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Cost effectiveness of screening for Chlamydia trachomatis: a review of published studies

E Honey, C Augood, A Templeton, I Russell, J Paavonen, P-A Mårdh, A Stary, B Stray-Pedersen

Objective: Screening for Chlamydia trachomatis in the lower genital tract may contribute to the prevention of pelvic inflammatory disease in women. The purpose of this review was to critically appraise, and summarise studies of the cost effectiveness of screening for C trachomatis.

Methods: A literature search was conducted on Medline and in Health Star from 1990–2000. Keywords were C trachomatis, screening, cost effectiveness. Bibliographies of reviewed articles were also searched. The population studied was asymptomatic sexually active women under 30 years of age in a primary care setting. The intervention assessed was screening for lower genital tract infection with C trachomatis and the outcomes studied were cases of C trachomatis detected, cases of PID prevented, and associated costs. Studies were assessed using the Drummond criteria for economic evaluations. They were assessed qualitatively as they were too heterogeneous to allow quantitative analysis.

Results: 10 studies were included. All were modelled scenarios and all found screening to be more cost effective than simply testing symptomatic women, although all were based on probabilities that were assumed. Six of the studies focused on DNA based testing, three of them using urine. The models showed screening to be cost effective at prevalences of 3.1–10.0%, and cost saving (overtesting symptomatic women) at a prevalence as low as 1.1%, if age was used as a selection factor and DNA based tests were used in urine samples.

Conclusions: At the prevalence of infection expected in the target population, all studies suggest screening is cost effective. However, the assumptions used in the models have been difficult to confirm and there is a need for more data, particularly on the risk of complications in women with asymptomatic lower tract infection.

Chlamydia trachomatis is the most common, curable, bacterial sexually transmitted disease.1 It is a major cause of pelvic inflammatory disease (PID), which in turn is a major cause of infertility and ectopic pregnancy.2–5

The prevalence of lower tract infection with C trachomatis varies from 2–25%6–9 and is highest in young people. Infection with C trachomatis places a considerable burden on health services throughout the developed world.6 The infection is asymptomatic in 75% of women and at least 50% of men,6 thus lower genital tract infection remains largely undetected.

Current screening practices differ throughout Europe and North America. For example, in Sweden there is an active detection policy targeting women under 25, whereas in the United Kingdom there is no formal screening programme.7–9 Most of the evidence that supports screening for C trachomatis as a way of preventing PID is derived from epidemiological data.2,3,11–13

The only randomised controlled trial (RCT) of screening for C trachomatis was conducted in the United States6 and demonstrated that selective screening reduced the incidence of PID by 56% during 1 year of follow up.

A number of studies14–21 have assessed the cost effectiveness of screening for asymptomatic C trachomatis. This review attempts to appraise these studies and to make recommendations for future practice and research.

METHODS

Articles addressing the cost effectiveness of screening for C trachomatis were identified by a systematic computerised literature search and by searching the reference lists in relevant articles. An economic evaluation was considered eligible for inclusion if it assessed screening for C trachomatis in primary care, defined as the first point of contact for healthcare provision, or family planning clinics (FPC) and the main focus was on sexually active women under the age of 30. Studies examining men alone were excluded. The outcomes assessed were cases of PID prevented or cases of C trachomatis detected.

The computerised literature search was performed in Medline, EMBASE, Health Star, and the NHS economic evaluation database (NEED). The MeSH key word “Chlamydia trachomatis” was expanded to “Chlamydia.” The results of this search were combined with those of mass screening, economic evaluation, cost, cost benefit, and cost effective. The search was performed on literature from 1990–2000 because attitudes to screening and diagnostic technology have changed considerably in the past decade. Randomised controlled trials (RCT) of screening were also sought. The results of the search detected four studies that were not reported on NEED.

The following types of economic evaluations were nominated before assessment.

• A cost effectiveness analysis (including cost minimising), with a unidimensional outcome such as PID prevented

• A cost-utility analysis, where quality and quantity of life were examined—none of the studies located fell into this category

• A cost-benefit analysis, where benefits were valued and compared with costs and benefits of an alternative strategy.

