of references	Non-pregnant women; pregnant women, and men in the US	Does screening reduce PID in non-pregnant women? Does screening reduce the prevalence of chlamydia?	1330	9	Reduction in PID: one RCT in high risk women; two time trend analyses in Sweden. Reduction in chlamydia prevalence: no adequate controlled studies; eight uncontrolled studies	Good evidence that screening women at risk reduces the incidence of PID and fair evidence that community-based screening reduces prevalence of infection. Fair evidence that screening women at low risk could detect extra cases, but small benefit. No direct evidence that screening men could reduce the incidence of new infections in women	Review used for USPSTF recommendations in USA. Comprehensive methods and evidence tables. Only one reviewer. English language only. Not all important methodological limitations recognized or taken into account
Meyers *et al*.[20]	PubMed July 2000 to July 2005 Review of references and discussions with authors Update of Nelson *et al*.[19]	Non-pregnant women; pregnant women, and men in the US	As above, plus: does screening for chlamydial infection reduce adverse health outcomes in men, reduce adverse health outcomes in women, or reduce the incidence of infection in women?	452	1	Reduction in PID: one RCT in female and male school students (termed high risk because of age), with 1 year follow-up in women	In non-pregnant women, one poor quality RCT supporting evidence above. No new randomized or non-randomized prospective controlled studies of screening men for chlamydial infection and the ability of screening programmes to reduce the incidence of infection among women	Review used for revised USPSTF recommendations in USA. Only one database searched. Two independent reviewers. English language only. Ostergaard *et al*.[24,31] not taken into account as evidence of male screening contributing to reduced PID in women

GUM, genitourinary medicine; IUD, intra-uterine device; PID, pelvic inflammatory disease; RCT, randomized controlled trial; STI, sexually transmitted infection; TOP, termination of pregnancy; USPSTF, United States Preventive Services Task Force.

[a]Review questions are those specified by the authors. Only questions and included studies directly related to evidence for the effectiveness of screening are included here. Reviews also examined evidence for chlamydia prevalence, risk factors, accuracy of diagnostic tests and cost-effectiveness.

Table 2 Characteristics of included studies, by screening approach, design and outcome

Study, Design, Dates	Study population	Intervention	Control
Register-based screening			
Scholes *et al.*[23] Individual RCT October 1990 to May 1992	Women, 18–34 years, health maintenance organization, USA. Selected as being at high risk of chlamydia	Invitation to be screened for chlamydia at a study health clinic. Cervical swabs tested by EIA and culture	Usual care Women saw primary care physician as required
Østergaard *et al.*[24] Cluster RCT January 1997 to April 1998 Same trial as Østergaard *et al.*[30]	Women and men, mean age 18 years, 17 schools, Aarhus County, Denmark	Home sampling kits sent. Urine or vaginal specimen, NAAT test. Information about chlamydia. Partner notification for positive cases	Usual care Offer of free chlamydia testing at STI clinic or other physician. Information about chlamydia. No partner notification advice
Hodgins *et al.*[25] Cluster RCT March 1996 to July 1998	Women and men in 14 Inuit villages of 120–1800 people, Canada	All adults encouraged to take urine specimen to health centre. NAAT test. Multi-media sexual health campaign	Existing services Chlamydia testing offered opportunistically to women presenting for cervical smears, antenatal care, STI care
Cohen *et al.*,[28] Cluster CCT September 1995 to September 1998	9–12th grade students (15–18 years), eight schools, Louisiana, USA	Five screening rounds 1995–98. Urine specimens, NAAT test Information about STI, consequences, prevention. Partner notification	Usual care 1995–97 Urine specimens for NAAT testing 1997–98. Partner notification
Opportunistic screening			
Giertz *et al.*,[26] Individual RCT September 1983 to September 1984	Women under 25 years requesting abortion, one hospital, Sweden	Screening pre-op from cervix, culture and DFA. Doxycycline if positive before surgery	Usual care Diagnostic testing for chlamydia post-op if pelvic infection suspected clinically
Penney *et al.*[27] Individual RCT 1995–96	Women requesting abortion, four hospitals, Scotland, UK	Screening pre-op from cervix, EIA. Doxycycline if positive. Referral to STI clinic	Universal antibiotic prophylaxis Doxycycline and metronidazole
Herrmann *et al.*[29] Time trend study 1988–93	Database of chlamydia tests, University Hospital, Uppsala, Sweden	1988, STI prevention programme started in Uppsala, Sweden. Testing by culture	Time period before screening started

