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## **What is the excess risk of infertility in women following genital chlamydia infection? A systematic review of the evidence.**

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## ABSTRACT

**Objective:** To summarise evidence on the attributable risk of infertility following chlamydial infection in women by performing a systematic review.

**Methods:** Twelve databases were searched, limited to peer-reviewed papers published from January 1970 until September 2007. Conference abstracts and reference lists from reviews published since 2000 and from key articles were hand-searched. Studies were selected for review if they met the following criteria: (i) the study population comprised females of child-bearing age (defined as 15-45 years) and incorporated a comparison group of women documented as 'chlamydia negative'; (ii) the study outcomes included either infertility or successful pregnancy; and, (iii) the study design was one of the following: cohort, randomised controlled trial, 'before and after' studies, screening trials and systematic reviews. Studies were excluded if they described genital infections that either did not include *Chlamydia trachomatis* or described genital chlamydial co-infection, where no data were available for *Chlamydia trachomatis* infection alone.

**Results:** 3349 studies were identified by the search. One study satisfied the inclusion criteria, a longitudinal investigation measuring pregnancy rates in adolescent females with and without current chlamydial infection at baseline. This study reported no significant difference in subsequent pregnancy rates, however, it had serious methodological limitations, which restrict its conclusions.

**Conclusions:** Our systematic review demonstrates the absence of valid evidence on the attributable risk of post-infective tubal factor infertility following genital chlamydial infection. Our findings contribute empirical data to the growing debate surrounding prior assumptions about the natural history of chlamydial infection in women.

## INTRODUCTION

Concerns about the public health impact of genital chlamydial infection have generated considerable policy interest in the UK; a National Chlamydia Screening Programme is currently being implemented throughout England and national guidelines on chlamydial infection have also been widely adopted in Scotland.<sup>1-3</sup> Proactive targeted screening for chlamydial infection has been justified by four attributes of chlamydial infection; its high general population prevalence (recently estimated at 3% in UK residents aged under 25 years);<sup>4</sup> its substantial transmission potential;<sup>5</sup> the recent development of simple, non-invasive tests;<sup>2,5</sup> and its potential for acute and chronic morbidity.<sup>5,6</sup>

In this last respect, however, the evidence base appears weak; although numerous case control studies have reported an association between serological evidence of prior chlamydial infection and tubal infertility, this evidence is of limited value, for two reasons. First, case control studies have to rely on serological methods for ascertainment of prior genital *Chlamydia trachomatis* infection; serological methods (before the advent of peptide-based, species-specific assays) are universally acknowledged to exhibit poor validity and reliability for this purpose.<sup>7</sup> Second, case control studies generate ratio measures rather than absolute measures of effect. Although ratio measures can demonstrate an association between chlamydial infection and infertility, they cannot directly quantify the excess risk of infertility attributable to chlamydial infection, which is the crucial information required to counsel patients and, at a population level, to estimate the proportion of infertility cases that might be averted by chlamydia screening programmes. In addition, the control populations are often selected from very different populations (notably pregnant women) which may give a falsely low estimate of infertility in the unexposed

group and thus, an exaggerated estimate of the effect of chlamydial infection on infertility.

Quantifying excess (or attributable) risk is fundamentally important at many levels; individual women diagnosed with apparently uncomplicated chlamydial infection frequently request prognostic information on their subsequent risk of infertility and policymakers need robust cost effectiveness evidence to underpin prevention strategies. One of us (LW) recently reviewed patient information materials used by Genitourinary Medicine (GUM) clinics across the UK; almost invariably, these contained no information on quantitative infertility risk, despite the importance of this issue to women diagnosed with chlamydial infection.<sup>8</sup> We therefore conducted a systematic review of the literature to summarise existing evidence on the attributable risk of infertility following chlamydial infection.