Two reviewers (EH and CA) used the Drummond criteria22–25 to assess the methodology of the economic evaluations included in the systematic review (table 1). The criteria concur with the Task Force on Principles for Economic Analysis of Health Care Technology.26 The criteria are scored on the basis of a number of important issues including the identification of a focused and relevant question about a healthcare intervention, the level of

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evidence used to measure the effectiveness of the intervention, and the validity of any assumptions in the evaluation. The use of a sensitivity analysis to assess the robustness of the evaluation and the generalisability of the findings are also scored. The scores attributed on the Drummond checklist were not weighted. Interobserver variability in the study assessment was quantified using kappa coefficient. Owing to heterogeneity no attempt was made to pool the results of the individual studies.

RESULTS

Ten economic evaluations and one RCT were identified. The RCT demonstrated that screening for C. trachomatis reduced the subsequent risk of PID, odds ratio 0.44 (0.2 to 0.9). This RCT is the strongest available evidence that screening for C. trachomatis is effective and is described as grade I evidence. All other studies in this review were the result of economic modelling and not primary data collection. In five of the economic evaluations the prevention of PID was the measure of benefit assessed, while in the remainder C. trachomatis detected or cured was the measure. The agreement between the two reviewers (EH and CA) over the methodology of the economic evaluations had a kappa coefficient of 0.76 (p <0.001). Three of the economic evaluations were by the same group of authors. Two of the studies scored poorly (less than 5/20). Although they are included in table 2, they were excluded from further analysis.

In addition a further study was identified. This economic evaluation is set in the Netherlands and focuses on opportunistic screening of both men and women in general practice. The age range within the evaluation is 13–65 years. These two factors meant it did not meet the inclusion criteria for the systematic review. It is not the less an interesting evaluation as it models the possible effect of screening this population for a period of 10 years, and demonstrates that a screening programme would have to run for a minimum of 5 years to create any savings.

The studies are summarised below. Howell et al asked if asymptomatic women under 30 in a family planning clinic (FPC) were to be screened, which would be the most cost effective test—cell culture, EIA (enzyme immunoassay), DNA probe, LCR, or PCR (polymerase chain reaction) either on urine or endocervical samples. The effectiveness of the strategies was based on a prevalence study conducted in the same population. The probabilities used in this review were derived from the literature and are based on cohort studies. The costs included are direct costs and the weighted costs of sequelae. The outcome measure was PID. The study was modelled on a cohort of 18 000 women, with a prevalence of infection of 6.5%. The cost if there was no screening was $2.2 million (£1.42 million) and 497 cases of PID; screening using EIA prevented 240 cases of PID and saved $887 000 (£571 577) over no screening. However, nucleic acid amplification based tests (NAA) used on urine prevented 306 cases of PID and saved an additional $287 000 (£184 935) over EIA. The use of a NAA based test remained the most cost effective method of screening with a prevalence as low as 3.2%. The most cost effective scenario was a NAA based test used on a cervical swab in those women requiring a pelvic examination and on urine in those who did not.

Howell et al asked if it was more cost effective to screen asymptomatic women in a FPC using the Centre for Disease Control and Prevention (CDC) criteria, or to screen all women under 30 or to universally screen all women when compared to no screening. The effectiveness of the strategies was determined as part of a cohort study set in the family planning clinics. Certain variables used in the model were derived from primary data collection at the time of screening—for example, physician time. The probabilities of consequences among women with untreated chlamydial infection were derived from a review of cohort studies in the literature. The costs used

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**Table 1 Drummond checklist for the appraisal of economic evaluations**