CCT, controlled clinical trial; DFA, direct fluorescent antibody test; EIA, enzyme immuno assay; NAAT, nucleic acid amplification test; RCT, randomized controlled trial; STI, sexually transmitted infection.

Table 3 Results from included studies

Study, Design, Dates	Outcomes	Randomized or enrolled	Events	Effect estimate (95% CIs)
Register-based screening				
Scholes *et al.*[23] Individual RCT	Incidence of PID per 10 000 wm at 1 year Uptake of screening (%)	Randomized 36 547 women (ratio 1:2 intervention:control) Enrolled 2607 women at high risk (ratio 1:1.6 intervention: control)	PID Intervention: 9 (8/10 000 wm) Control: 33 (18/10 000 wm) Screening uptake: Intervention 645/1009 (64% of enrolled) Control: not reported	Risk ratio 0.44 (0.20–0.90) Not applicable
Østergaard *et al.*[24] Cluster RCT Screening uptake reported in[30]	Treatment for PID (%) at 1 year Chlamydia prevalence (%) at 1 year Uptake of screening (%)	Randomized Intervention: 2603 women, 1733 men Control: 2884 women 1689 men Eligible responders (sexually active) Intervention: 928 women, 442 men Control: 833 women, 246 men Agreed to 1 year follow up (women) Intervention: 867 women Control: 833 women	PID Intervention: 9/443 (1.9%) Control: 20/487 (5.3%) Prevalence: Intervention: 13/443 (2.6%) Control: 32/487 (8.1%) Screening uptake: Intervention f: 867 (33% of randomized) Intervention m: 430 (25% of randomized) Control f: 63 (2% of randomized) Control m: 4 (<1% of randomized)	Mean difference 3.4% (−0.4 to 7.2%) 5.5% (0.95–10.0%) Clustering accounted for Comparison of percent Women and men: $P < 0.001$
Hodgins *et al.*[25] Cluster RCT March 1996 to July 1998	Chlamydia prevalence (per 1000) at 1 year Uptake of screening (%)	14 villages randomized, two excluded Intervention: 5250 Control: not reported	Prevalence Intervention pre, post (per 1000): 37.1, 24.2 Control pre, post (per 1000): 28.1, 26.1 Screening uptake: Intervention: f, 29%; m, 16% Control: not reported	Odds ratio intervention group post vs pre 0.65 (0.52–0.81) Clustering, matched design, and control group change not accounted for
Cohen *et al.*[28] Cluster CCT September 1995 to September 1998	Chlamydia prevalence in intervention and control schools 1997–98 (%) Uptake of screening (%)	Parental consent Intervention: 52–65% Control: 64% Intervention: 1099 women, 1094 men Control: 2605 women, 2458 men	Prevalence Intervention f: 58/562 (10.3%) Intervention m: 19/588 (3.2%) Control f: 168/1411 (11.9%) Control m: 79/1242 (6.4%) Screening uptake: Year 1, 56%; year 2, 65%; year 3, 52%	Comparison of percent Women: $P > 0.05$ Men: $P < 0.01$ Clustering not accounted for.
Opportunistic screening				
Giertz *et al.*[26] Individual RCT September 1983 to September 1984	Post-abortal PID up to 4 weeks post-op (%)	560 women randomized	Post-abortal PID Intervention: 14/288 (5%) Control: 25/259 (10%)	Risk ratio 0.50 (0.27–0.95)
Penney *et al.*[27] Individual RCT 1995–96	Suspected PID 8 weeks post-op (%)	1703 women randomized	Suspected post-abortal PID Intervention: 54/791 (6.8%) Control: 35/755 (4.6%)	Risk ratio 1.47 (0.97–2.23)
Herrmann *et al.*[29] Time trend study 1988–93	Chlamydia prevalence (per 1000)	119 892 chlamydia test results from 1985 to 1993	Prevalence Pre-intervention f: 1985, 107 per 1000; 1987, 78 per 1000 Post-intervention f: 1988, 58 per 1000; 1993, 32 per 100 Pre-intervention m: 1985, 183 per 1000; 1987, 108 per 1000 Post-intervention m: 1988 105 per 1000, 1993, 71 per 1000	