## **METHODS**

### **The review question**

The review sought to answer the following question: 'What is the attributable risk of infertility following one or more episodes of genital *Chlamydia trachomatis* infection in women of reproductive age?' Attributable risk is defined as the proportion of women infected with *Chlamydia trachomatis* who subsequently develop infertility attributable to the chlamydial infection.

### **Search terms, databases and search strategy**

A search strategy was developed in collaboration with information scientists at the Centre for Reviews and Dissemination, University of York, UK (Web Table).

A comprehensive list of databases was searched, with appropriate adaptation of the key words for each database search (Table 1). The search was limited to published peer-reviewed papers from January 1970 until September 2007; the earlier time boundary was selected because it was judged to reflect the earliest time point from which diagnostic methods for chlamydial infection became available.

Although this was primarily a systematic review of peer-reviewed literature, conference abstracts were also searched, using the 'Inside Conferences' and 'Biosis Previews' electronic databases to September 2004. Reference lists from reviews published since 2000 and from key articles were hand-searched to identify any further relevant papers. We did not personally contact researchers to identify ongoing research studies or unpublished reports; non-English language papers were not included in the review, as our resources would not have supported their translation.

### **Inclusion and exclusion criteria**

Studies were selected for review if they met the following criteria: (i) the study population comprised females of child-bearing age (defined as 15-45 years) and, in addition to women with genital chlamydial infection, also incorporated a comparison group of women documented as uninfected with *Chlamydia trachomatis*; (ii) the study outcomes included either infertility (defined as failure of a couple to achieve pregnancy despite 12 months of regular unprotected sexual intercourse and/or referral to a specialist infertility service) or successful pregnancy; and, (iii) the study design was one of the following: cohort, randomised controlled trial, 'before and after' studies, screening trials (where information on outcomes are given) and systematic reviews.

Conversely, studies were excluded if: (i) the study population comprised females under 15 years or older than 45 years; (ii) they described genital infections that either did not include *Chlamydia trachomatis* or described genital chlamydial co-infection, where no data were available for *Chlamydia trachomatis* infection alone; (iii) they focused on pelvic inflammatory disease only and data on one of the outcomes described in the inclusion criteria were unavailable.

The first reviewer scanned the abstracts and titles using the criteria described above and categorised them into two libraries: 'papers for further analysis' and 'papers not relevant'. The former consisted of abstracts of original articles, reviews, and titles, for which no abstract was available, but which incorporated key words relevant to the study. To assess reliability, a second reviewer evaluated a 10% random sample of both libraries. Following resolution of any differences, both reviewers agreed on those abstracts or titles for which full papers were retrieved and the papers to be included in the review.

## **Study Quality Assessment**

Papers selected for review were assessed for methodological quality by the two reviewers using the criteria described by Levine et al.<sup>9</sup>



## RESULTS

Twelve databases were searched for relevant articles, generating a library of 3349 abstracts and titles for review. Fifty papers were identified as potentially relevant to the research question; these included nine primary research papers, ten review articles published since 2000 and 31 papers retrieved from the 'title only' group. Of these 50 selected papers, forty-nine failed to satisfy the inclusion criteria; 33 were review or review-type articles and not primary research studies, eight articles did not address the outcome of interest and eight were not an appropriate study design. One additional paper was identified from a review paper but this was also rejected on the basis of study design.<sup>10</sup> (Figure 1)

The one study which satisfied the inclusion criteria was a longitudinal investigation, measuring pregnancy rates in adolescent females with and without evidence of current chlamydial infection at baseline; no statistically significant difference in pregnancy rates at the end of the follow-up period was found (Table 2).<sup>11</sup> However, the study's methodological limitations diminish the precision of its statistical estimates and the overall validity of its conclusions, further discussed below.

First, the study was conducted in Indianapolis, USA between 1985 and 1990, at a time when the gold standard laboratory diagnostic test (tissue culture) was relatively insensitive. This is likely to have resulted in incorrect misclassification of a proportion of chlamydia infected women into the 'uninfected' group at the study outset.