<table>
<thead>
<tr>
<th>Drummond list</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a well designed question asked in an answerable form?</td>
<td>[No 0, yes 2]</td>
</tr>
<tr>
<td>Was a comprehensive description of the competing alternatives given?</td>
<td>[No 0, yes 2]</td>
</tr>
<tr>
<td>Was there evidence that the programmes effectiveness had been established?</td>
<td>[No 0, yes 2]</td>
</tr>
<tr>
<td>Were all the important and relevant costs and consequences for each alternative identified?</td>
<td>(Neither costs or consequences 0, one of two or most of both 1, both 2)</td>
</tr>
<tr>
<td>Were costs and consequences measured accurately in appropriate physical units?</td>
<td>(No 0, partially 1, all 2)</td>
</tr>
<tr>
<td>Were costs and consequences valued credibly?</td>
<td>(Neither 0, one of two or most of both 1, both 2)</td>
</tr>
<tr>
<td>Were costs and consequences adjusted for differential timing?</td>
<td>(No 0, yes 2)</td>
</tr>
<tr>
<td>Was an incremental analysis of costs and consequences of alternatives performed?</td>
<td>[No 0, yes 2]</td>
</tr>
<tr>
<td>Was a sensitivity analysis performed?</td>
<td>(No 0, some but insufficient 1, yes 2)</td>
</tr>
<tr>
<td>Did the presentation and discussion include all issues of concern to users?</td>
<td>(No 0, partial 1, most 2)</td>
</tr>
</tbody>
</table>
Table 2 Details of all studies including the allocated Drummond score

<table>
<thead>
<tr>
<th>Author/date</th>
<th>Type of study</th>
<th>Test</th>
<th>Outcome</th>
<th>Case of PID prevented</th>
<th>Sensitivity analysis</th>
<th>Score on Drummond criteria (max 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Howell et al (1999)</td>
<td>Model</td>
<td>LCR urine</td>
<td>Age based testing or universal treatment in high prevalence groups</td>
<td>233 cases of PID prevented saving of $800/PID</td>
<td>Yes, varied prevalence, cost, uptake and sensitivity</td>
<td>16</td>
</tr>
<tr>
<td>2 Howell et al (1998)</td>
<td>Model</td>
<td>DNA amplification in urine or cervical swab in asymptomatic women less than 30 years.</td>
<td>306 cases of PID prevented saving $3689/PID</td>
<td>Yes varied prevalence, cost, uptake and sensitivity</td>
<td></td>
<td>17</td>
</tr>
<tr>
<td>3 Howell et al (1998)</td>
<td>Model</td>
<td>Urine based NAA</td>
<td>Age based screening at less than 10.2% prevalence. Universal screening over 10.2% prevalence. Both in FPC.</td>
<td>85 cases of PID prevented saving $3585/PID</td>
<td>Yes, varied prevalence, cost, uptake and sensitivity</td>
<td>17</td>
</tr>
<tr>
<td>4 Paavonen et al (1998)</td>
<td>Model</td>
<td>NAA on urine</td>
<td>Cost effective in low prevalence (3.9%) population using DNA based test assuming 90% return rate</td>
<td>50% of sequelae prevented cost $45 per case of Ct*</td>
<td>Yes, extensive</td>
<td>15</td>
</tr>
<tr>
<td>5 Marazzo et al (1997)</td>
<td>Cross sectional study to provide data</td>
<td>EIA in several settings</td>
<td>Selective screening in GUM. Universal screening in FPC. Both with EIA.</td>
<td>44 674 cases of Ct* prevented a saving of $987 per case 47 025 cases prevented a saving of $667</td>
<td>Yes</td>
<td>18</td>
</tr>
<tr>
<td>6 Genc and Mardh (1996)</td>
<td>Model</td>
<td>NAA</td>
<td>Cost effective in asymptomatic women in FPC with DNA based test at 6% prevalence, positives treated with azithromycin.</td>
<td>NA</td>
<td>None was performed</td>
<td>12</td>
</tr>
<tr>
<td>7 Sellors et al (1992)</td>
<td>Model</td>
<td>EIA</td>
<td>Selective screening using set criteria in low prevalence populations. Effective using EIA.</td>
<td>NA</td>
<td>Yes</td>
<td>17</td>
</tr>
<tr>
<td>8 Buhaug et al (1990)</td>
<td>Model</td>
<td>Culture</td>
<td>Cost effective in GP in women &lt;24 every 2 years $1477 per case of PID prevented</td>
<td>No</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Excluded Cohen et al</td>
<td>Model</td>
<td>NAA</td>
<td>School based screening was cost effective.</td>
<td>3</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Excluded Humphreys et al</td>
<td>Model</td>
<td>Universal screening in FPC</td>
<td></td>
<td>5</td>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