CCT, controlled clinical trial; RCT, randomized controlled trial; f, female; m, male; wm, woman months; mth, months; PID, pelvic inflammatory disease.

non-randomly selected group of five schools with no screening. The infection rate in intervention compared with control schools was lower at follow-up in boys but not in girls (Tables 2 and 3). In both studies, there was no baseline assessment or treatment in control groups, so, at follow-up, both incident and prevalent infections would be detected, whereas only incident infections would be detected in intervention schools. Hodgins *et al*.[25] invited all adults in six Inuit villages in Canada to provide urine specimens as part of an intensive sexual health education and promotion campaign. Chlamydia prevalence 1 year after screening in intervention villages fell (Tables 2 and 3). In six comparison villages where there was no campaign but opportunistic testing was available, prevalence 1 year later had not changed.

Opportunistic screening

Effects on reproductive tract morbidity in women

We found two randomized trials (2263 women) investigating the effects of opportunistic chlamydia screening on pelvic inflammatory disease in women requesting surgical termination of pregnancy.[26,27] In women in Sweden offered pre-operative chlamydia screening and treatment, the risk of post-abortal pelvic inflammatory disease was about half that in women in the control group who received diagnostic testing if they had post-operative symptoms (risk ratio 0.50, 0.27–0.95, Tables 2 and 3).[26] Details of randomization, concealment and blinding of outcome assessment were not reported. The other study compared a strategy of pre-operative screening using an enzyme linked immunoassay followed by treatment of positive cases with universal peri-operative antibiotic prophylaxis in Scotland.[27] The study was terminated before reaching the required sample size, but there was weak evidence of more episodes of post-operative pelvic inflammatory disease at 8 weeks with the screening strategy than with universal prophylaxis (risk ratio 1.47, 0.97–2.23, Tables 2 and 3). Re-infection was not assessed as an outcome, but partner management in women randomized to screening was poor: of 45 women with positive chlamydia or gonorrhoea tests, 4 partners were documented to have received treatment.[27]

Effects on chlamydia transmission

We included one ecological study that reported time trends in diagnosed chlamydia rates in Uppsala County, Sweden.[29] Herrmann and Egger used microbiology records and population data before and after chlamydia testing in health care settings became widespread.[29] In 1988, chlamydia became a notifiable infection, and partner notification was mandatory. Five youth clinics providing free chlamydia testing and treatment were established, and there was a publicity campaign. Chlamydia testing was also available in other health care settings, but the activities were not coordinated as a screening programme. Chlamydia rates per 1000 tests were reported by year for 3 years before opportunistic testing became widely available (1985–87) and 6 years after (1988–93). The chlamydia infection rate fell in both time periods in both women and men. An increase in male rates at the end of the study period was noted as an indication of increasing incidence.

Discussion

Our systematic review assessed evidence for the effectiveness of chlamydia screening in preventing chlamydia-associated morbidity or transmission of infection. Trial reporting quality was generally poor, and there were methodological weaknesses that could have biased the results of all included studies. In two randomized trials, a single round of register-based screening was associated with a reduced incidence of pelvic inflammatory disease in women at 1 year. Information about the effects of any chlamydia screening approach on transmission of infection was difficult to interpret. Trials of opportunistic chlamydia screening have only been conducted in women undergoing surgical termination of pregnancy. We found no evidence for the effectiveness of opportunistic screening in any other population, of multiple rounds of any screening approach or about the harms of chlamydia screening (Table 4).