Second, the sample size afforded limited statistical power, compounded by substantial attrition of the study population, with only 104 (21%) of the original cohort of 496 women available for participation in the follow-up telephone survey. There was

uncertainty about the mean follow-up time and whether this differed between the three study groups.

Third, measurement and analysis of confounding variables (including age, socio-economic circumstances, contraceptive use, frequency of intercourse and number of sexual partners) were inadequate.

Crucially, more than half of the overall survey sample reported current contraceptive use (oral contraception, condoms or both); however, pregnancy outcomes were, however, neither stratified by contraceptive use nor analysed by multivariable modelling methods to investigate the confounding effects of contraceptive use on pregnancy outcomes.

In summary, Katz et al found no association between a history of treated chlamydial infection and infertility in their study population, but the caveats described above seriously limit these conclusions. As no other eligible studies could be located in our systematic review, it was not possible to obtain valid evidence on the attributable risk of infertility following genital chlamydial infection in women.

## DISCUSSION

In summary, our systematic review demonstrates the absence of valid evidence on the attributable risk of infertility following genital chlamydial infection and an overall dearth of research on the natural history of chlamydial infection in women.

Although an extensive search for evidence was systematically conducted, we acknowledge that our study does have limitations; researchers in the field were not personally contacted about any unpublished research studies and non-English language papers were not included in the review. However, the authors have sufficient awareness of current health services research on chlamydia testing policy to be satisfied that this boundary (selected for pragmatic reasons) was unlikely to have introduced bias.

To our knowledge, this is the first published systematic review of the evidence base on attributable risk of infertility following genital chlamydial infection. **While the focus of our study was to examine the attributable risk of genital chlamydial infection, we fully recognise the polymicrobial nature of pelvic inflammatory disease (PID) and thus, subsequent infertility. Accordingly, we defined our exclusion criterion to select only studies where data were available on genital chlamydial infection, even in those with concurrent infections.**

Genital chlamydial infection has been judged to fulfil the required criteria for establishment of a screening programme.<sup>12</sup> This judgment was, however, based on assumptions about the natural history of infection that are now being increasingly questioned. Indeed, there are still many unanswered questions regarding the persistence of chlamydial infection; in a one-year follow up study a 45% clearance rate of infection per year was found in women who had received no antibiotic

treatment; in addition, none of the women developed clinical PID.<sup>13</sup> However, distinguishing between persistent infection and re-infection may be difficult also.

Our systematic review advances the **current debate about the potential health benefits that may be gained from chlamydia screening** by demonstrating empirically the lack of evidence on attributable risk.<sup>14-18</sup> **Data from two randomised control trials of screening versus no screening or normal care demonstrated a greater than 50% decrease in the incidence of PID.**<sup>19,20</sup> However, these have since been criticised because of the considerable potential for both selection and measurement bias. Scholes et al analysed outcomes in only a small proportion of the women randomised and ascertainment of the main outcome measure (PID) was made by case note review (as opposed to laparoscopic diagnosis or use of systematic, criterion-based clinical examination).<sup>19</sup> In addition, the study did not evaluate an opportunistic approach to screening, which is the current strategy being advocated in the UK and in most other countries. **In the study by Ostergaard et al there was a high level of loss to follow up of both the screening and the control group and possible under-reporting of PID and it was unclear what effect these may have had on the screening trial.**<sup>20</sup> **Recent key contributors to this debate include van Valkengoed et al and Low et al.**<sup>16,18</sup> Van Valkengoed et al generated modelled estimates of the risk of tubal factor infertility at 0.02%, substantially lower than previous estimates which have ranged between 1.5 and 16%.<sup>16</sup> The authors concluded that current assumptions over-estimate the probability of complications and accordingly the health gain and cost savings associated with chlamydia screening. **Low et al presented data from a 15 year follow up of a retrospective population-based cohort of women (aged less than 25 in 1985) in Uppsala, Sweden. They estimated the cumulative incidence of infertility at between 3-7% depending on whether the woman had ever tested or ever been diagnosed with chlamydia and concluded that this was lower than expected from previous published estimates.**<sup>14,18</sup> Thus, there is a growing

body of published data which suggest that the reduction in reproductive morbidities resulting from chlamydia screening programmes may be over-estimated and that further research is required.