*Chlamydia trachomatis
were direct costs and were calculated from the primary study. The costs of the sequelae were derived from other models. The women were tested with a NAA based test using an endocervical swab if a pelvic examination was indicated and urine if it was not. The outcome measure was PID prevented. They found screening all women under 30 would prevent the greatest number of cases of PID. This would still offer a saving over not screening even when the prevalence of infection was as low as 1.1%. However it was not the most effective strategy as a large number of unnecessary tests are performed. In their sensitivity analysis if the prevalence increased from 6.6% to 10.0% then universal screening became the most cost saving strategy.

Paavonen et al asked if screening asymptomatic women under 25 at STD (STDs) clinics. The effectiveness of the strategies was estimated from a cross sectional survey of women in a FPC and in a STD clinic. The probabilities used were derived from a literature review and are as such based on the best available evidence. These probabilities are high however. For example they estimate that symptomatic PID will develop in up to 40% of women with untreated chlamydial infection and this is intuitively too high. The costs included are both direct and indirect and are explicitly stated and credible. The main outcome measure was C trachomatis detected. The cost per case detected was $46 (£29.6) if participation was 75% compared to a cost of $50 (£32.2) if no screening was performed. The net saving in the population, with a prevalence of C trachomatis infection of 3.5%, was $3.5 million (£2.25 million). The threshold prevalence in this study was 3.9% but savings increased with prevalence. This study had added value in that it examined the health benefits of C trachomatis screening. Compared with no screening, screening and treating with the antibiotic azithromycin would result in 62% more cured ing. Compared with no screening, screening and treating with C trachomatis was based on a pilot study of screening. The probability of outcomes of untreated chlamydial infections were possible overestimated and were not subject to a sensitivity analysis. The study included both direct and indirect costs but with only a brief description of the breakdown of those costs. The likelihood of complications in women who are infected is not given. Costs were subjected to discounting and this varied from 5–10%. Although an explicit sensitivity analysis was not performed, randomly chosen probabilities were entered from the defined ranges. The outcome measure was cured C trachomatis infection. The main conclusion was that with a prevalence of 6% or more screening with a NAA based test was the most cost effective strategy.

Sellors et al asked if it was better to screen young sexually active women in a FPC, universally or selectively (comparing two different selection strategies) using culture, EIA, or culture and DFA on endocervical samples. The probabilities of outcomes of untreated chlamydial infections were derived from the literature. The costs used are the direct costs involved in the collection, analysis and treatment of screening and are explicitly stated. Furthermore the costs associated with the sequelae are not explained. The sequelae are estimated to occur 8 years in the future and the costs are discounted by 5% per year. A sensitivity analysis was conducted over the costs and probabilities of the consequences of chlamydial infection, on the performance of the selective criteria and the threshold prevalence was calculated for each scenario. The outcome examined was C trachomatis detected. This was a cost minimising evaluation concentrating on costs saved rather than cases of C trachomatis detected. The selective criteria were cervicitis, intermenstrual bleeding, discharge, or urinary frequency. Using these criteria they tested 53.3% of women and detected 83.3% of cases. On the basis of a new sex partner in the previous year 75.4% of women were tested and 93.3% of cases detected. They demonstrated that, while costing less, selective screening detected less cases of C trachomatis. This conclusion may in part be influenced by the choice of EIA as a test.

Buhaug et al asked if it was cost effective to screen asymptomatic young women for C trachomatis in general practice using culture of endocervical samples when compared with no screening. The effectiveness of the strategy was calculated from one follow up study. The consequences and probability of the consequences of untreated chlamydial infections were estimated from the published literature. It is striking in this study that there was the assumption that 95% of those with a positive test would come forward for treatment and this would be successful in 90%. The costs in this model include direct and indirect costs and seem appropriate by today's standards but are perhaps high for 1990. The main outcome measure was PID prevented. The authors also modelled the effect of screening on anticipated PID and ectopic pregnancies. They found screening to be cost effective among 18–24 year olds with a prevalence of infection of 8.4% (range 3.5–13.4%). This review had added interest as the authors varied the prevalence and the consequences of infection, with age. It is also interesting, that even using culture, the most expensive method for the detection of C trachomatis, screening was still cost effective.