Strengths and weaknesses

The strengths of this review were that we conducted comprehensive literature searches of multiple databases without language restrictions, and used rigorous methods to identify, appraise and synthesize the evidence. It is, therefore, unlikely that we excluded any important studies during the dates covered by the search. The main weakness of the review was that it was not possible to combine effect estimates statistically for most comparisons because of the small numbers of studies, and differences in the interventions, populations or data reporting. Incomplete reporting of methods made it difficult to interpret the findings of many studies.

Comparison with other systematic reviews

The results of our systematic review differ from others,[17–22] which concluded that there was fair or good evidence to recommend chlamydia screening. First, by stratifying results according to the organizational approach to chlamydia screening, we showed that any evidence of a beneficial effect applied only to register-based interventions, and this was limited by poor trial quality. Second, we found some evidence that chlamydia screening in men might contribute to a reduction in the incidence of pelvic inflammatory disease in women (Table 4). The cluster randomized

Table 4 Summary of randomized controlled trial evidence of effects of chlamydia screening in non-pregnant women, pregnant women and men, on primary outcomes[a]

Intervention	Evidence assessed	Result
Register-based chlamydia screening		
Non-pregnant women at increased risk	One randomized trial in women with high scores on a risk assessment invited to attend a physician's office[23]	Reduction in pelvic inflammatory disease at 1 year
	One randomized trial in 18 to 19-year-old female and male high school students invited to mail home-collected specimens.[24,31] Increased risk because of young age	Reduction in pelvic inflammatory disease at 1 year
Non-pregnant women not at increased risk	No randomized trials found	
Men	One randomized trial in 18- to 19-year-old female and male high school students invited to mail home-collected specimens[24,31]	Reduction in pelvic inflammatory disease in women at 1 year could have been contributed to by screening and treatment of men as well as women Reduction in chlamydia rate in screened women at 1 year No data about outcomes in men
Pregnant women	No randomized trials found	
Regular repeated invitations to women or men to be screened for chlamydia	No randomized trials found	
Harms of screening	No randomized trials found	
Opportunistic chlamydia screening		
Non-pregnant women at increased risk	No randomized trials found	
Non-pregnant women not at increased risk	No randomized trials found	
Men	No randomized trials found	
Pregnant women	No randomized trials found in women continuing pregnancy	
	One trial in women undergoing surgical termination of pregnancy, compared with no screening[26]	Reduction in post-abortal pelvic inflammatory disease at 4 weeks
	One trial in women undergoing surgical termination of pregnancy, comparing antibiotic prophylaxis with screening and treatment of positive cases[27]	Weak evidence of a reduction in post-abortal PID in women given prophylaxis compared with screening and treatment of positive cases
Regular repeated invitations to women or men to be screened for chlamydia	No randomized trials found	
Harms of screening	No randomized trials found	

[a]Primary outcomes of chlamydia screening: incidence of short-term (PID) or long-term (tubal infertility or ectopic pregnancy) complications in women; adverse pregnancy outcomes; neonatal morbidity; change in chlamydia prevalence.

trial by Østergaard and colleagues[31] involved both male and female students. If we presume that some students at least were in shared sexual networks, the reduction in pelvic inflammatory disease in women[24] could be attributed in part to screening and treatment of chlamydia-infected men. The United States Preventive Services Taskforce[20] reviewed the same trial but concluded that there were no studies showing that chlamydia screening in men produces benefits in women. New Canadian guidelines on sexually transmitted infections noted a gap in the evidence about chlamydia screening in men, citing the US review.[32] Third, we did not find the results of time trend studies to be consistent with randomized controlled trial results.[19,21,22] The only eligible study in our review showed that chlamydia rates were falling in Uppsala County, Sweden, before opportunistic testing became widespread.[29]