This review has highlighted the absence of high quality evidence to answer questions commonly posed by the increasing numbers of women daily who receive a diagnosis of lower genital tract chlamydial infection within proactive opportunistic screening programmes in the UK and elsewhere. Current evidence is unable to provide women with any reliable estimates of the likelihood of serious reproductive health complications. At a wider population level, because the absolute risk of infertility following chlamydial infection is unknown, policymakers find themselves similarly ill-equipped to quantify the population impact of chlamydial infection on reproductive morbidity, and therefore face uncertainty about the proportion of PID and infertility that is preventable by chlamydia screening.

There are a number of possible approaches to address the major gap in the evidence base. The optimal epidemiological method, a cohort study design, for estimating the absolute risk of infertility attributable to chlamydial infection would now be considered unethical; it would require an extensive follow-up period in untreated women, careful measurement and control of potential confounding variables (including age, contraceptive usage, socio-economic circumstances and sexual behaviour) and accurate measurement of infertility/successful pregnancy outcomes. This necessitates an extremely large sample size and, accordingly, considerable resources. It would also be extremely difficult to gain ethical approval for a cohort study designed to monitor adverse outcomes among women with untreated chlamydial infection within a policy context that actively promotes testing and treatment.<sup>21</sup> There is already good evidence that treating people with genital chlamydial infection is beneficial in relation to short term morbidity, such as urethritis

or epididymitis;<sup>2,5</sup> moreover, numerous case control studies have demonstrated that women with infertility have a significantly greater chance of having been infected with chlamydia than those who are fertile.<sup>5,6</sup> What remains unknown, however, is the absolute magnitude of the increased risk of infertility that is attributable to *Chlamydia trachomatis* infection.

If undertaking a cohort study is not feasible, remaining options for estimation of attributable risk would involve statistical modelling of the risk of progression to pelvic inflammatory disease following chlamydial infection. **With this methodological approach, assumptions about the polymicrobial aetiology of PID and other dynamic transmission-related factors that may influence the outcome of chlamydial infection could be factored into the analysis.** Alternatively, ecological analyses comparing nations or regions might offer useful insights.<sup>22</sup> Such an analysis might involve comparing reproductive data from countries with differing approaches to screening policy. The resulting data will ensure that the future direction of chlamydia screening programmes in the UK and elsewhere is based on the best available evidence.

## REFERENCES

1. Fenton KA, Ward H. National chlamydia screening programme in England: making progress. *Sex Transm Inf* 2004; **80**: 333-334
2. Scottish Intercollegiate Guidelines Network. *Management of genital Chlamydia trachomatis infection*. No. 42. Edinburgh: SIGN, March 2000.
3. Scottish Programme for Clinical Effectiveness in Reproductive Health. National audit of the management of genital *Chlamydia trachomatis* infection. April 2003. [www.abdn.ac.uk/spcerh/publications](http://www.abdn.ac.uk/spcerh/publications) (accessed March 2006)
4. Fenton KA, Korovessis C, Johnson AM et al. Sexual behaviour in Britain: reported sexually transmitted infections and prevalent genital Chlamydia trachomatis infection. *Lancet* 2001; 358: 1851-1854.
5. Stamm WE. *Chlamydia trachomatis* infections of the adult. In: Holmes KK, Mardh PA, Sparling PF, et al., eds. *Sexually transmitted diseases*. 3<sup>rd</sup> edition New York: McGraw Hill, 1999: 407-422
6. Cates WJR. and Wasserheit JN. Genital chlamydial infections: epidemiology and reproductive sequelae. *Am J Obstet Gynecol* 1991; **164**: 1771-1781.
7. Carder C, Mercey D, Benn P. *Chlamydia trachomatis*. *Sex Transm Inf* 2007; **82** (Suppl IV): iv10-iv12.
8. Duncan B, Hart G, Scoular A, Bigrigg A. Qualitative analysis of psychosocial impact of diagnosis of Chlamydia trachomatis: implications for screening. *BMJ*. 2001; 322:195–199.