Thus the method used to detect C trachomatis varied among the models. Six used an NAA based detection system, half of these in urine. Although now proposed as the gold standard, NAA testing is still not routinely offered in all settings. This review indicates that while nucleic acid amplification based tests can cost more than alternative tests their greater sensitivity makes them more cost effective. In a screening scenario the relatively high false negative rates using non-NAA based tests may limit any longer term savings.
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Consequences included</th>
<th>Probabilities (amongst uncured Ct* infection)</th>
<th>Test</th>
<th>Discounted</th>
<th>Cost effective at prevalence</th>
<th>Cost saved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Howell et al (1999)</td>
<td>PID, Chronic pelvic pain</td>
<td>30% (40% symptomatic)</td>
<td>LCR urine</td>
<td>3%</td>
<td>Age based testing less than 25 if prevalence less than 9% or universal treatment in high prevalence groups</td>
<td>$800/PID</td>
</tr>
<tr>
<td>2 Howell et al (1998)</td>
<td>PID, Chronic pelvic pain, Ectopic, Infertility, Urethritis, Epididymitis, Neonatal conjunctivitis and pneumonia</td>
<td>30% symptomatic</td>
<td>Comparing tests</td>
<td>3%</td>
<td>Yes</td>
<td>$3689/PID</td>
</tr>
<tr>
<td>3 Howell et al (1998)</td>
<td>PID, Chronic pelvic pain, Ectopic, Infertility, Urethritis, Epididymitis, Neonatal conjunctivitis and pneumonia</td>
<td>30% (40% symptomatic)</td>
<td>Urine based NAA</td>
<td>3%</td>
<td>Age based in FPC if less than 30 years if less than 10.2 prevalence</td>
<td>$3585/PID</td>
</tr>
<tr>
<td>4 Paavonen et al (1998)</td>
<td>Among Ct* positives, PID, Infertility, Ectopic, Epididymitis, Neonatal conjunctivitis and pneumonia</td>
<td>60% (20% symptomatic)</td>
<td>NAA on urine</td>
<td>4%</td>
<td>Universal screening in FPC at 3.9% prevalence if uptake 75% using DNA based test assuming 90% return rate</td>
<td>50% of sequelae prevented cost $4.5 per case Ct* detected</td>
</tr>
<tr>
<td>5 Marrazzo et al (1997)</td>
<td>PID, Chronic pelvic pain, Infertility, Ectopic, Epididymitis, Neonatal conjunctivitis and pneumonia</td>
<td>15–40%</td>
<td>EIA in several settings</td>
<td>5%</td>
<td>Universal screening with EIA if prevalence greater than 3.1% in FPC</td>
<td>$1100/PID</td>
</tr>
<tr>
<td>6 Genc and Mardh (1996)</td>
<td>PID, Chronic pelvic pain, Ectopic, Infertility, Urethritis, Epididymitis, Neonatal conjunctivitis and pneumonia</td>
<td>Pooled probability of consequence</td>
<td>NAA</td>
<td>5–10%</td>
<td>Universal screening cost effective in asymptomatic women at FPC with DNA based test at 6% prevalence if treated with azithromycin</td>
<td></td>
</tr>
<tr>
<td>7 Sellors et al (1992)</td>
<td>Cervicitis, PID, Ectopic, Infertility</td>
<td>20% (3% of untreated Ct*)</td>
<td>EIA</td>
<td>5%</td>
<td>Selective screening using set criteria in low prevalence &lt;2% populations with EIA effective</td>
<td></td>
</tr>
<tr>
<td>8 Buhaug et al (1990)</td>
<td>PID, Ectopic, Infertility</td>
<td>Varied with age</td>
<td>Culture</td>
<td>5%</td>
<td>Cost effective in general practice in women less than 24 every 2 years</td>
<td></td>
</tr>
</tbody>
</table>
The threshold population prevalence of *C. trachomatis* over which the evaluations were cost effective varied from 3.1–10.0%. Screening can be cost saving at a prevalence as low as 1.1%, when age is used to select women and NAA based tests are used in urine samples, although the large numbers of unnecessary tests diminishes effectiveness. This variation in the threshold prevalence rate is explained by the very wide range of costs used in the models. It may also be explained by the decision in three evaluations not to include indirect costs. These costs, which are incurred by society and individuals, are important, although there is still much debate about their inclusion in an economic evaluation. In two studies azithromycin in a single dose was used to treat the infection. These studies had a threshold prevalence of 3.9% and 6.0% respectively. In the remainder doxycycline for 7 days was the standard treatment used. Both regimens have similar effectiveness but compliance is better with azithromycin. The probabilities of return for treatment and treatment failure ranged from 65–90% and 75–97% respectively, but at all these levels screening was still cost effective.