Interpretation of the evidence

It has been argued that further randomized trials of the primary outcomes of chlamydia screening are unnecessary.[33] Our review suggests that clinical equipoise remains because the quality of trials so far does not allow the benefits or harms of chlamydia screening to be quantified accurately enough.[11,12,14] Both trials of register-based screening must have overestimated the effect of screening:[23,24] *Chlamydia trachomatis* is implicated in about 30% of acute pelvic inflammatory disease,[34] so even if screening and treatment could prevent all cases resulting from ascending chlamydia, a halving of the overall risk of pelvic inflammatory disease is implausible. Seven of nine cases of pelvic inflammatory disease in the trial by Scholes and colleagues[23] were in women tested for chlamydia, so the intervention did not prevent these cases. Furthermore, results from women at high risk of chlamydia in this trial might not be generalizable to all women younger than 25 years, and additional contacts with those invited for screening could have exaggerated uptake or changed behaviours, which might have increased differences in outcomes between groups. In the trial by Østergaard *et al*.,[24] open outcome assessment could have increased the estimated effect if symptoms were more likely to be assigned to pelvic inflammatory disease in the unscreened group and to other causes in the screened group. Differential enrolment rates and high losses to follow-up might also have resulted in systematic differences between intervention and control groups. The large effects seen in trials have not been replicated in observational studies. Rates of hospitalization for pelvic inflammatory disease among 28 000 new recruits in the United States Army were similar in screened compared with unscreened women after 18 months (relative risk, adjusted for age, race, education and aptitude 0.94, 95% CI 0.69–1.29).[35] This slight reduction and the lower overall hospitalization (adjusted relative risk 0.94, 95% CI 0.90–0.99) among screened women could reflect an unmeasured 'healthy screenee' effect.[5]

The ways in which the interventions examined could have prevented pelvic inflammatory disease have not been examined critically. A single screening test could only have a substantial direct effect if most infections detected were recently acquired and were treated before causing upper genital tract inflammation. This is unlikely because chlamydia persists asymptomatically for up to 5 years after diagnosis,[36] so most infections in a previously unscreened population would already have been present for some time and might already have caused tubal damage. Alternatively, high enough levels of screening uptake and partner notification would interrupt community transmission and reduce exposure. Once off screening uptake of 33% among school students in half the schools in one Danish community would probably not have reduced transmission substantially,[24] and health maintenance organization members are not a geographical community, so transmission is unlikely to have been affected.[23] Neither trial reported partner treatment rates.[23,24] In one trial that examined pre-abortion screening, only 10% of male partners of women with either chlamydia or gonorrhoea were treated.[27] Mathematical models provide the only source of information about how chlamydia screening would prevent pelvic inflammatory disease in the long term. In these models, the reduction in pelvic inflammatory disease depends on reducing transmission at a population level by yearly repeated screening, treatment and partner notification to reduce the risk of exposure to chlamydia, and not to an individual effect of interruption of ascending infection.[37–39]

Implications for chlamydia screening programmes

Distinguishing between register-based and opportunistic approaches is important for operational reasons because the way in which a screening programme is delivered in practice should reproduce the benefit to the target population observed in clinical trials.[5] In the United States, the Preventive Services Task Force requires direct evidence that the entire screening service achieves the primary health outcome.[40] In the United Kingdom[5,41] and New Zealand,[42] national screening committees require evidence of effectiveness from high-quality randomized trials of the screening programme that is to be delivered. In most countries that recommend chlamydia screening of specified groups of asymptomatic individuals, tests are offered opportunistically, usually in health care settings. Our review shows that published trials about opportunistic chlamydia screening provide indirect short-term evidence of inadequate quality. Even where opportunistic screening services are coordinated nationally

with defined service standards, coverage of regular screening and outcomes of opportunistic screening are difficult to measure because health service data on screening uptake are not routinely linked to data on chlamydia-associated complications and neither data source is linked to population records. Current data from the best-performing region in the National Chlamydia Screening Programme in England show that, in contrast to predicted uptake of 50%,[43] only 2.5% of 16- to 24-year-olds were screened in the past year,[44] and chlamydia positivity rates remain at 10–11%.[1] There are no performance indicators for the primary outcomes.[45] The Chlamydia Screening Implementation project in the Netherlands will show whether or not the uptake of a register-based approach with repeated yearly screening invitations[6] can achieve the results observed by Scholes *et al*. [23] and Østergaard *et al*.[24]