9. Levine M, Walter S, Lee H, Haines T, Holbrook A, Moyer V, for the Evidence-Based Medicine Working Group. Users' guides to the medical literature IV. How to use an article about harm. *JAMA* 1994; 271: 1615-19.
10. Clark KL, Howell MR, Li Y, et al. Hospitalization rates in female US army recruits associated with a screening program for *Chlamydia trachomatis*. *Sex Transm Dis* 2002; 29:1-5.
11. Katz BP, Thom S, Blythe MJ, Arno JN, Caine VM, Jones RB. Fertility in adolescent women previously treated for genitourinary chlamydial infection. *Adolesc Pediatr Gynecol* 1994; 7: 147-152.
12. Department of Health. Second Report of the UK National Screening Committee. London: The Stationery Office, 2000.
13. Morre SA, van den Brul AJ, Rozendaal L, Voorhorst FJ, de Blok S, Meijer CJ. The natural course of asymptomatic *Chlamydia trachomatis* infections: 45% clearance and no development of clinical PID after one year follow-up. *Int J STD & AIDS* 2002; 13 (Suppl2): 12-18.
14. Low N, Egger M. What should we do about screening for genital chlamydia? *Int J Epidemiol* 2002; 31: 891-893.
15. Honey E, Templeton A. Prevention of pelvic inflammatory disease by the control of *C trachomatis* infection. *Int J Gynaecol Obstet* 2002; 78: 257-261.



16. van Valkengoed IGM, Morre SA, van den Brule AJC, Meijer AJLM, Bouter LM and Boeke AJP. Overestimation of complication rates in evaluations of *Chlamydia trachomatis* screening programmes – implications for cost-effectiveness analyses. *Int J of Epidemiol* 2004; 33: 416-425.
17. Hu D, Hook EW 3<sup>rd</sup>, Goldie SJ. The impact of natural history parameters on the cost-effectiveness of *Chlamydia trachomatis* screening strategies. *Sex Transm Dis* 2006; 33(7): 428-436.
18. Low N, Egger M, Sterne JAC et al. Incidence of severe reproductive tract complications associated with diagnosed genital chlamydial infection: the Uppsala Women's Cohort Study. *Sex Transm Inf* 2006; 82: 212-218.
19. Scholes D, Stergachis A, Heidrich FE, Andrilla H, Holmes KK, Stamm WE. Prevention of pelvic inflammatory disease by screening for cervical chlamydial infection. *N Engl J Med* 1996; 334:1362-1366.
20. Ostergaard L, Andersen B, Moller JK, Olesen F. Home sampling versus conventional swab sampling for screening of *Chlamydia trachomatis* in women: a cluster-randomized 1-year follow-up study. *Clin Infect Dis* 2000; 31: 951-957.
21. Senok A, Wilson P, Reid M et al. Can we evaluate population screening strategies in UK general practice? A pilot randomised controlled trial comparing postal and opportunistic screening for genital chlamydial infection. *J Epidemiol Community Health* 2005; 59:198-204.

22. Low N. Current status of chlamydia screening in Europe. *Eurosurveillance* Weekly 2004;10(41) 041007.

[www.eurosurveillance.org/ew/2004/041007.asp#5](http://www.eurosurveillance.org/ew/2004/041007.asp#5) (accessed December 2006)

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### **Contributors**

AS, GH, MR, PW and DG designed the study, obtained funding and provided comments on the review protocol. LW performed the systematic review with AS in a supervisory role and as second reviewer. LW, AS and DG drafted the manuscript and all authors contributed to manuscript revisions. LW and AS prepared the final paper.