Incremental analysis was performed in six studies, demonstrating how much more one strategy cost over the next most effective strategy.

**DISCUSSION**

In this systematic review all the economic evaluations assumed de facto that screening for *C. trachomatis* was effective and then went on to agree that screening asymptomatic women for *C. trachomatis* is cost effective and indeed cost minimising over whatever scenario is currently offered. Medically this finding is unsurprising. The presumed consequences of lower genital tract infection with *C. trachomatis* are PID, ectopic pregnancy, and infertility—all of which can be very expensive in terms of both healthcare costs and lost productivity. Economic modelling can provide quick, accurate, and robust answers where an exploration of potential outcomes can be undertaken using a sensitivity analysis. However, this is dependent on the probabilities entered being substantiated by strong evidence. All of the models appraised in this review suffered from a lack of strong evidence to support their assumptions and are vulnerable therefore to bias in their findings and conclusions.

For example, the models have used probabilities and assumptions for the consequences of untreated *C. trachomatis* infection, which have been derived from a group of women who were culture positive for *C. trachomatis*. The assumption is that being culture positive is the same as being positive in a NAA based test, which is unlikely in relation to bacterial load alone. None of the models have used primary data from a cohort of women who have been screened for *C. trachomatis* using a sensitive diagnostic test and then followed up over time. None of the models including those published later used data derived from the Scholes study, the strongest evidence to date that screening is effective in preventing PID.

Although the models did conduct sensitivity analysis of prevalence rates, age groups, and types of screening, in only one of the studies did the researchers vary the uptake of screening. The other analyses were based on the presumption that the whole cohort accepted screening. However in the Scholes study, screening was accepted by only 64% and a similar finding was noted by Grun et al. It is of course possible that uptake may improve with the advent of urine based testing as well as self testing using vulval swabs. Clearly there is a need for much more data if the cost effectiveness of screening is to be successfully modelled. These data would best be provided in the context of well conducted clinical trials.

There is now evidence, albeit from only one RCT, that screening for *C. trachomatis* is effective. One case of PID will be prevented for every 85 women screened; furthermore screening has been shown to reduce the rate of ectopic pregnancy within 1 year of introduction. However it is difficult to be certain that screening for *C. trachomatis* has been solely responsible for the fall in ectopic pregnancies or for the reduction in women with PID seen in Sweden, as screening interventions will have both a primary and secondary preventive action. Any national screening programme will increase awareness among the people at risk as well as healthcare professionals and this alone may bring about change.

**CONCLUSION**

This systematic review of the cost effectiveness of screening young asymptomatic women for *Chlamydia trachomatis* suggests that screening is cost effective at the prevalence of chlamydial infection expected in the relevant population. However, the assumptions upon which the models have been based are not always derived from sound evidence, particularly with respect to the subsequent risk of PID in women testing positive using newer sensitive nucleic acid based diagnostic tests. Further unanswered questions relate to the prevalence and reinfection rates of *C. trachomatis* after a screening programme has been established. There is an urgent need for more data derived from well conducted clinical trials to inform the discussion and help with national policies and recommendations.

**ACKNOWLEDGEMENT**

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