Implications for the evaluation of chlamydia screening

Uptake of screening is not an adequate surrogate endpoint for trials of chlamydia screening because the level of coverage predicting a defined reduction in morbidity or transmission is not known.[46] Objective endpoints, such as ectopic pregnancy or tubal infertility, often require invasive diagnosis and are too rare or delayed to be used realistically in trials. Pelvic inflammatory disease is the most commonly used biological outcome because it is the most frequent acute complication of lower genital tract chlamydia and is strongly associated with impaired fertility.[34] Clinical diagnosis is, however, known to be insensitive, non-specific and subjective.[34,47] If misclassification applies similarly to both screened and unscreened groups, the effect size would be attenuated. The diagnosis of lower abdominal symptoms could, however, be different in screened and unscreened women if the investigator is influenced by the chlamydia screening status. Since practitioners usually cannot be blinded to the screening allocation in trials, symptoms reported in follow-up consultations should be recorded in a standard way, with the final outcome assessment made by an independent blinded committee.

A reduction in chlamydia transmission, attributable to screening, would provide good primary evidence of effectiveness. Comparing chlamydia test positivity after a single screening round biases the result in favour of the screened group, which includes incident infections, while infections in the control group include prevalent infections that might have been present before the trial started. Ideally, the effect of chlamydia screening on chlamydia transmission would be determined in a population in whom prevalent infections had been detected and treated, for example following a prevalence study with high participation, follow-up, treatment and partner notification rates. The chlamydia screening intervention would then be implemented in randomly assigned areas over two or more screening intervals. The final comparison would be made between screened and unscreened communities in a follow-up prevalence survey.

This systematic review provides information about the limitations of published evidence about the effectiveness of chlamydia screening, which can be used to inform future research and decisions about the introduction of chlamydia screening programmes. Where chlamydia screening interventions have already been introduced, our findings can be used to help design studies to determine the most effective way to deliver and monitor the outcomes of chlamydia screening. Interventions that combine the advantages of both register-based and opportunistic screening approaches could reach a higher proportion of the target population than either method alone.[48] For example, regular postal invitations could be supplemented with opportunistic offers to eligible individuals who have not responded. Alternatively, an initial opportunistic offer of testing could be followed up by postal invitations to non-attenders. The effectiveness and cost-effectiveness of chlamydia screening require further evaluation in randomized trials over multiple screening rounds with primary biological endpoints to show that the programme does more good than harm at reasonable cost.

Supplementary Data

Supplementary Data are available at *IJE* online.

Funding

United Kingdom National Institute for Health and Clinical Excellence.

Acknowledgements

N.L., N.B., L.N. and A.S. are, or have been, employed by the University of Bern, which received funding from the United Kingdom National Institute for Health and Clinical Excellence (NICE). Parts of the research referred to in this article were commissioned by NICE to inform the development of its guidance on the prevention of sexually transmitted infections and under-18 conceptions. The opinions expressed in the article are those of the authors and not the institute. This article does not constitute NICE guidance. The authors thank Shelagh Redmond for assistance with bibliographic and database management for the review.

Conflict of interest: None declared.

KEY MESSAGES

- Chlamydia screening is widely believed to be an effective and cost-effective intervention to improve reproductive and sexual health.
- The results of randomized controlled trials have overestimated the benefits of chlamydia screening on preventing pelvic inflammatory disease.
- The chlamydia screening interventions that have been evaluated in randomized controlled trials are not those that are implemented in practice.
- Clinical equipoise about the balance of benefits and harms of chlamydia screening programmes remains.

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