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(All authors declare that the answer to the questions on your competing interest form [bmj.com/cgi/content/full/317/7154/291/DC1](http://bmj.com/cgi/content/full/317/7154/291/DC1) are all 'No' and therefore have nothing to declare.)

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### **Key messages**

1. This systematic review demonstrates an absence of evidence on the attributable risk of infertility following genital chlamydial infection and an overall lack of research on the natural history of chlamydial infection in women.
2. Only one primary research study was identified from the literature search; however, some methodological limitations resulted in its rejection from the review. Thus, no measure of assurance on the risk of infertility, as a result of a positive chlamydia diagnosis, to inform women who are undergoing chlamydia testing, could be made from this research.

3. Chlamydia screening programmes are based on previous assumptions about the natural history of infection, in particular the likelihood of developing infertility. Most of this evidence is derived from case-control studies or those based on hospital and clinic-based populations - these are inappropriate types of study from which to provide a level of the risk of developing infertility following chlamydial infection.
4. This study, in combination with other recent publications, indicates that the previous assumptions on progression rates to infertility are no longer valid.
5. The proportion of pelvic inflammatory disease and infertility that is preventable by chlamydia screening remains unknown.

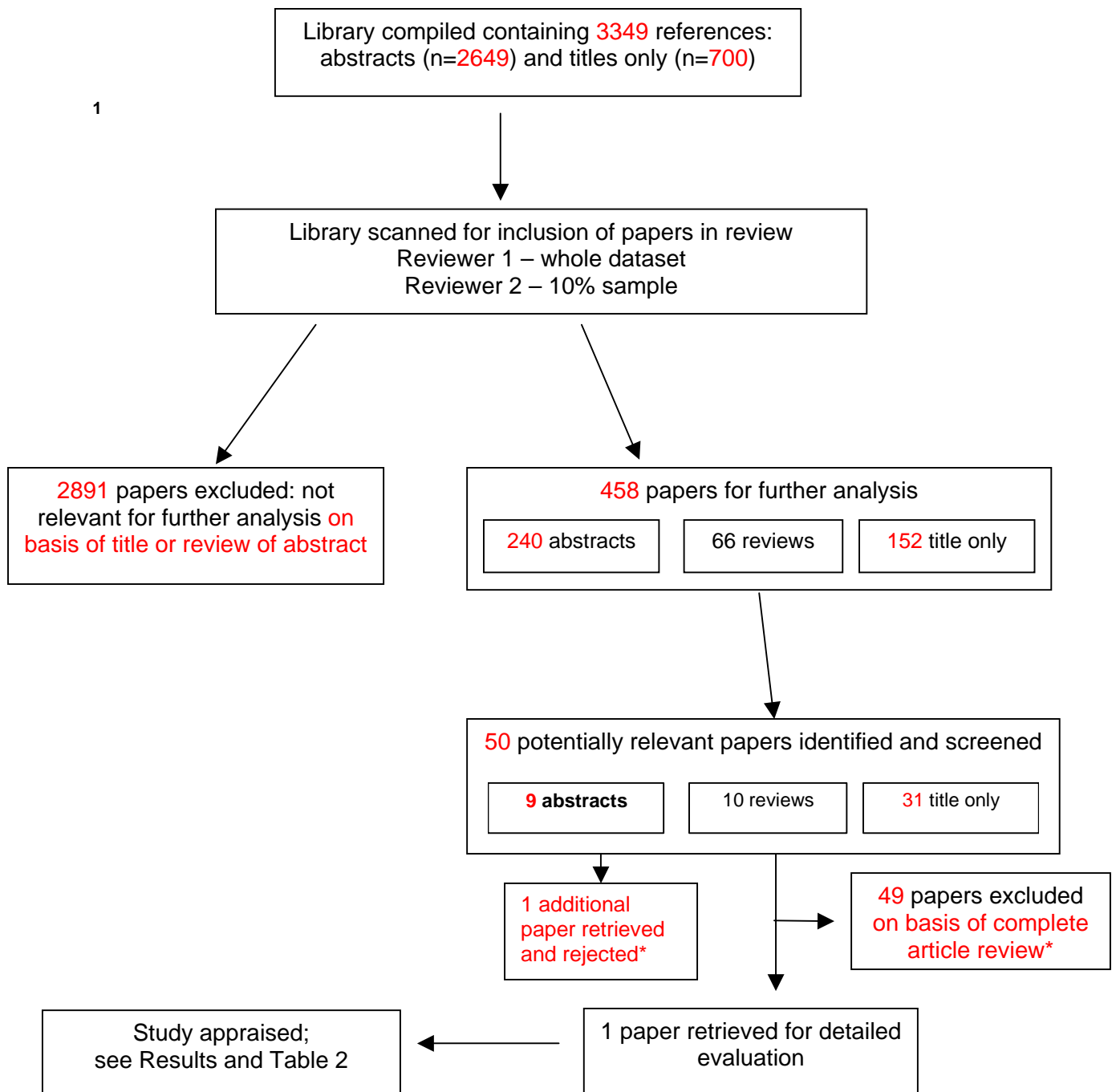
**Web Table: Search terms and strategy used for searching Medline database**

<p>Search terms</p>	<ol style="list-style-type: none"> <li>1. Woman/Women/Female</li> <li>2. <i>Chlamydia trachomatis</i> / Chlamydia infections</li> <li>3. Infertility             <ul style="list-style-type: none"> <li>- tubal factor infertility</li> <li>- impaired fertility</li> </ul> </li> <li>4. Pregnancy             <ul style="list-style-type: none"> <li>- pregnancy outcome</li> </ul> </li> <li>5. Chlamydia heat shock protein</li> <li>6. Anti-chlamydial antibodies</li> </ol>
<p>Search Strategy</p> <p>MEDLINE 1966 – Sept week 2 2007 (Ovid interface)</p>	<ol style="list-style-type: none"> <li>1. chlamydia trachomatis/</li> <li>2. chlamydia infections/</li> <li>3. (chlamydia\$ adj2 (infection\$ or trachoma\$)).ti,ab.</li> <li>4. 1 or 2 or 3</li> <li>5. chlamydia pneumoniae/</li> <li>6. 4 not 5</li> <li>7. exp women/</li> <li>8. female/</li> <li>9. (woman or women or female\$).ti,ab.</li> <li>10. or/7-9</li> <li>11. exp infertility/</li> <li>12. (infertil\$ or subfertil\$ or sub-fertil\$).ti,ab.</li> <li>13. ((tubal\$ or tube\$) adj2 (fertil\$ or infertil\$ or subfertil\$ or factor\$ or conceiv\$ or conception\$ or pregnan\$)).ti,ab.</li> <li>14. ((impair\$ or problem\$ or difficult\$ or substandard\$ or sub-standard\$ or inabilit\$) adj2 (conceiv\$ or conception\$ or pregnan\$ or fertil\$ or infertil\$)).ti,ab.</li> <li>15. chlamydia\$ heat shock protein\$.ti,ab.</li> <li>16. ((antichlamydia\$ or anti chlamydia\$) adj2 (antibod\$ or anti bod\$)).ti,ab.</li> <li>17. pregnancy/</li> <li>18. pregnancy outcome/</li> <li>19. pregnan\$.ti,ab.</li> <li>20. or/11-19</li> <li>21. 6 and 10 and 20</li> <li>22. animals/</li> <li>23. human/</li> <li>24. 22 not (22 and 23)</li> <li>25. 21 not 24</li> <li>26. (comment or letter or editorial).pt.</li> <li>27. 25 not 26</li> <li>28. limit 27 to yr=1970 – 2007</li> </ol>

**Table 1: Databases and time periods searched.**

Database	Date(s) searched and (system used)
MEDLINE	1966 – September Week 2, 2007, (OVID)
Embase	1980 - wk 38 2007 (OVID)
CINAHL	1982 – September week3, 2007 (OVID)
Health Management Information Consortium (HMIC)	September 2004 edition, (OVID)
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library 2004, issue 3 ( <a href="http://www.update-software.com/clibng/cliblogon.htm">http://www.update-software.com/clibng/cliblogon.htm</a> )
Database of Abstracts of Reviews of Effectiveness (DARE)	18/10/04 CRD administration database
Health Technology Assessment database	18/10/04 CRD administration database
National Research Register (NRR)	Issue 3, 2004 <a href="http://www.update-software.com/National/">http://www.update-software.com/National/</a>
Popline	Updated 18/10/04 ( <a href="http://db.jhuccp.org/popinform/basic.html">http://db.jhuccp.org/popinform/basic.html</a> )
Science Direct	1970-2004 ( <a href="http://www.sciencedirect.com/">http://www.sciencedirect.com/</a> )
Inside Conferences	1993- October 2004 Oct (Dialog)
Biosis Previews	1993-October 2004 Oct (Dialog)

**Figure 1: Synopsis of process and results of the systematic review.**



\* Articles which did not meet the inclusion criteria were excluded for the following reasons: 33 papers were review or review-type articles and not primary research studies (one additional paper was identified from reading these articles but this was rejected on the basis of an inappropriate study design); eight did not address the outcomes of interest and eight were not an appropriate study design.

**Table 2: Characteristics, extract from the results, and summary of the primary research study.<sup>9</sup>**

Design and Participants	Setting	Outcome measures	Cohort groups in follow up*	No. (%) in telephone survey subgroup (n=104, 21%)**	% pregnant	% live births	Summary of study results
<p>Retrospective cohort study.</p> <p>Adolescent women enrolled in a chlamydia screening programme.</p> <p>Original cohort of 496 sexually active women aged between 11 and 20 years (mean age 19.7 years).</p>	<p>Public health adolescent clinics in Indianapolis, USA.</p> <p>Participants recruited between October 1985 and February 1990</p> <p>Telephone interviews conducted June-August 1990.</p> <p>Follow-up interval: 1.5 – 4 years</p>	<p>Pregnancy and live births using:</p> <p>1.hospital activity data (from hospital discharge and pregnancy test performed)</p> <p>2. telephone survey – self reported pregnancy, data on sexual activity and contraceptive use</p>	Group 1: no evidence of chlamydia infection (n=319)	64 (20)	70.3	50.0	<p>1. No significant difference in pregnancy rates or live birth rates across the three groups after adjusting for sexual activity and contraceptive use (data from the telephone survey participants).</p> <p>2. Data from hospital in- and out-patient records during the follow-up period indicated that five cases of PID occurred, three in the uninfected group (who subsequently delivered live infants) and two in the single infection group. In this latter group, two ectopic pregnancies also occurred.</p> <p>3. No overall association between history of treated chlamydial infection and infertility</p>
			Group 2: Single chlamydia infection (n=109)	21 (19)	66.7	61.9	
			Group 3: multiple chlamydia infections (n=68)	19 (28)	63.2	52.6	
			Total (original cohort) n = 496	<i>p value***</i>	<i>0.83</i>	<i>0.58</i>	

\*The three groups were defined based on laboratory *Chlamydia trachomatis* tissue culture results. Infection is diagnosed on the basis of the ability to grow *Chlamydia trachomatis* in tissue culture followed by detection of chlamydia inclusion bodies by immunofluorescence. Those with no infection had at least two negative results.

\*\*number and percentage of original cohort in follow up

\*\*\*p value for chi-squared test of comparison between the three groups.

